Optimising management in ANCA-associated vasculitis

Joanna Tieu

MBBS/BMedSc FRACP

Adelaide Medical School

University of Adelaide

December 2021

Table of Contents

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide.

I acknowledge that copyright of published works contained within this thesis resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of a National Health and Medical Research Council Postgraduate Scholarship, the Ken Muirden overseas training fellowship, Margorie Hooper Scholarship, Arthritis SA postgraduate rheumatology grant, and an Australian Government Research Training Program Scholarship.

Joanna Tieu

December 2021

Acknowledgements

The journey of this PhD has been made possible by many.

To Professor Catherine Hill, from beginning to end you have provided steady guidance, support, encouragement and friendship. Thank you for knowing when and how to introduce me to new ideas, challenges, and opportunities. I appreciate your mentorship immeasurably.

Professor David Jayne, I remain in awe in many ways- of your mastery of clinical medicine, your wise insights and your unwavering calm. Thank you for taking me on as an unknown quantity, and your enthusiasm in mentoring myself and others in the world of vasculitis.

To Professor Susanna Proudman, thank you for your encouragement, willingness to contribute and keen grammatical eye.

Thank you to everyone I had the great pleasure of working with in the Cambridge Vasculitis and Lupus unit. Very special thanks to Rona Smith, Pani Gopaluni, Mark McClure, Kim Cheema and Federica Mescia.

I thank the many collaborators and patients who have provided invaluable input and/or contributed data to the work included in this thesis. In particular, Hans Nossent, Helen Keen, Peter Merkel and Gunnar Tommason for their support of this work.

Thank you to both Sue Lester and Rachel Black whose opinions and guidance on all things data, PhD and life I've come to truly value and rely on. I thank Professor Les Cleland for supporting the initial stages of my candidature.

I acknowledge the funding support received from the National Health and Medical Research Council, Arthritis Australia, Royal Australasian College of Physicians and Arthritis South Australia.

Thanks to my parents for your sacrifices for a brighter future. Last, but certainly not least, thanks to my brother William, who has been my buddy through life and an unconditional support. Thank you for being there through the good and bad, for the tough love and keeping my thoughts in perspective.

Abbreviations

AAV	ANCA-associated vasculitis
AAV-PRO	ANCA-associated vasculitis patient reported outcomes
AIHW	Australian Institute of Health and Wellbeing
AIPW	Augmented inverse propensity score weighted
ANCA	Anti-neutrophil cytoplasm antibody
ANZVASC	Australia New Zealand Vasculitis Society
c-ANCA	Cytoplasmic anti-neutrophil cytoplasm antibody
BCC	Basal cell carcinoma
BVAS	Birmingham Vasculitis Activity Score
BVAS/WG	Birmingham Vasculitis Activity Score/Wegener's Granulomatosis
CD20	Cluster of differentiation 20
CDA	Combined damage assessment
COD	Cause of death
CVID	Common variable immunodeficiency
DCVAS	Diagnostic and Classification criteria in Vasculitis Study
EGPA	Eosinophilic granulomatosis with polyangiitis
ELISA	Enzyme Linked Immunosorbent Assay
EMA	European Medicines Agency
ENT	Ear, nose, throat; Otolaryngology
Eq-5D	EuroQoL Group 5-Dimension 5-Level questionnaire
EULAR	European League Against Rheumatism
EUVAS	European Vasculitis Society
FFS	Five Factor Score
GPA	Granulomatosis with polyangiitis
HMDC	Hospital Morbidity Data Collection
HRQoL	Health-related quality of life
ICD	International Classification of Disease
ICD-O	International Classification of Disease for Oncology
IgG	Immunoglobulin G, gammaglobulin

IL-5	Interleukin-5
LOVAS	Low-Dose Glucocorticoid Vasculitis Induction Study
MAINRITSAN	Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis
MCOD	Multiple cause of death
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
NMSC	Non-melanoma skin cancer
OMERACT	Outcome Measures in Rheumatology
OR	Odds Ratio
p-ANCA	Perinuclear anti-neutrophil cytoplasm antibody
PAN	Polyarteritis nodosa
PR3	Proteinase-3
PROMIS	Patient-Reported Outcome Measurement Information System
PEXIVAS	Plasma Exchange and glucocorticoids for treatment of anti-neutrophil cytoplasm antibody associated vasculitis
PGA	Physician global assessment
PtGA	Patient global assessment
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RITAZAREM	Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis
RTX	Rituximab
SARS-CoV-2	Severe Acute Respiratory Syndrome associated Coronavirus 2
SCC	Squamous cell carcinoma
SF-36	Short Form-36
SLE	Systemic Lupus Erythematosus
UCOD	Underlying cause of death
VDI	vasculitis damage index
WA	Western Australia
WARDER	Western Australia Rheumatology Epidemiology Register
WHO	Word Health Organisation

Appendices

Appendix 1	WARDER data preparation
Appendix 2	Rituximab for the maintenance of remission in AAV: cumulative summary of participant responses
Appendix 3	Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis [publication]
Appendix 4	Long-term maintenance rituximab in ANCA associated vasculitis: relapse and infection prediction models [publication]
Appendix 5	RITAZAREM data preparation
Appendix 6	Perspectives of glucocorticoid use in patients with rheumatoid arthritis [publication]
Appendix 7	Improving benefit-harm assessment of glucocorticoid therapy incorporating the patient perspective: The OMERACT glucocorticoid core domain set [publication]
Appendix 8	South Australian Epidemiology of ANCA-associated vasculitis proposal

List of Tables and Figures

Included publications

Tieu, J., S. Lester, W. Raymond, H. Keen, C. L. Hill and J. Nossent (2022). Mortality and cause of death in patients with ANCA-associated vasculitis and PAN in Australia: a population-based study. Rheumatology (Oxford). 61(3):1062-1071.

Tieu, J., S. Lester, W. Raymond, H. Keen, C. L. Hill and J. Nossent (2022). "Cancer in Anti-Neutrophil Cytoplasm Antibody-Associated Vasculitis and Polyarteritis Nodosa in Australia: A Population-Based Study." ACR Open Rheumatology. 2022:4(3):223-230.

Tieu J, Smith R, Basu N, Brogan P, D'Cruz D, Dhaun N, Flossmann O, Harper L, Jones RB, Lanyon PC, Luqmani RA, McAdoo SP, Mukhtyar C, Pearce FA, Pusey CD, Robson JC, Salama AD, Smyth L, Watts RA, Willcocks LC, Jayne DRW (2020). "Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines." Rheumatology (Oxford) 59(4): e24-e32.

Tieu, J., R. M. Smith, S. Gopaluni, D. S. Kumararatne, M. McClure, A. Manson, S. Houghton and D. R. W. Jayne (2021). "Rituximab Associated Hypogammaglobulinemia in Autoimmune Disease." Frontiers in Immunology 12: 671503.

Appendices

Kronbichler A, Kerschbaum J, Gopaluni, J. Tieu, F. Alberici, R. B. Jones, R. M. Smith and D. R. W. Jayne (2018). "Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis." Ann Rheum Dis 77(10): 1440-1447.

McClure ME, Y. Zhu, R. M. Smith, S. Gopaluni, J. Tieu, T. Pope, K. E. Kristensen, D. R. W. Jayne, J. Barrett and R. B. Jones (2021). "Long-term maintenance rituximab for ANCA-associated vasculitis: relapse and infection prediction models." Rheumatology (Oxford) 60(3): 1491-1501.

Tieu, J., J. T. Cheah, R. J. Black, R. Christensen, N. Ghosh, P. Richards, J. Robson, B. Shea, L. S. Simon, J. A. Singh, P. Tugwell, M. Boers, M. A. A. Garibay, C. Campochiaro, S. Decary, M. de Witt, A. P. Fernandez, H. I. Keen, L. King, A. Hinojosa-Azaola, C. Hofstetter, I. Gaydukova, M. D. George, L. Gupta, S. Lyne, A. Makol, C. Mukhtyar, W. M. Oo, M. Petri, H. L. Pisaniello, S. E. Sattui, O. Russell, V. Teixeira, K. Toupin-April, C. Uhunmwangho, M. Whitstock, K. Yip, S. L. Mackie, S. M. Goodman and C. L. Hill (2021). "Improving benefit-harm assessment of glucocorticoid therapy incorporating the patient perspective: The OMERACT glucocorticoid core domain set." Semin Arthritis Rheum 51(5):1139-1145.

Venter, G., J. Tieu, R. Black, S. Lester, N. Leonardo, S. L. Whittle, E. Hoon, C. Barrett, D. Rowett, R. Buchbinder and C. L. Hill (2021). "Perspectives of Glucocorticoid Use in Patients with Rheumatoid Arthritis." ACR Open Rheumatol 3(4): 231-238.

Thesis outline

From early descriptions of vasculitis to our currently understanding of the vasculitides, there has been continual evolution of the concepts on pathogenesis, classification, management and the impacts on patients.

This is a thesis by publication, with an overarching aim of optimising therapy in anti-neutrophil cytoplasm antibody (ANCA)- associated vasculitis (AAV).

The first chapter provides an overarching background for the subsequent chapters, providing an historical perspective on disease, disease manifestations including AAV subgroups and some of the impacts of AAV to patients.

Chapter 2 provides insights into the impacts of AAV in Australia. Using data-linkage of WA hospitalisation, emergency department and death registry data, mortality including cause of death in patients with AAV and polyarteritis nodosa (PAN) were compared against the general population and controls. Data-linkage of WA hospitalisation and cancer registry data enabled analysis of cancer rates in patients with AAV/PAN compared with the general population.

Chapters 3 and 4 examines the use of rituximab in AAV in the United Kingdom. Chapter 3 includes a literature review examining the evidence for use of rituximab in the maintenance of remission in AAV, and the results of a Delphi exercise conducted to develop consensus guidelines on the use of rituximab for the maintenance of remission in AAV. Chapter 4 examines the longer-term outcomes of patients who have develop rituximab associated hypogammaglobulinaemia in a quaternary referral centre.

Chapter 5 examines the health-related quality of life (HRQoL) of patients with a relapse of AAV amongst patients in the multi-centre RITAZAREM study. This presents an unpublished manuscript examining the HRQoL of these patients during the induction phase of this study and compares the HRQoL in patients who received two different glucocorticoid regimens for induction of remission.

Finally, chapter 6 provides a discussion on the thesis and directions for future research.

Chapter 1 – Introduction

1.1 An historical perspective

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is an organ- and life-threatening systemic vasculitis. Current classification criteria recognise three subtypes of AAV: granulomatosis with polyangiitis (GPA, formerly Wegener's Granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg Strauss Syndrome) [1]. Although now grouped as AAV, early descriptions of these conditions were published well before being united by a common antibody and separation from polyarteritis nodosa (PAN).

In 1866, Kaussmaul and Maier described "periarteritis nodosa", a systemic inflammatory condition in a man with neurological, gastrointestinal and renal manifestations [2, 3]. Nodular thickening of blood vessels on histological samples was identified at autopsy. Similar cases were subsequently reported including Eppinger's diagnosis of periarteritis nodosa after re-evaluating samples from a patient described by Carl Von Rokintansky in a 1852 case report. The term polyarteritis nodosa was coined in the early 1900s [4, 5]. Identification of histologic vasculitis was often ascribed to PAN. A microscopic form, "microscopic polyarteritis" was recognised based on histologic differences [6], with subsequent groups describing the clinical characteristics of the disease as a separate entity [7, 8]. "Microscopic polyangiitis" was recognised as a condition distinct from PAN in subsequent classification criteria [9].

In 1939, Friedrich Wegener defined a specific condition with granulomatous inflammation, vasculitis and necrosis on autopsy specimens of patients with renal failure and rhinosinusitis [10], building on his report of two patients in 1936 [11]. This linked the findings from Peter McBride's description in 1897 of midfacial granulomas in a man with "rapid destruction of the nose and face" [12], with similar case reports also describing the vasculitic manifestations, including that of Heinz Klinger in 1931, which he considered "borderline variants of periarteritis nodosa" [13]. Gabriel Godman and Jacob Churg recognised Wegener's contribution to understanding of the condition in 1954 by using the term "Wegener's Granulomatosis" [14]. Better insight into Wegener's support and likely involvement in the Nazi regime triggered a movement towards a terminology change in the clinical and academic community, removing

the eponymous name in favour of granulomatosis with polyangiitis in the 2012 revision of the Chapel Hill Consensus Conference on nomenclature of vasculitis [15, 16].

In 1951, Jacob Churg and Lotte Strauss described their findings of "allergic granulomatosis, allergic angiitis and periarteritis nodosa" on histopathology in 13 patients who presented with asthma, fever and hypereosinophilia [17]. Although later commonly known as Churg Strauss Syndrome, efforts to remove eponymous nomenclature of vasculitides resulted in adoption of "Eosinophilic granulomatosis with polyangiitis"[1].

1.2 Clinical manifestations and classification of AAV

The identification of ANCA along with increasing knowledge of the clinical patterns associated with each AAV subtype have not only improved understanding of AAV, but also clarified its classification.

Davies and colleagues in 1982 first identified the antibodies with cytoplasmic staining of neutrophils on direct immunofluorescence, that we now identify as ANCA, when examining for other known autoantibodies in patients with necrotising segmental glomerulonephritis who had renal histology "indistinguishable from that of microscopic polyarteritis nodosa" [18]. The link between ANCA with cytoplasmic staining (c-ANCA) and GPA was subsequently established by Van der Woude and colleagues in 1985 [19]. Since this time, ANCA have been linked with MPA and EGPA, ANCA with perinuclear staining (p-ANCA) have been identified, proteinase-3 (PR3) and myeloperoxidase (MPO) were identified as antigenic targets for c-ANCA and p-ANCA respectively and evolution of enzyme linked immunosorbent assays (ELISA) for detection of PR3- and MPO-ANCA have enabled greater sensitivity and specificity for AAV diagnosis [20].

Experimental studies have supported the pathogenic role of MPO-ANCA [21] and PR3-ANCA [22]. Although ANCA (PR3 and MPO) titres are typically high at diagnosis or periods of high disease activity, and fall with treatment, the utility of ANCA to predict disease relapse has not been definitively established [23].

Manifestations of AAV typically arise from small vessel vasculitis (in all of GPA, MPA and EGPA) and granulomatous inflammation (in GPA and EGPA). Sequelae of vasculitic manifestations include pulmonary haemorrhage, attributed to a pulmonary capillaritis, and a pauci-immune glomerulonephritis. Granulomatous inflammation is commonly identified in inflammatory lesions of the upper and lower respiratory tract.

Constitutional symptoms and respiratory involvement are common to the majority of patients with AAV, with necrotizing glomerulonephritis frequently identified in patients with GPA and MPA. Notably, GPA and MPA have several overlapping disease characteristics, and are often grouped together in observational studies and clinical trials. In spite of these commonalities, key distinctions between these two subtypes exist. The development of granulomatous inflammation and a greater risk of relapse are observed in patients with GPA. GPA typically presents with sinopulmonary disease and is associated with PR3-ANCA whereas MPA is typically associated with MPO-ANCA. Importantly, overall prognosis, the response to treatment and rate of relapse also differs by disease subtype [24]. International data indicates that GPA is characterised by frequent relapses whereas mortality is greater in patients with MPA [25].

In clinical studies, EGPA is frequently considered a separate entity to GPA and MPA. As the name suggests, eosinophilic and granulomatous inflammation are typical and peripheral blood eosinophilia is associated with EGPA. The classic presentation of EGPA consists of a prodromal phase with asthma and sinusitis, culminating in a vasculitic phase. This subtype is associated with MPO-ANCA in approximately 40% of patients [26, 27].

The unique characteristics of each disease subtype is reiterated by their separation in successive iterations of international consensus on nomenclature and classification criteria (Table 1) [1, 28, 29]. These have evolved from the American College of Rheumatology (ACR) 1990 classification criteria which omitted MPA and Chapel Hill Consensus Conference (CHCC) nomenclature that was not designed for disease classification and therefore led to poor discrimination between AAV subtypes, to the European Medicines Agency (EMA) expert consensus algorithm derived to improve classification of disease, and more recently the data driven proposed ACR/European League Against Rheumatism (EULAR) classification criteria derived from the Diagnostic and Classification Criteria for Vasculitis (DCVAS) study [1, 28-32].

Table 1.1: Nomenclature and classification of AAV

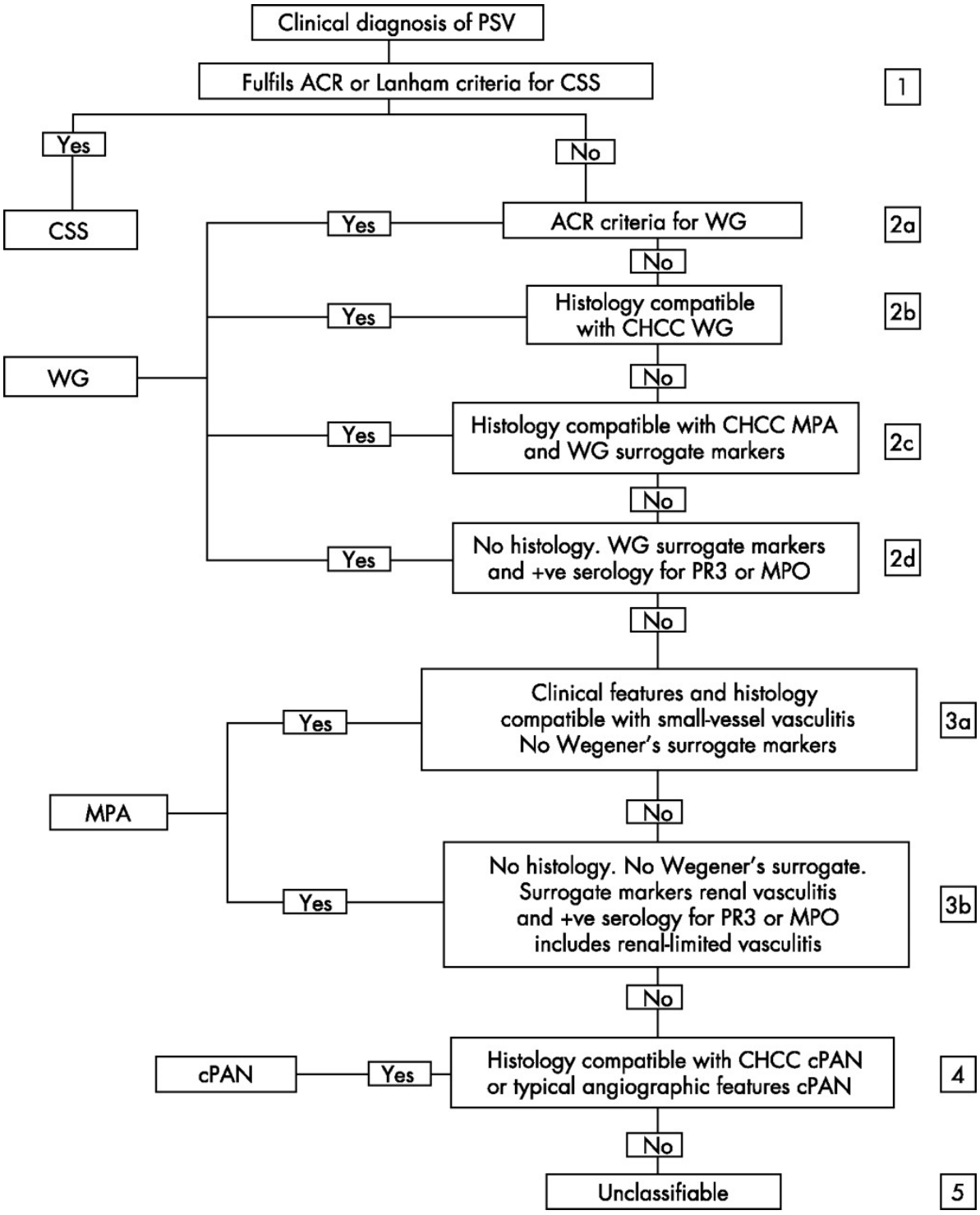
	Granulomatosis with polyangiitis (GPA)	Microscopic polyangiitis (MPA)	Eosinophilic granulomatosis with polyangiitis (EGPA)
ACR 1990 [30, 31]	1. Nasal or oral inflammation 2. Abnormal chest radiograph 3. Urinary sediment 4. Granulomatous inflammation on biopsy	*Not included*	1. Asthma 2. Eosinophilia 3. History of allergy 4. Mononeuropathy or polyneuropathy 5. Pulmonary infiltrates, non-fixed 6. Paranasal sinus abnormality 7. Extravascular eosinophils
CHCC 1994 nomenclature [9]	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common.	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotising glomerulonephritis is very common. Pulmonary capillaritis often occurs.	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia.
EMEA 2007 [28]	*See figure 1*		
CHCC 2012 nomenclature [1]	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common.	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.

ACR/EULAR proposed classification criteria 2019 (DCVAS study) [29]	Bloody nasal discharge, ulcers, crusting, congestion or blockage, or septal defect/perforation (+3) Cartilagenous involvement* (+2) Conductive or sensorineural hearing loss (+1) Pauci-immune glomerulonephritis (+1) cANCA or PR3-antibody (+5) pANCA or MPO-antibody (-1) eosinophil count ≥ $1x10^9$/L (-4) Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy (+2) Inflammation, consolidation, or effusion of the nasal/paranasal sinuses on imaging (+1) Total score of ≥ 5 is needed for classification	Pauci-immune glomerulonephritis (+3) Bloody nasal discharge, ulcers, crusting, congestion or blockage, septal defect/perforation (-3) pANCA or MPO-antibody positive (+6) fibrosis or ILD on chest imaging (+3) cANCA or PR3-antibody (-1) eosinophil count ≥ $1x10^9$/L (-4) Total score of ≥ 6 is needed for classification	Obstructive airways diseases (+3) Nasal polyps (+3) Mononeuritis multiplex or motor neuropathy (+1) Eosinophil count ≥ $1x10^9$/L (+5) Extravascular eosinophilic predominant inflammation/eosinophils in bone marrow (+2) cANCA or PR3-antibody (-3) microscopic haematuria (-1) Total score of ≥ 5 is needed for classification
Genetic associations [33, 34]	*PR3-ANCA: HLA-DPB1, PRTN3, SERPINA1*	*MPO-ANCA: HLA-DQ*	*TSLP BIM CDK6 GATA3 BACH2 LPP/BCL6* *ANCA negative: GPA33, IL5*

ACR American College of Rheumatology, CHCC Chapel Hill Consensus Conference, EMEA European Medicines Agency, EULAR European League Against Rheumatism, DCVAS Diagnostic and classification criteria for Vasculitis, ANCA anti-neutrophil cytoplasm antibody, c-ANCA cytoplasmic-AMCA, p-ANCA perinuclear-ANCA, PR3 proteinase-3, MPO- myeloperoxidase

* cartilaginous involvement: inflamed ear or nose cartilage or hoarse voice/stridor, endobronchial involvement or saddle nose deformity

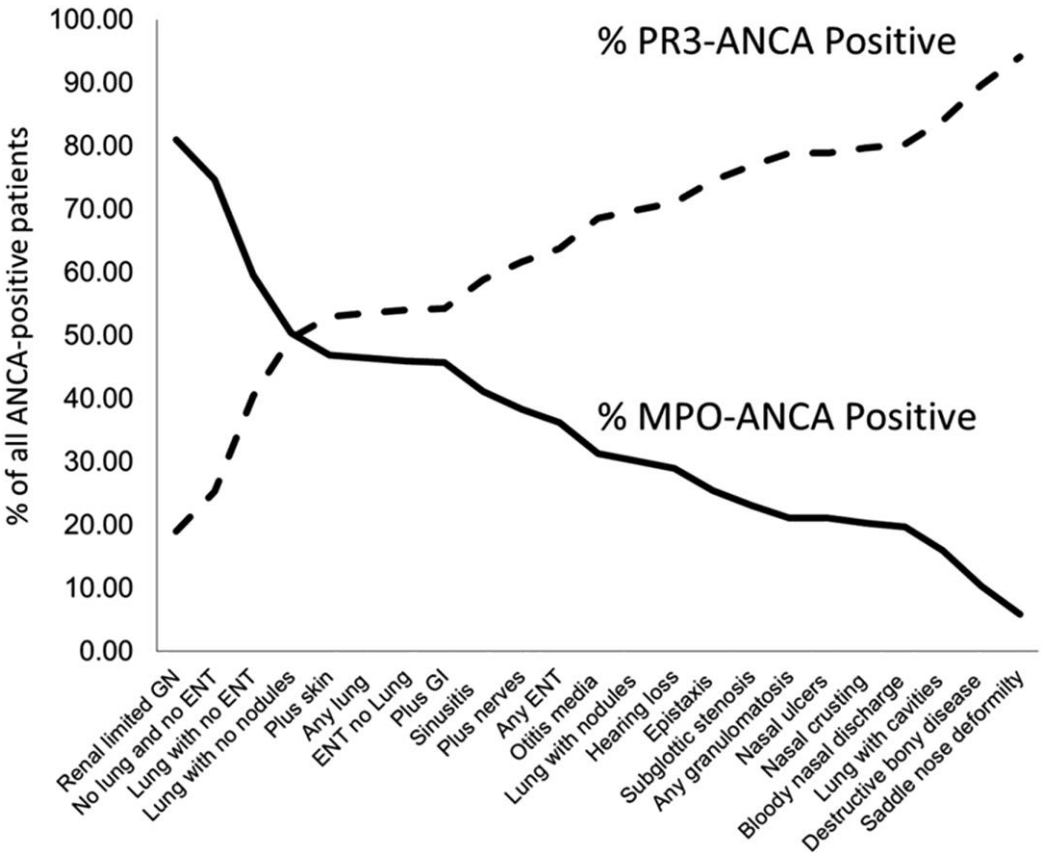
Figure 1.1: European Medicines Agency algorithm for the classification of ANCA-associated vasculitides and polyarteritis nodosa [28]



ANCA specificity is an increasingly important factor in classification, as a determinant of disease phenotype and prognosis in addition to its underlying pathogenesis. Although GPA is classically associated with PR3-ANCA, and MPA/EGPA associated with MPO-ANCA, cohort studies demonstrate stronger prognostic distinctions based on ANCA status than disease subgroups [35]. Figure 2 highlights the substantial overlap between disease characteristics distinguished by ANCA specificity, but also characteristics that are more distinctive of each. Differences associated with ANCA specificity are reiterated in further studies examining long-term damage in AAV patients and lung imaging findings in AAV [36, 37]. Similarly, in patients with a diagnosis of EGPA, different disease manifestations and outcomes are noted according to ANCA status [38, 39].

Crucially, a genome wide association study demonstrated that patients with PR3-ANCA and MPO-ANCA are genetically distinct (Table 1) [33]. Further, the same group showed that in patients with EGPA, underlying genetic associations, clinical phenotype and treatment response could be delineated based on ANCA status (MPO- positive versus negative) [34].

Figure 2 Frequency of disease manifestations in ANCA-associated vasculitis patients with PR3-ANCA and MPO-ANCA positivity, reproduced *from: Jenette & Nachman CJASN 2017 [40]*



1.3 Epidemiology of AAV

Estimates of the incidence and prevalence of AAV and its subtypes have varied across regions [41], affected by method of patient ascertainment and the changing classification criteria to identify patients. Progress in diagnosis including ANCA testing and greater success in treatment of AAV and comorbidities contribute to the suggested changes in incidence and prevalence of disease. Diagnosis and classification of AAV and PAN have changed over time. The French Vasculitis Study Group registry has highlighted this evolution, patients with PAN diagnoses fell from 55% of patients before 1980 to just 9% after 2010, commensurate with a rise in GPA diagnoses from 0% before 1980 to 46% after 2010 [42].

Many studies have used single source registry cohorts, including Australasian studies. Australian studies have reported AAV prevalence of up to 189 per million and incidence of up to 14 per million when AAV subtypes have been combined [43, 44]. Estimates have been based on outpatient-based data and ANCA testing from 1985 to 2005 in two centres [44], or GPA hospitalisation data alone from 1995 to 2005 [43], but not both.

Most studies have been conducted in countries where the majority of patients are of European descent, where GPA is more common than MPA [45]. In contrast, in Japan and China, MPA is more common than GPA. Comparisons of observational cohorts of patients with GPA and MPA in Japan and the United Kingdom greater MPO-ANCA positivity, differences in disease manifestations, sex distribution and age of onset are observed [46, 47]. Where examined, the rate of AAV amongst patients of European descent is greater than patients of African, Afro-Caribbean and Maori descent [48-50]. Albeit with small groups, French and American studies suggest younger onset and a more refractory and/or relapsing course in patients of African descent [49, 51].

1.4 Management of AAV

The treatment of AAV can be broadly divided into two phases: induction of remission and maintenance of remission. Remission in these studies reflect the absence of overt signs or symptoms of vasculitis activity in the face of ongoing therapy. Clinical trials have typically grouped GPA and MPA together, with EGPA studied separately due to recognised differences in disease manifestations and treatment response. Additionally, studies have differentiated

patients with “severe” organ- or life- threatening disease, and those with non-severe disease. Based on disease severity, consideration of patient factors and potential adverse effects, treatment(s) are selected to induce remission. This is followed by agent(s) to prevent relapse, that is “maintain remission”.

Despite the rarity of AAV, the number of RCTs that have been conducted to answer important questions on how to treat this disease is a remarkable achievement for the vasculitis community [52-63]. These RCTs have been made possible through extensive multinational collaboration, with multi-centre trials the norm.

The results of these RCTs have enabled evidence-informed guideline development for the management of AAV, which provide the general framework for treatment, with treatment based on the severity of disease. This includes the EULAR/ERA-EDTA consensus guidelines published in 2016 [64] and American College of Rheumatology/Vasculitis Foundation guideline for the management of AAV published in 2021 [65].

Figure 3: 2016 European League of Rheumatism/European Renal Association-European Dialysis and Transplantation Association recommended algorithm for the management of ANCA-associated vasculitis [64].

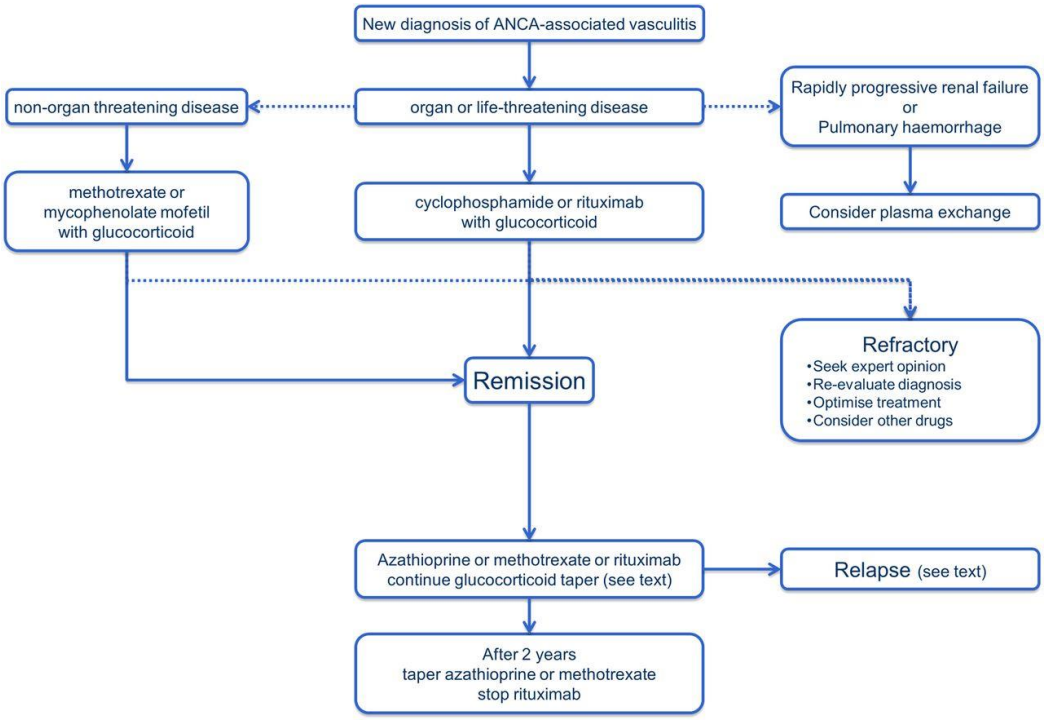
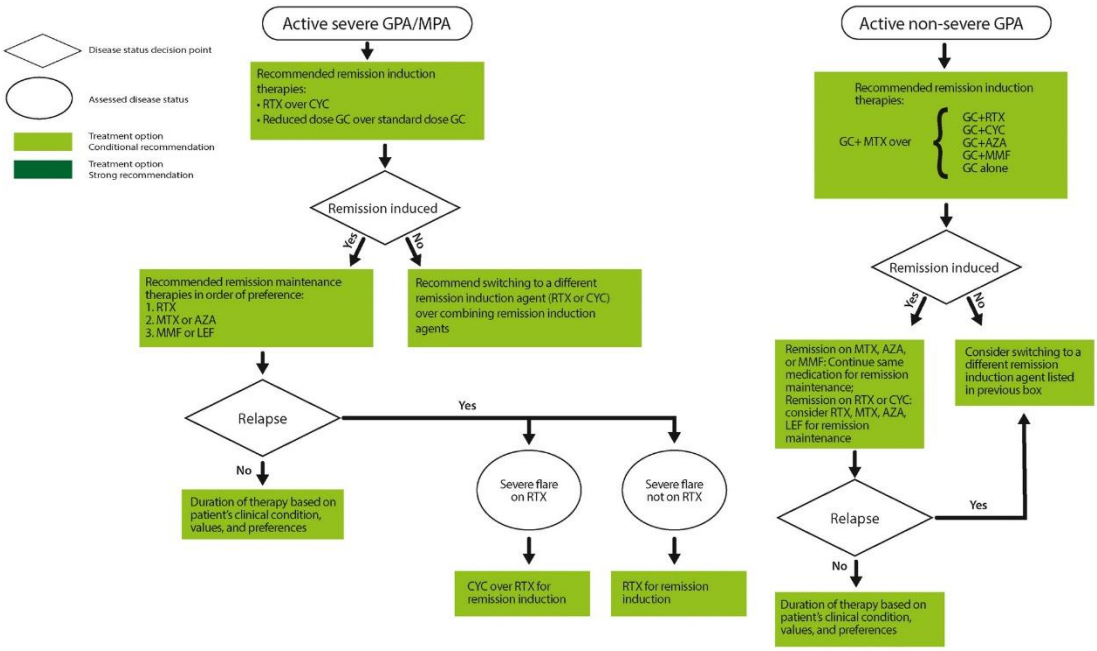
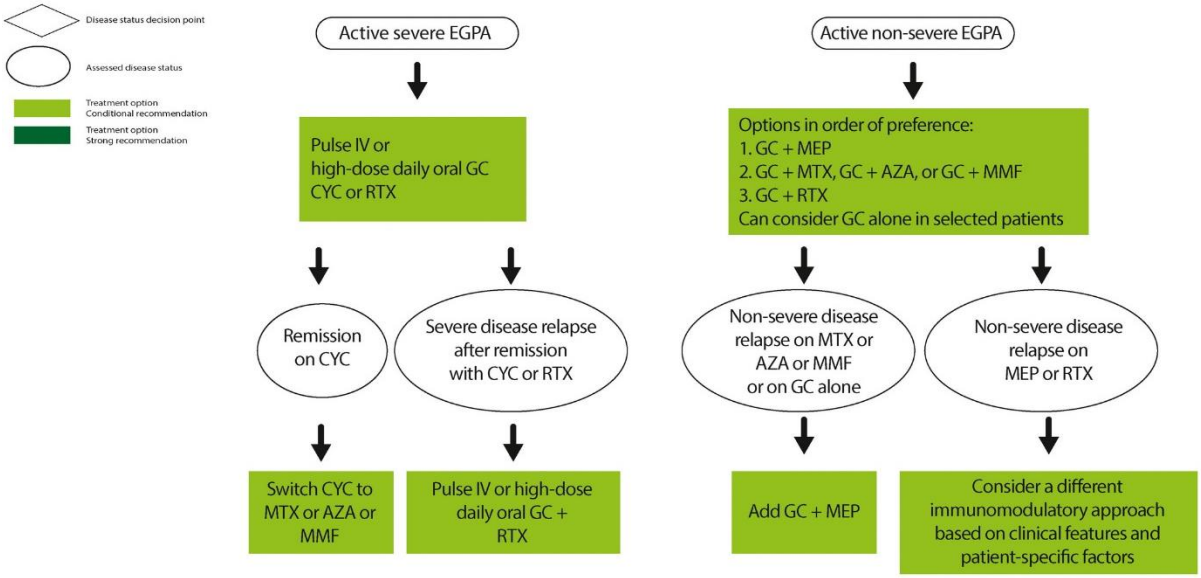


Figure 4: 2021 American College of Rheumatology recommendations for treatment of Granulomatosis with Polyangiitis and Microscopic Polyangiitis [65]



AZA = azathioprine, CYC = cyclophosphamide, GC = glucocorticoids, LEF = leflunomide, MMF = mycophenolate mofetil, MTX = methotrexate, RTX = rituximab

Figure 5: 2021 American College of Rheumatology recommendations for treatment of Eosinophilic Granulomatosis with Polyangiitis [65]



AZA = azathioprine, CYC = cyclophosphamide, GC = glucocorticoids, IV = intravenous, MEP = mepolizumab, MMF = mycophenolate mofetil, MTX = methotrexate, RTX = rituximab

1.4.1 GPA/MPA

Early studies established the efficacy of cytotoxic chemotherapy and glucocorticoids to induce remission [66, 67], and the use of combination cyclophosphamide and glucocorticoids dramatically altered the prognosis from a typically fatal disease if left untreated, to one of high morbidity and risk of relapse. Subsequent studies describing longer term experience using this combination recognised the toxicity of both agents, with characteristic glucocorticoid adverse effects, high rates of serious infection, haemorrhagic cystitis, malignancy and ovarian failure [68].

Comparisons of pulsed with oral cyclophosphamide administration, continued cyclophosphamide with switching to azathioprine, cyclophosphamide with methotrexate or mycophenolate in patients with less severe disease, and cyclophosphamide with rituximab, have provided alternatives to the original prolonged high dose cyclophosphamide and glucocorticoid regimen [52-55, 58, 69, 70]. More recently, plasma exchange has been shown to be less useful in the routine management of severe AAV, equivalent long-term outcomes have been confirmed in patients receiving lower dose glucocorticoid with induction therapy, and successful induction of remission without the protocoled use of glucocorticoid shapes the future direction of induction therapy [57, 63].

Relapse of disease is common, with up to 50% of patients relapsing after successful induction of remission on follow-up [61, 68, 71, 72]. The damage accrual from relapses includes complications from active disease, but also from treatment, with higher intensity immunosuppression required to re-induce remission following relapse. These are balanced against adverse effects of maintenance immunosuppression. The mainstay of maintenance therapy has been azathioprine, with methotrexate used as an alternative [52, 73]. Though relapse occurs in spite of maintenance therapy, greater immunosuppression provides greater protection from relapse; this has been demonstrated with higher cumulative doses of cyclophosphamide, prolonged glucocorticoid and prolonged non-glucocorticoid maintenance treatment regimens [54, 62, 70, 72, 74].

Rituximab, a monoclonal antibody directed against CD20 which induces B cell depletion, has equivalent efficacy to cyclophosphamide for induction of remission for newly diagnosed patients, but is superior for relapsing disease [55, 58]. It has also been examined as a therapeutic agent for the maintenance of remission in AAV in observational studies and four randomised controlled trials [59-62, 75-85]. Rituximab has been demonstrated to be superior to

azathioprine in the maintenance of remission, and similarly to prolonged azathioprine and prednisolone further reducing relapse risk, extended rituximab therapy to 46 months after first remission reduces relapse compared with rituximab cessation 18 months after first remission [62].

A point of frustration that remains from early studies is the absence of a reliable predictor of disease relapse. Although a number of risk factors for relapse are known, the roles of ANCA and B cells (in rituximab therapy) in guiding therapy have been examined but have not been proven consistently reliable for routine use in guiding treatment [23]. In the REMAIN trial, comparing withdrawal of azathioprine and prednisolone maintenance therapy with extended treatment after cyclophosphamide induction and an 18-24 month azathioprine and prednisolone maintenance period, withdrawal of maintenance therapy increased the risk of relapse over the 30 month trial period [74]. Moreover, ANCA positivity at trial entry conferred an increased risk of relapse, with 51% of ANCA positive patients at trial entry relapsing compared with 29% of patients who were ANCA negative (odds ratio (OR) 2.57, 95% confidence interval (CI) 1.16 to 5.68). Similarly, in the rituximab era, although tailoring maintenance treatment with ANCA and B cells has been trialled, they have not consistently been reliable for predicting relapse [59, 60, 78-81, 85]. In *post-hoc* analyses of an RCT comparing the use of rituximab to cyclophosphamide for the induction of remission in GPA and MPA, in patients with PR3-ANCA positive disease, a two-fold PR3-ANCA titre increase or PR3-ANCA return predicted recurrence of severe disease within 12 months [86]. Interestingly, the association between ANCA and subsequent relapse was true for those who had received rituximab induction, but not those who had received cyclophosphamide with azathioprine maintenance therapy. One observational study evaluating rituximab use for maintenance of remission noted that among 54 patients who became ANCA negative, ANCA return was noted in 13 (24%), of whom 10 (77%) subsequently relapsed [80]. Return of ANCA was noted to be associated with major relapse, but not minor relapse. Similarly, in the longer-term follow-up of patients who had been randomised to receive 6 monthly rituximab after cyclophosphamide induction, ANCA positivity at time points after completing rituximab therapy was associated with increased risk of relapse [61]. Return of B cells was not consistently predictive of relapse.

1.4.2 EGPA

Patients with EGPA have been excluded from the large RCTs that have characterised the advancements in treatment for MPA and GPA, owing to differences in disease characteristics and response to treatment [1, 34]. The French Vasculitis Group have driven a treatment approach based on poor prognostic indicators, incorporated into a five-factor score (FFS), derived for use in EGPA and PAN and revised in 2011 for all AAVs and PAN [87-90]. The FFS includes age greater than 65 years, renal insufficiency, cardiac insufficiency, severe gastrointestinal involvement, and the absence of otolaryngological involvement (is the latter being associated with better prognosis) [90]. These French Vasculitis Group studies support the use of cyclophosphamide in combination with glucocorticoids in patients with at least one item from the FFS and glucocorticoids alone in patients with no items from the FFS. Notably, these studies have been small, and the large cumulative burden of glucocorticoids remains an important issue in EGPA patients, prompting the use of other disease modifying agents in clinical practice [91]. There is additional recognition of the frequent use of glucocorticoids to treat "non-vasculitic" relapses characterised by sinonasal and asthma symptoms.

Drawing from experience in MPA and GPA, rituximab has also been used in patients with EGPA with success reported in observational cohorts [92, 93]. Better responses have been observed in patients who are ANCA positive, which is likely related to similarities in the underlying pathogenesis of disease [33, 92]. An ongoing RCT comparing rituximab to cyclophosphamide for induction of remission in EGPA has been undertaken [94].

More recently mepolizumab, a monoclonal antibody targeting IL-5 which regulates eosinophil proliferation, maturation and differentiation has been trialled in EGPA [95]. Patients with relapsing or refractory EGPA already receiving treatment with glucocorticoids with or without additional immunosuppressive therapy were randomised to receive mepolizumab or placebo [95]. Although patients receiving mepolizumab were in remission for a longer duration of the study than those receiving placebo, 47% of patients receiving mepolizumab did not meet criteria for disease remission during the 52-week study period [95]. Mepolizumab also enabled greater weaning of prednisolone; patients randomised to receive mepolizumab had lower average daily prednisolone/prednisone doses and greater percentage reductions in prednisolone/prednisone doses than those receiving placebo.

1.5 Impact of AAV

As our understanding of AAV continues to advance and the options for treatment expand, optimisation of management relies on reducing the impact of AAV. The success of induction strategies means that up to 90% of patients will achieve remission and throughout the patient's journey, there remains a complex interplay between disease and the benefits and harms of treatment.

1.5.1 Mortality

Historically, the primary concern for patients with AAV was its high fatality [96, 97]. In an early case series from 1958, average survival was 5 months; with renal, respiratory and cardiac disease being most common causes of death (COD) [96]. As successful treatment options have been introduced, mortality has improved; greater early survivorship has led to greater recognition of the longer-term effects of AAV, treatment-related morbidity, and their impact on mortality [66, 68].

Despite improvements in mortality [38, 98], a recent meta-analysis demonstrated that the risk of death in AAV patients remains 2.7 times that of the general population [99]. Mortality in patients with AAV has not been formally examined in Australia and therefore not included in this meta-analysis. Higher mortality is observed in patients from RCTs with MPO-ANCA, older age at diagnosis, with higher disease activity and severe renal impairment at diagnosis [100]. The risk of mortality in AAV patients is highest early after diagnosis and higher mortality compared with the general population persists beyond this early period [101]. In a combined analysis of data from European Vasculitis Society (EUVAS) trials conducted between 1995 and 2002, active vasculitis was a primary or contributing factor in 50% of deaths in the first year [100]. At the same time, infection was a primary or contributory COD in almost all deaths in the first year [100]. In addition to uncontrolled disease activity and short-term treatment related sequalae, disease related damage, multimorbidity and longer-term treatment toxicities contribute. In the combined EUVAS trial data, beyond the first year, death from active vasculitis is less common, with deaths being related to infection, cardiovascular disease, malignancy and pulmonary fibrosis [100].

Population-based studies in patients with AAV have examined mortality more broadly. In these studies, death in AAV patients has also been attributed to cardiovascular disease [102], malignancy [103] and renal disease [101, 103]. Traditionally, underlying COD has been for summary statistics for mortality. Multiple COD, using both underlying and contributory COD, is increasingly used to examine COD in population-based data. Commonly, death is a result of multiple life-limiting comorbid conditions and assigning a single underlying COD (UCOD) can be relatively arbitrary. When UCOD are considered alone, the mortality burden from other important diseases can be under-represented [104]. As highlighted above, in a combined analysis of EUVAS trials, vasculitis and infection were primary or contributory to death in 50% and almost 100% of deaths in the first year. When only primary, or underlying, causes are considered, as existing population-based studies in AAV have done, there may be under-representation of the multi-morbidity contributing to mortality in these patients. Furthermore, in these population-based studies, there are limited data of the changes in mortality burden in patients with AAV over time.

1.5.2 Morbidity

Damage associated with AAV includes the irreversible consequences of AAV and treatment related adverse effects, and provides another lens through which we can examine the impact of AAV. Both disease and treatment related damage are considered and for the vasculitis damage index (VDI), are scored when persistent for at least 3 months.

Combined VDI data from EUVAS trials of patients with MPA and GPA from 1995 to 2009 with up to 7 years of follow-up from 535 patients revealed high levels of damage accrual [36]. Renal damage items were common, particularly to patients with MPO-ANCA/MPA. Patients with PR3-ANCA/GPA had nasal blockage or crusting, and hearing loss more commonly recorded. Damage items possibly attributable to treatment were amongst the 10 most common items, including hypertension, osteoporosis, malignancy and diabetes. Older age and higher disease activity scores at diagnosis were associated with higher damage scores [105]. Further, cumulative glucocorticoid exposure and more frequent relapses were associated with higher damage scores.

In long term follow-up of EUVAS trials, damage was observed to occur early and continued to accrue over time [36]. Though data were incomplete, by 6 months 81.5% of these newly diagnosed AAV patients had at least one damage item recorded and fewer than 10% of patients

had no damage recorded in long-term follow-up. Similarly, assessment of multimorbidity in linked data of patients with AAV in Scotland suggested accrual of co-morbidities develops early after diagnosis and is associated with disproportionately higher healthcare expenditure in these patients [106].

Morbidity related to treatment can be wide ranging and difficult to separate from morbidity related to the disease itself. Most commonly, there has been a focus on malignancy and infections. Recognising the contribution of treatment to the morbidity of patients with AAV, RCTs in AAV have frequently evaluated regimens with reduced dose or duration of immunosuppression for both efficacy and safety [54, 63, 69, 107].

The increased rates of cancer seen in patients with AAV have been attributed to immunosuppressive agents; other mechanisms including paraneoplastic phenomena, shared aetiologic factors and chronic immune activation are possible. Notably, reductions in cancer risk have been associated with lower cyclophosphamide exposures [108]. Other mechanisms including paraneoplastic Reports from observational cohorts and population-based data in Europe have identified greater rates of genitourinary cancers, haematological cancers and non-melanoma skin cancers (NMSC) [109-113]. The impact of a cancer diagnosis on patients' outcomes and treatment decisions is understudied; previous studies have also not demonstrated consistently the impact of cancer on mortality [101-103].

The occurrence of infections early after diagnosis increases mortality in the first year after diagnosis [114, 115], and severe infections (requiring hospitalisation or intravenous antimicrobials) are associated with greater damage and mortality [116]. Recent trials have challenged long-held views on the need for high doses of glucocorticoids to induce remission [57, 63, 107]. Whilst the link between glucocorticoids and infections are well established, these trials have demonstrated that less glucocorticoid can be used successfully to induce remission, but also that fewer infections are observed with these regimens.

In RCTs evaluating the efficacy of therapeutic agents for induction or maintenance of remission, glucocorticoids have typically remained the same in both arms, making direct comparisons between agents difficult. The use of rituximab has raised additional concerns of hypogammaglobulinaemia, which can contribute to infection risk. Rituximab maintenance trials have not been powered to detect differences in adverse events. Whilst infections are commonly reported, particularly respiratory tract infections, rates of hypogammaglobulinaemia have remained low [59-62]. Despite low rates in RCTs, hypogammaglobulinaemia in long-term

observational cohorts has been reported [76, 77, 79, 117]. Their contribution to infections and the longer-term outcomes of these patients remains understudied.

1.5.2 Health-related quality of life

Health-related quality of life (HRQoL) of patients with AAV is impaired in patients with both active and inactive disease [118-120]. Beyond the impact of AAV on mortality and morbidity, it remains important in RCTs to determine if interventions have an impact on HRQoL for these patients using appropriate measures. The HRQoL of patients with AAV has typically been measured using the short-form 36 (SF-36) questionnaire, which examines eight health domains and provides summary physical and mental component scores. As an overall measure of HRQoL, in addition to AAV related disease activity, disease related damage, treatment effects and comorbidities are likely to influence patients' HRQoL. Considerable work has been conducted using OMERACT methodology to identify core outcomes (domains) incorporating both patient and clinician/researcher input, which has led to the development and validation of the AAV patient reported outcome measure (AAV-PRO) [121, 122].

Patients' HRQoL has been examined in randomised controlled trials using the SF-36 (prior to the AAV-PRO development) where equivalent efficacy has been demonstrated in both arms, with no substantial differences between treatment strategies [52, 55, 58]. In the French MAINRITSAN trial, where patients receiving rituximab had fewer relapses than those receiving azathioprine, changes in physical component scores were better in the rituximab group but mental component scores were better in the azathioprine group [120].

HRQoL in AAV patients is incompletely explained by disease activity [118, 119, 123]. In addition to disease activity, fatigue, pain, sleep disturbance, sex, age and mood disturbance can contribute to poor HRQoL [123-127]. Further, glucocorticoids contribute to the impaired HRQoL of AAV patients [126]; in qualitative work, AAV patients report both positive glucocorticoid effects in reducing disease activity and increased energy, but also negative effects related to sleep, depression and anxiety, metabolic changes, and concerns about long-term effects [128]. The improved HRQoL seen with the complement inhibitor avacopan, has been related to the substantially reduced glucocorticoid exposure and better disease activity in patients in this group [57].

The consequences of impaired HRQoL on patients' outcomes are also poorly understood. The impacts on work, family and social roles are highlighted in the OMERACT qualitative work

involving both patients and clinicians/researchers and are incorporated in the AAV-PRO [121, 122]. In a single-centre study of GPA patients under 40 years of age in Germany, of 51 patients who were employed at diagnosis, 28 were unemployed when surveyed, with women more affected than men (78% vs 29% becoming unemployed) [129]. In a single-centre study of patients with AAV in Australia, 29/47 (61.7%) of patients felt that their ability to work had been negatively affected by AAV and 21/47 (44.7%) reported financial instability [130]. Fatigue was cited by 13 patients in this study as having a negative impact on work participation [130]. Compared with patients who were employed, GPA patients who were unemployed had lower general health, physical function, role physical and social function domain scores on SF-36 questionnaires. Patients with AAV report unemployment and reduced workplace participation because of disease, with fatigue, depression and weight suggested as additional factors [129-131].

Less quantifiable are the effects on patients' social roles and supports. In work conducted by the OMERACT vasculitis working group, in-depth qualitative interviews with patients emphasise the impacts of AAV and its treatment on patients' social contact and social roles [121]. These additionally highlight themes of "being the source of other people's worry" and "dependency on others". Although one study using SF-36 questionnaires did not identify impaired HRQoL in spouses of patients with AAV [132], a subsequent qualitative study exploring patient and informal carers' experiences reported on the physical and emotional impacts on both patients and carers, which developed into the "need for constant vigilance" and "fear of the future" [133].

In addition to the recognised burden of AAV on an individual level, the health economic burden of AAV has been considered. This has been assessed largely in population-based data linkage studies in Europe and North America, where unsurprisingly, healthcare costs are greater in patients with AAV, driven by the costs of inpatient admissions for patients with severe organ- and life- threatening manifestations, and increase substantially due to relapse [134-136]. Importantly, these studies are based on costs of inpatient and/or outpatient care and often do not consider the impacts on paid employment, unpaid commitments, work participation, and carers.

1.6 Thesis aims

The aims of this thesis were:

1. To evaluate the risk of mortality and examine the causes of death in Australian patients with AAV/PAN (Chapter 2)
2. To examine overall and time-varying rates of incident cancer in patients with AAV/PAN compared with the general population in Australia (Chapter 2)
3. To develop guidelines for the use of rituximab for the maintenance of remission in AAV (Chapter 3)
4. To explore the characteristics of patients with autoimmune disease who develop rituximab associated hypoogammaglobulinaemia and their long-term outcomes (Chapter 4)
5. To describe the HRQoL of patients with a relapse of AAV, and compared HRQoL after treatment with two different glucocorticoid regimens for AAV (Chapter 5)

Chapter 2 – Impacts of ANCA-associated vasculitis and polyarteritis nodosa in Australia

2.1 Introduction

This chapter includes manuscripts that report on the impact of AAV and PAN on mortality and malignancy in Western Australia [137, 138]. Although two previous studies have estimated the rates of AAV in Australia [43, 44], neither has evaluated the impact on mortality or malignancy. Studies that have examined these outcomes have done so in European, North American and Korean populations [98, 100-103, 108-113, 139-142]. Data in the context of the Australian healthcare setting and context have been lacking.

Both papers included in this chapter use linked data from the West Australian Rheumatology Epidemiological Register (WARDER), described in greater detail in section 2.2. Data from 1980 to 2015 were linked to WA hospitalisation and emergency department data, WA death data and WA cancer registry data. Discussed in further detail below are some of the methodological challenges of the data cleaning and analysis processes for these two papers. Issues inherent to linked healthcare datasets related to their primary administrative functions. Methodological challenges for these two projects provided important learning in data management in large datasets, data cleaning and data preparation for analyses in large longitudinal datasets.

Death from AAV has been studied in European and North American studies; mortality rates in AAV patients remain higher than the general population and although death has been attributed to active vasculitis [100, 101], infection [100, 101, 103], cardiovascular disease [102, 103], malignancy [100, 103] and renal disease [101, 143], the timing of these contributors to mortality over long-term has not been examined. In an analysis of one-year mortality amongst patients enrolled into EUVAS studies between 1995 and 2005, early infections and adverse events from treatment were associated with greater mortality one year after diagnosis [115]. Similar to AAV, vasculitis, infection and malignancy have been commonly attributed as primary CODs in patients with PAN [144].

Although studies have consistently demonstrated greater survivorship over time, multimorbidity occurring soon after diagnosis has become increasingly apparent. Despite this, population-based mortality studies in AAV have evaluated primary (underlying) COD alone, rather than all contributory COD [102, 103, 145].

The paper in this chapter “Mortality and cause of death in patients with ANCA-associated vasculitis and polyarteritis nodosa in Australia: a population-based study” provides the first Australian data on mortality in AAV and PAN patients [137]. We compared mortality in patients with AAV/PAN against both the general population and age-, sex- and temporally matched controls. Excess mortality was demonstrated in patients with AAV and PAN compared with the general population and controls. We identified greatest excess mortality early after diagnosis. By examining COD in AAV/PAN patients and controls, we were able to demonstrate distinct temporal patterns in the contributions of vasculitis, infection, non-infective respiratory disease, malignancy, cerebrovascular disease and ischaemic heart disease to mortality over long-term follow-up.

Data regarding malignancy in Australian patients with AAV/PAN have been lacking. Although the risk of common cancers in the general population such as breast and colorectal cancer do not appear to be increased in patients with AAV/PAN, higher rates of non-melanoma skin cancers (NMSC), haematological cancers and genitourinary cancers has been reported. Immunosuppressive agents have often been implicated, although other mechanisms including paraneoplastic phenomena, shared aetiologic factors and chronic immune activation are possible. Few studies have examined timing of cancers after the diagnosis of AAV and PAN. Further, although European studies have not demonstrated greater rates of melanoma in AAV patients, the risk of melanoma in Australian AAV/PAN patients warranted investigation in view of Australian’s higher ultra-violet exposure and higher population rates of melanoma.

The second paper included in this chapter “Cancer in anti-neutrophil cytoplasm antibody associated vasculitis and polyarteritis nodosa in Australia: a population-based study” examines these evidence gaps [138]. In this paper, we compared cancer rates in patients with AAV/PAN with WA population rates, age- and sex-matched. Higher rates of incident cancer in AAV/PAN patients were identified, specifically in GPA/EGPA patients. Increased cancers were explained by lung and haematological cancers occurring early after diagnosis, and skin and genitourinary cancers which peaked at 5 and 10 years after diagnosis respectively.

Using a data linkage approach, these two papers provide the first Australian “real-world” data on mortality and malignancy in AAV/PAN patients. The results further current knowledge on the drivers of mortality in patients with AAV/PAN in the long-term, highlight the challenges of comorbidities in the long-term management of AAV/PAN, and contextualise cancer risk in the Australian setting.

2.2 Dataset description and methodological challenges

2.2.1 Data Linkage

The role of existing data sources for epidemiological research is increasing. Administrative health care data are routinely collected for several reasons, not least to enable the day-to-day functioning of the source health care system. This data also allows assessment and comparison of healthcare service utilisation and the cost of these services to the healthcare system, which in Australia is largely publicly funded by a universal healthcare system along with patient contributions. Administrative healthcare data can include hospitalisations, outpatient encounters with medical practitioners and allied health practitioners, medicines, and procedures. In some settings including Australian private healthcare, and the United States, this is referred to as claims data as reimbursement of healthcare encounters including hospitalisations, outpatient appointments, blood tests and imaging studies are recorded when the expense is "claimed" from an insurer.

More recently, electronic medical records (EMRs) have been implemented in healthcare settings. These records not only hold details on patient symptoms and signs, but also medical illnesses, investigations, drug prescriptions, hospitalisations, and social histories. Despite complexities in data extraction and quality, this is rich source of healthcare data that can be used for auditing of health care utilisation, patient outcomes and, with the integration of patient reported outcome data into EMRs, outcomes and experiences from the patient's perspectives.

Additionally, many developed countries have routine national data collections, which provide insights into the population including life expectancy and the health status of the population and subgroups. In Australia, government held databases extend beyond the healthcare setting, with data on electoral role, education, housing, correctional services and use of social service income support being included.

Population based studies and data-linkage can provide a wider vantage point by which to view patient interactions with the healthcare system. Data linkage allows for the merging of data from multiple sources, facilitating better understanding of service utilisation, planning of service provision, public health interventions and setting clinical and research priorities. Australia lacks a unifying identifier for all government and administrative databases. Australian population-based data linkage services therefore employ algorithms using probabilistic algorithms to match individuals across databases.

These data can provide invaluable information on what occurs in “real-world” practice. Analyses from these data sources are complementary to analyses from observational studies and RCTs.

2.2.2 Population based studies and AAV/PAN

Typically, AAV and PAN have both been studied in observational cohorts and RCTs. These studies have furthered classification and treatment in these patients as highlighted in the thesis background, and there are several advantages of the data from these studies. Patients studied typically meet or fulfill specific inclusion criteria including classification criteria for disease or disease subgroups, and additional clinical and laboratory data are often available. Importantly, exclusionary criteria are applied, particularly in RCTs, so that observed differences can be attributed to treatment effect(s) rather than confounding factors.

Population data typically obtain diagnoses based on clinicians’ best assessment of the clinical presentation. These data are also limited by what is already collected and the clinical data stored. Though greater heterogeneity exists amongst these patients’ clinical features, it arguably provides a more realistic representation of clinical practice.

Differences between patients in observational studies and RCTs have also been demonstrated in AAV, which likely relate to selection criteria for studies. Compared with GPA and MPA patients enrolled in French and North American registries, patients included in RCTs have been older, had higher disease activity scores and more frequent renal involvement [146]. Moreover, comparisons of these groups have shown greater relapse rates amongst patients with GPA in RCTs than those in registries. Comparisons between AAV and/or PAN patients in population-based studies and observational studies or RCTs have not been performed.

Another important distinction in considering the patient groups in these studies is the method of inclusion. To be included in registries and RCTs, patients are recruited with consent being obtained prior to patient enrolment. Ongoing data collection relies on active participation from patients and may contribute to a degree of selection bias. Moreover, uncommon outcomes such as malignancy require large patient groups for analyses and longer-term outcomes such as malignancy and mortality are affected by attrition over time. In population-based data however, strict protocols and the use of de-identified data allow for use of existing data without specific recruitment or specific study consent. Importantly, given the severe, life-threatening nature of these vasculitides for some patients, those who die during an index admission, are unable to

provide informed consent or do not participate in registries and RCTs due to any number of reasons can still be included in population-based studies using administrative data.

With greater access to administrative healthcare data and recognition of the unique perspective this provides, population-based approaches are increasingly used to evaluate the epidemiology [50, 145] and longer term outcomes in AAV, including mortality [102-104, 145], co-morbidities [106, 147] and health care utilisation [106, 148].

2.2.3 WARDER

The West Australian Rheumatology Epidemiological Register (WARDER) is a data linkage study, using administrative and mandatorily reported data to characterise and investigate the rheumatic disease condition burden and risk of complications in Western Australia (WA).

The linked datasets include:

- WA Hospital Morbidity Data Collection (HMDC)
- WA Emergency Department data collection
- WA cancer registry
- WA Births, Deaths and Marriages death data

The HMDC dataset includes a comprehensive data collection for hospital admissions in WA. This excludes admissions for psychiatric or perinatal care. Data collected include demographic data, primary diagnosis code (i.e., reason for admission), up to 20 secondary diagnosis codes, procedure codes, date, and duration of hospitalization. All diagnosis codes are assigned based on defined International Classification of Disease (ICD) codes. For the duration of data linkage in this dataset, ICD-9 and ICD-10 are used.

The Emergency Department data collection includes data for all emergency department attendances at public hospitals in WA. Data collected includes demographic data, information related to episodes of care in the emergency department (e.g., date of presentation, triage category) and primary diagnosis using ICD codes.

The WA cancer registry collects data from all mandatorily reported cancers in WA. These are collected from pathology reports, oncologists, radiation oncology treatment records and ophthalmologists. Data collected includes demographic data, diagnosis date, cancer details

including morphology and topography data using ICD for Oncology (ICD-O) codes. Only cancers with "malignant" behaviour codes are included, i.e. benign, carcinoma *in situ*, cancers "suggestive of malignancy" are not routinely included. Australian cancer registries, including the WA cancer registry, do not include squamous cell carcinoma (SCC) of the skin and basal cell carcinoma (BCC) of the skin. Reports from multiple sources are consolidated to one record for each report.

The WA Births, Deaths and Marriages registry death data included all recorded deaths in WA, which are sent to the national mortality register, held by the Australian Institute of Health and Wellbeing (AIHW). Data include date and COD which includes an assigned underlying COD and contributory CODs. From 1980 to 1997, no contributory CODs were available. Following this date, both underlying COD and contributory CODs were available in the dataset. These are coded and classified according to the International Statistical Classification of Diseases and Related Health Problems.'

2.2.4 Methodological considerations using WARDER dataset

Appendix 1 includes the STATA do file for data preparation for analyses for the cancer and mortality analyses in this chapter. The description of the considerations specific for diagnosis of AAV/PAN, cancer, mortality including COD are included below.

Diagnosis of AAV/PAN

Data for diagnoses were derived from both hospitalisation and COD data, which are recorded using international classification of disease (ICD)- version 9 and 10 codes. In both ICD-9 and ICD-10, codes for AAV subgroups and PAN reflected historic nomenclature changes. In line with nomenclature changes and recognition of AAV subgroups as a separate entity from PAN, ICD codes have changed over time. Separation of MPA from PAN occurred in the 5th edition of ICD-10; thus, both shared a single diagnosis code in ICD-9 and ICD-10 until the 5th edition (implemented in WA hospitalisation codes in 2007), when MPA was given a separate code. Both GPA and EGPA shared a single diagnosis code in ICD-9 and had separate diagnosis codes in ICD-10. Additional clinical data including disease manifestations and ANCA status were not available owing to the nature of the data linkage process and therefore application of classification criteria was not possible. The manuscripts included in this chapter have therefore included

patients with both AAV and PAN. Other studies using population-based data have been similarly shaped by ICD coding structures [41, 50]. AAV and PAN have been studied together in prior studies using ICD codes [50] or clinical data are used to assist in verifying diagnosis [102, 103, 149].

The WARDER dataset used both ICD-9 and ICD-10, with grouping of AAV and PAN depicted in Table 2. The ICD code structures influenced the subgroups analysed in both papers included in this chapter. Moreover, patient level clinical data and laboratory data are not linked in WARDER, prohibiting the application of additional criteria to further classify patients. Notably, in a separate study conducted in WA where patients with AAV were identified using ICD diagnosis codes from hospital discharge summaries, clinical characteristics of 64/74 (91%) patients met classification criteria for AAV using the EMEA classification algorithm [150]. The same standards for both coding and auditing processes were used for the data in this study, supporting the reliability of the ICD based diagnoses for patients in WARDER. Moreover, this is not dissimilar to the accuracy of AAV diagnosis using administrative databases in the United States and United Kingdom [149, 151].

Date of diagnosis was taken as the first time and AAV or PAN ICD code was used in the WARDER dataset. Though this may not be precise for some patients, it is the first opportunity to identify a diagnosis date in the WARDER dataset. It is also recognised that symptom onset to diagnosis is often affected by delays, particularly in patients without organ or life-threatening manifestations at onset [152, 153].

Patients in whom AAV or PAN were diagnosed as outpatients and never required an inpatient admission were not included in the linkage process for WARDER, which is a potential source of selection bias. A key advantage of the dataset is the inclusion all public and private hospital systems in the state, which may not be included in registries or cohorts occurring through select sites.

Table 2.1 International Classification of Disease codes used for identifying patients with AAV/PAN

	ICD-9	ICD-10	
	1980 – 1999	*2000 – 2005*	*2006 – 2014*
AAV			
GPA	446.0	M31.3	M31.3
EGPA		M30.1	M30.1
MPA	446.4	M30.0	M31.7
PAN			M30.0

AAV: ANCA-associated vasculitis, GPA: granulomatosis with polyangiitis, EGPA: eosinophilic granulomatosis with polyangiitis, MPA: microscopic polyangiitis, PAN: polyarteritis nodosa

The Hospital Mortality Database Collection (HMDC) used ICD-9 until 1999, when ICD-10 was used for diagnosis classifications. The 5th edition was adopted in 2007.

GPA and EGPA shared a diagnosis code in ICD-9 and had separate diagnosis codes in ICD-10.

PAN and MPA shared a diagnosis code until the 5th edition ICD-10 update (adopted in HMDC in 2007) when separate codes were used.

Cancer data

Cancer diagnosis and classification

Identification of cancer diagnoses used ICD-O codes and cancer related deaths in death registry data used ICD-9 and ICD-10 codes respectively, according to the year of death. These codes differ for cancer diagnoses and is reflected in the data cleaning process included in Appendix 1.

Cancer classifications were structured to match WA cancer reporting data to allow for comparisons with population data.

The ICD-O structure classifies cancers according to the organ affected (topography) and histopathological type (morphology). Solid organ cancers can be classified by topography. Haematological cancers, however, are better defined by morphology than topography as morphology rather than topography determines treatment and prognosis. Therefore, morphology codes were used to classify haematological cancers. Where haematological cancers occurred in solid organs, these were re-classified as haematological cancers.

Cancer recurrences

Cancer recurrence reporting is not mandatory, though may be reported to the cancer registry. The overall rate of incident cancer was considered in analyses with specific cancers (breast, lung, genitourinary, pancreatic, colorectal, prostate, skin and haematological) analysed based on existing literature on cancer in AAV/PAN. The remaining cancers were considered in an "other cancer" group.

Recurrences were not analysed, with the following rules applied to ensure this was adhered to:

- Recurrences or duplicates of individual specific cancer types were identified when there was more than one report of the same cancer type (specific solid organ or haematological). Recurrences and duplicates were removed, with the first report retained.
- Where multiple reports of "other cancer" existed, cancers that had already been reported in a specific organ system of interest were considered recurrence or duplicates and removed.
- Where multiple reports of "other cancer" existed, cancers within the same organ system were considered recurrences or duplicates and removed.
- Haematological cancers representing likely transformations (e.g., myelodysplastic syndrome followed by acute myeloid leukaemia) were considered akin to a recurrence and the subsequent report removed.

Where there were multiple reports of the same cancer type (specific solid organ or haematological), the first report was taken for date of diagnosis.

Mortality Data

Death registry data are collected from death certificates completed by a medical officer, which follows international standards set by the WHO. Death certificates record demographic data, date of death and cause of death.

Causes of death

The UCOD, often considered the primary COD, is “the disease or injury that initiated the train of events leading directly to death, or the circumstances of the accident or violence that that produced the fatal injury” [154]. The UCOD is typically used when examining causes of death, including in AAV and PAN [102, 103, 144].

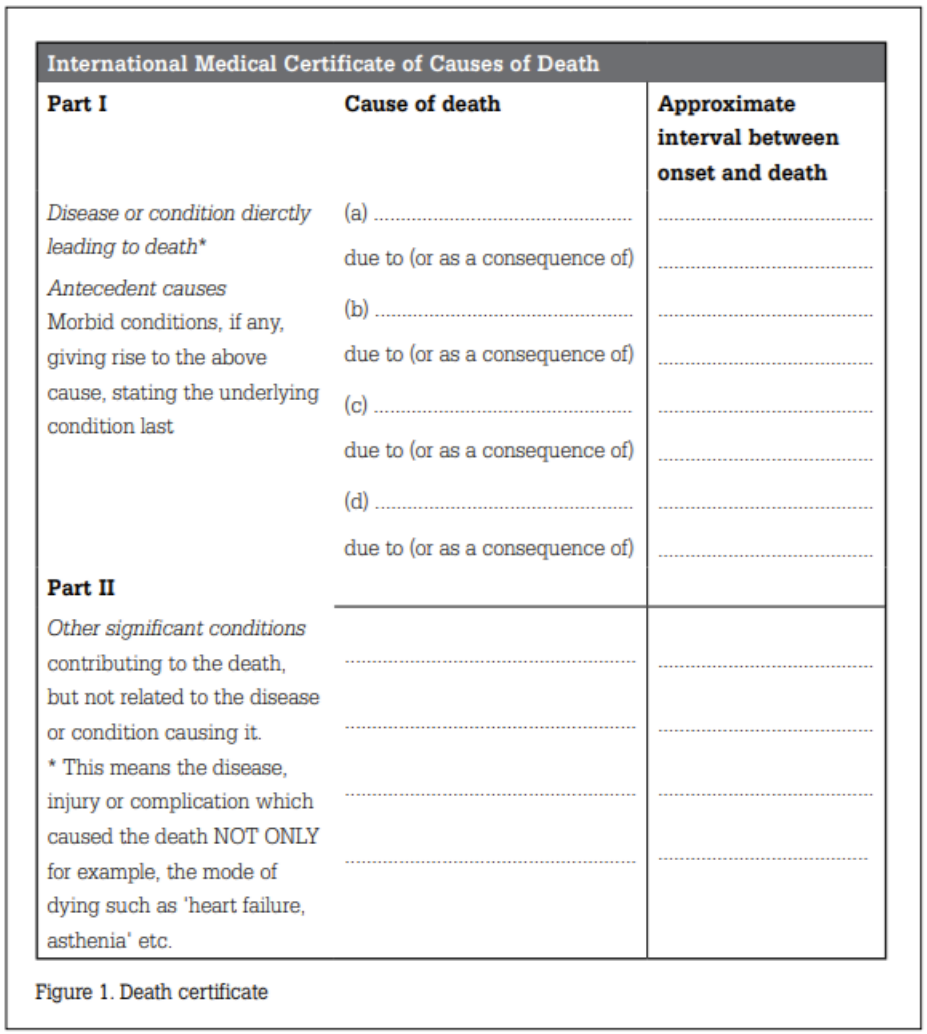
In addition to the UCOD contributory, or associated, COD are conditions deemed significant to the person’s death by the medical practitioner completing the death certificate, but not considered the underlying cause.

The term multiple cause of death (MCOD), including UCOD and contributory COD, has arisen to provide a broader picture of the joint role of disease(s) in contributing to death, recognising that death may not occur from a single cause. Death often occurs in a person with multiple life-limiting comorbid conditions and specifying a single UCOD can be relatively arbitrary. When UCOD are considered alone, the mortality burden from other important diseases can be under-represented [104]. This is highlighted in long-term data from five EUVAS trials in AAV where key COD were deemed contributory to as many deaths as it was a “primary” COD [100].

Causes of death listed on death certificates are recorded in two parts:

- Part I includes the disease or condition directly leading to the person’s death, and antecedent causes, which contributed
- Part II includes other significant conditions contributing to death

Figure 5 Death certificate causes of death listings



International Medical Certificate of Causes of Death		
Part I	**Cause of death**	**Approximate interval between onset and death**
*Disease or condition dierctly leading to death**	(a)	.....
	due to (or as a consequence of)	.....
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)	.....
	due to (or as a consequence of)	.....
	(c)	.....
	due to (or as a consequence of)	.....
	(d)	.....
	due to (or as a consequence of)	.....
Part II		
Other significant conditions contributing to the death, but not related to the disease or condition causing it. * This means the disease, injury or complication which caused the death NOT ONLY for example, the mode of dying such as 'heart failure, asthenia' etc.	.....	.....
	.....	.....
	.....	.....
	.....	.....

Figure 1. Death certificate

For example, death may be due to a myocardial infarction in the setting of a Pseudomonas aeruginosa bacteraemia from a foot ulcer, with comorbid type 2 diabetes mellitus and peripheral vascular disease. Other comorbidities may include hypertension, chronic kidney disease, chronic obstructive airways disease and treated colorectal cancer. The medical officer completing the death certificate must select the conditions to list in Part I and Part II of the death certificate. Using UCOD alone may not adequately account for the contributions of all comorbidities.

The text from all COD is converted to the relevant ICD diagnostic code for the year of death to form entity-axis-data, which includes both the ICD code and data specifying the position of each ICD code in the death certificate, as recorded by the medical practitioner.

Record-axis-data includes all COD, and specifies an UCOD. Record-axis-data generates UCOD and MCOD by applying WHO rules to entity-axis-data. Though the death certificate structure encourages practitioners to assign the UCOD, the algorithm ensures the default UCOD represents a plausible "sequence" from UCOD to the other antecedent causes listed, otherwise the algorithm facilitates reassignment of UCOD, and avoids ill-defined conditions being assigned as UCOD such as "senility", "acute respiratory failure" and "cardiac arrest, unspecified". The Australian Institute of Health and Wellbeing (AIHW) uses software to apply the algorithm to Australian COD data. Analyses in the mortality study used both UCOD and MCOD, recognising the importance of multi-morbidity in patients with AAV and PAN. Record-axis-data (both UCOD and all COD) were therefore used.

In WARDER, prior to 1997, no UCOD data was available. From 1997 to 1998, ICD-9 was used for both entity-axis-data and record-axis-data. From 1999 onwards, ICD-10 was used. Record-axis-data was derived from text manually for an additional 13 patients using WHO rules for assigning UCOD where text from death registry data was available without ICD diagnosis codes. The data preparation steps to identify pre-specified COD are included in Appendix 1.

2.3 Manuscript: Mortality and cause of death in patients with ANCA-associated vasculitis and polyarteritis nodosa in Australia: a population-based study

Statement of Authorship

Title of Paper	Mortality and cause of death in patients with ANCA-associated vasculitis and PAN in Australia: a population-based study
Publication Status	Published
Publication Details	Tieu J, Lester S, Raymond W, Keen HI, Hill CL, Nossent J. Mortality and cause of death in patients with ANCA-associated vasculitis and PAN in Australia: a population-based study. Rheumatology (Oxford). 2021 Jun 12:keab469. doi: 10.1093/rheumatology/keab469. Epub ahead of print. PMID: 34117869.

Principal author

Candidate name	Joanna Tieu
Overall percentage	75%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signature Date 08/11/2021

Co-author contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Susan Lester
Contribution	Contributed to study design and analysis, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 09/12/2021

Name of Co-Author	Warren Raymond
Contribution	Contributed to data acquisition, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 08/11/2021

Name of Co-Author	Helen Keen
Contribution	Contributed to data acquisition, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 09/11/2021

Name of Co-Author	Catherine Hill
Contribution	Contributed to study design and analysis, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 07/12/2021

Name of Co-Author	Johannes Nossent
Contribution	Contributed to data acquisition, study design, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 08/11/2021

Original article

Mortality and cause of death in patients with ANCA-associated vasculitis and polyarteritis nodosa in Australia—a population-based study

Joanna Tieu [1,2,3], Susan Lester[1,2], Warren Raymond[4], Helen I Keen[4,5], Catherine L Hill[1,2,6] and Johannes Nossent [4,7]

Abstract

Objectives. We compared survival and causes of death in Western Australian (WA) ANCA-associated vasculitis (AAV) and PAN patients with controls and the WA population.

Methods. In this data linkage study, we identified patients with incident AAV/PAN and age, sex and temporally matched controls 1980–2014 from the WA Rheumatic Disease Epidemiological Registry. Survival analyses and time-varying analyses were performed.

Results. Six hundred and fourteen patients with incident AAV/PAN were compared with 6672 controls; 229 AAV/PAN patients died over 5277 person-years of follow-up and 1009 controls died over 73835 person-years. Survival was reduced in patients with AAV/PAN compared with matched controls [hazard ratio (HR) 3.5 (95% CI: 3.1, 4.1)], and matched WA population rates [standardized mortality ratio 3.3 (95% CI: 2.9, 3.8)]. Greatest excess mortality in AAV/PAN patients was observed in the first year after diagnosis and remained higher than controls throughout follow-up. Greater excess mortality was observed in patients >60 years at diagnosis. In cause-specific analyses, mortality HR for vasculitis, infection and non-infective respiratory disease were greatest early after diagnosis and remained persistently elevated. The HRs for malignancy and cerebrovascular disease related deaths increased during follow-up, and were constant for ischaemic heart disease related deaths.

Conclusion. Mortality was increased in AAV/PAN patients compared with controls, with patients older at diagnosis at greater risk. These findings provide mortality risk for AAV/PAN in an Australian population, highlighting key contributors to mortality at different time periods over follow-up and potential areas of focus for reducing mortality.

Key words: ANCA-associated vasculitis, PAN, vasculitis, mortality, cause of death

Rheumatology key messages

- Excess mortality is highest in Australian patients with ANCA-associated vasculitis (AAV) and polyarteritis nodosa (PAN) early after diagnosis.
- Patients with AAV/PAN over 60 years of age at diagnosis had a higher risk of mortality.
- Distinct time-varying patterns for specific causes of death were identified in patients with AAV/PAN compared with matched controls.

Introduction

Survival in ANCA-associated vasculitis (AAV) and PAN patients has improved, but despite significant advances in diagnosis and treatment and supportive care, mortality remains elevated [1–6]. Whilst these vasculitides are organ- and life-threatening, death is often multifactorial, from disease related sequelae, treatment related complications and/or comorbid conditions. Improving our understanding of conditions attributed to death in AAV/PAN patients may assist in identifying strategies for further reducing mortality.

[1]Faculty of Health and Medical Sciences, University of Adelaide, [2]Rheumatology Unit, The Queen Elizabeth Hospital, [3]Rheumatology Unit, Lyell McEwin Hospital, Adelaide, [4]School of Medicine, University of Western Australia, [5]Rheumatology Department, Fiona Stanley Hospital, Perth, [6]Rheumatology Unit, Royal Adelaide Hospital, Adelaide and [7]Rheumatology Department, Sir Charles Gairdner Hospital, Perth, Australia

Submitted 28 February 2021; accepted 24 May 2021

Correspondence to: Joanna Tieu, Rheumatology Unit, The Queen Elizabeth Hospital, 38 Woodville Road, Woodville South, 5011, Australia. E-mail: joanna.tieu@adelaide.edu.au

CLINICAL SCIENCE

Long-term follow-up of randomized controlled trials (RCTs) and population-based studies has improved the understanding of mortality in AAV patients in Europe and North America [1, 2, 4, 7–9]. Death in AAV has been attributed to active vasculitis [4, 8], cardiovascular disease [1, 9], infection [1, 4, 8], malignancy [1, 8] and renal disease [4, 10].

Although previously considered a single disease entity, the distinction between PAN and AAV subtype microscopic polyangiitis (MPA) was suggested based on histological differences described from 1923, evolving to be recognized as distinct disease groups in updated nomenclature for vasculitis [11–13]. AAV and PAN have often been studied together due to phenotypic similarities [5, 14] and shared international classification of disease (ICD) codes [15, 16]. Similarly to AAV, deaths of patients with PAN are commonly attributed to active vasculitis, infection and malignancy [5].

In this study, we sought to evaluate the risk of mortality and examine the causes of death (underlying and contributory) in Australian patients with AAV/PAN.

Methods

Data source

Data for patients with AAV/PAN and controls were sourced from the Western Australian (WA) Rheumatic Disease Epidemiological Registry (WARDER), which contains population-level, linked health data for all patients requiring public or private hospital-level care for rheumatic disease conditions in Western Australia. The WARDER contains records from the Hospital Morbidity Data Collection (HMDC; 1980–2015) and Emergency Department Data Collection (EDDC; 2002–2015), WA Cancer (1982–2015), and WA Death Registers (1980–2015), which contain routinely collected data for all hospital admissions, emergency department visits, cancer development and death events throughout WA. These datasets are linked through a combination of probabilistic matching via the WA Data Linkage System. The high linkage accuracy (99.7%) allows longitudinal follow-up for individuals across administrative health datasets [17].

Extraction of all available data resulted in a dataset with longitudinal health data on demographics, principal and up to 21 secondary diagnoses, and principal and up to 10 secondary procedures, length of stay, ED discharge codes, and a complete death record for each study participant. Death registry data included date of death and cause of death (COD); this included the assigned underlying COD from 1982, both underlying and contributory COD were available from 1997 onwards. ICD codes were used for diagnoses in HMDC and COD in the WA Death registry. ICD-9 was used until June 1999, when ICD-10 was adopted.

Cohort definitions

Patients were classified as having AAV/PAN using ICD-9 or ICD-10 codes from hospitalization or death diagnosis fields for AAV subtypes [granulomatosis with polyangiitis (GPA), MPA, eosinophilic granulomatosis with polyangiitis (EGPA)], and PAN or equivalent historic nomenclature (Supplementary Table S1, available at *Rheumatology* online). Subgrouping of AAV/PAN patients used ICD code structures GPA/EGPA and MPA/PAN.

The date of first hospitalization or death registration listing ICD-9 or ICD-10 diagnosis code for AAV/PAN was taken as the date of diagnosis. Patients were classified as having incident AAV/PAN if a prior hospitalization was identified without AAV/PAN, or if born after January 1980.

A control cohort of 10 individuals for each AAV/PAN patient were identified from WADLS and were age, sex and temporally matched at AAV/PAN patient diagnosis date.

Outcome

World Health Organization guidelines allow COD listed by clinicians on death certificates to be classified as underlying causes and contributory causes. Underlying (or primary) COD refers to the 'disease or injury which initiated the train of morbid events leading directly to death' or 'circumstances of the accident or violence which produced the fatal injury' [18]. Contributory or associated COD is a condition deemed significant to the person's death by the medical practitioner completing the death certificate, but not considered the underlying cause. This includes significant pre-existing or comorbid conditions deemed contributory to death. Multiple COD refers to an approach including underlying and contributory COD. Death often involves multiple conditions that are each potentially fatal; using multiple COD may provide better understanding of the joint role of diseases and comorbidities in mortality.

Deaths and COD were ascertained from linkage to the WA Death Registry. Specific COD [vasculitis, ischaemic heart disease (IHD), acute and chronic renal disease, malignancy, ischaemic or haemorrhagic stroke, infection and non-infective respiratory disease], both underlying and contributory, were examined. ICD codes used for specific COD are listed in Supplementary Table S2, available at *Rheumatology* online.

Statistical analysis

Survival analyses, including relative survival methods, were performed in Stata v16.1 (StataCorp LLC, College Station, TX, USA), supplemented by user-written ado files.

The analysis included incident AAV/PAN patients and controls diagnosed (or index date matched) between 1980 and 31 December 2013, who were <85 years old at baseline. The end of study date was 31 December 2014, defined by the last death linkage date and allowed for a minimum of 12 months of follow-up. Follow-up times were right censored at 85 years of age, or 20 years' follow-up.

Demographic data at diagnosis (AAV/PAN patients) and controls were summarized using mean and S.D. for normally distributed data, or median and interquartile range. Survival in AAV/PAN and controls was estimated using Kaplan–Meier curves. Mortality hazard ratios (HRs) were calculated using the stpm2 Stata ado program [19]. This method uses spline-based modelling of the baseline hazard rate and estimates HRs that are comparable to those estimated by a Cox proportional hazards model, allowing for investigation of continuous time-varying trends in the HR. Constant HRs for prespecified follow-up time intervals of interest were estimated from piecewise exponential survival models after splitting the survival-time record for each patient and control into the appropriate follow-up intervals.

Observed deaths were also compared with expected values calculated from age, sex and calendar year matched WA population mortality rates [20]. Expected deaths were estimated at yearly intervals using the Stata strs ado program [21] and the Ederer II method. Standardized mortality ratios (SMRs), the ratio of observed to expected deaths, were estimated with mid-P confidence intervals.

Subgroup analyses of AAV/PAN patients were performed using comparisons with WA population data to account for any demographic or temporal differences between subgroups, which may affect mortality rates. Demographic comparisons for subgroups of AAV/PAN patients were compared using Student's *t*-test and the Wilcoxon rank sum test as appropriate for data distribution. Excess mortality rate (EMR), the difference between the observed and expected mortality rates, provides a measure of additional mortality directly attributable to disease.

Subgroup comparisons within AAV/PAN patients were analysed by the EMR ratio using Poisson regression with a custom link function provided in the strs ado program. Subgroup analyses were performed for sex, age at diagnosis and AAV/PAN subgroups. A period analysis was performed to determine whether there was change in AAV/PAN mortality rates over time. AAV/PAN patients were subdivided into two groups: 'pre-1997' (AAV/PAN patients diagnosed between 1983 and 1996, with follow-up right censored at 31 December 1996), and 'post-1997' (patients diagnosed after 1 January 1997 and followed up until the end of study). For this analysis, maximum follow-up time was right censored at 15 years.

Each pre-specified COD was analysed where it was assigned as an underlying COD (1983–2014) and multiple COD (i.e. where assigned underlying and/or contributory COD). COD analyses were performed using Stata stpm2cr ado [22], enabling evaluation of both the cause-specific and sub-distribution hazard functions (competing risks analysis) from the same model, and analysis of time varying trends. The cause-specific hazard analysis treated death from any other cause as a censored observation, whereas a sub-distribution hazard analysis treated death from any other cause as a competing risk. Both analyses were performed for each underlying COD, with the exception of vasculitis, where only a cause-specific analysis was performed for combined underlying/contributory COD. As contributory COD data were available 1997–2014, delayed entry was used.

Ethics

Ethical approval for linked data extraction was provided by the WA Health HREC (WADOH HREC# 2016.24).

Results

A total of 614 incident AAV/PAN patients were identified between 1983 and 2013 (inclusive), with 6672 matched controls. At diagnosis or match date, AAV/PAN patients and controls were well matched for age, sex and calendar year diagnosed (Supplementary Table S3, available at *Rheumatology* online). In total, 229 deaths occurred in AAV/PAN patients over 5277.12 person-years of follow-up, compared with 1009 over 73834.80 person-years of follow-up in controls.

Increased mortality in AAV/PAN patients compared with controls and the WA population

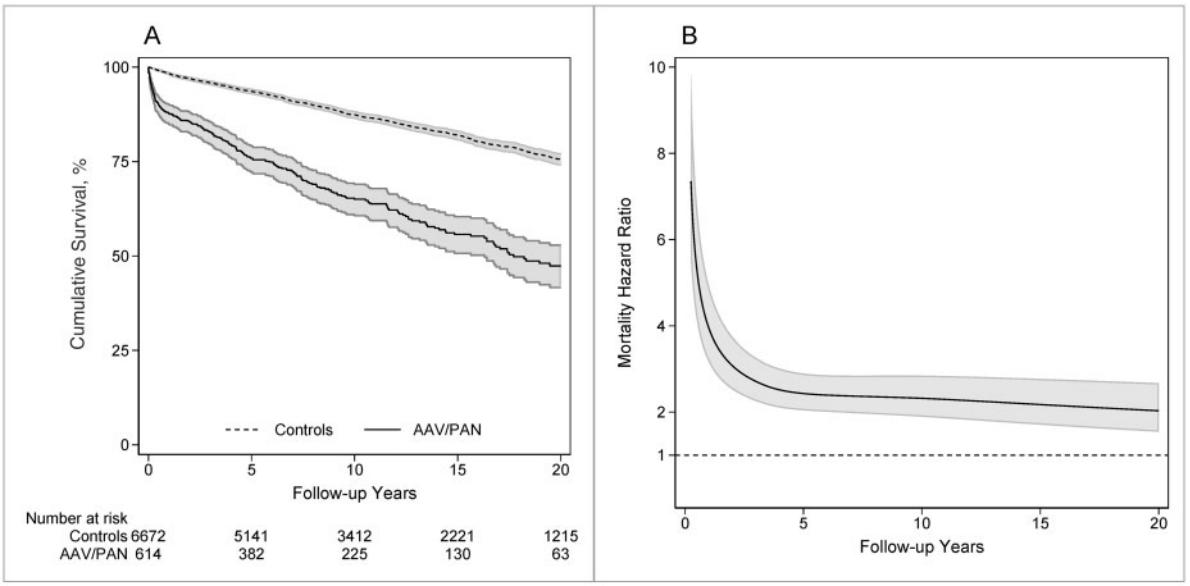
Survival in AAV/PAN patients was 88% (95% CI: 85, 90) at 1 year, 76% (95% CI: 72, 79) at 5 years, 65% (95% CI: 61, 69) at 10 years and 47% (95% CI: 42, 53) at 20 years after diagnosis (Fig. 1A). The overall mortality HR estimate for AAV/PAN *vs* controls was 3.5 (95% CI: 3.1, 4.1) (Table 1). Time varying HR analysis demonstrated that the highest risk of death was early after diagnosis, but the risk remained elevated throughout follow-up (Fig. 1B). This pattern is also observed in the discrete follow-up time interval mortality HRs for AAV/PAN patients compared with controls (Table 1).

Mortality for AAV/PAN patients and controls was also compared with those expected from matched WA population mortality rates. With 229 observed deaths and 68.4 expected, the overall SMR for incident AAV/PAN patients was 3.3 (95% CI: 2.9, 3.8) (Table 1). Similar to the comparisons against controls, discrete follow-up time SMR estimates for AAV/PAN patients compared with the WA population rates indicated that the highest risk of death was early after diagnosis (Table 1). Mortality in controls was equivalent to WA population mortality, SMR 0.97 (95% CI: 0.91, 1.03).

Mortality risk in subgroups of AAV/PAN patients

Pre-specified AAV/PAN subgroup analyses compared sex (female *vs* males), age ($<$60, $\geq$60 years), AAV/PAN subgroup (GPA/EGPA *vs* MPA/PAN) and time-period at diagnosis (post-1997 *vs* pre-1997). Deaths for each AAV/PAN subgroup were compared with expected deaths from matched WA population mortality rates to account for any demographic/temporal differences between subgroups, which may affect mortality rates. Mortality risks for each subgroup were first expressed

FIG. 1 Mortality in AAV/PAN compared with hospitalized controls



(**A**) Kaplan–Meier survival curves. (**B**) Time-varying mortality hazard ratio. Shaded areas represent 95% CIs. AAV: ANCA-associated vasculitis.

TABLE 1 Mortality during follow-up in AAV/PAN patients compared with both hospitalized controls and West Australian population mortality rates

Time since diagnosis (years)	AAV/PAN			Controls		HR[b]	SMR[c]
	Person years	Deaths	Expected deaths[a]	Person years	Deaths		
0–1	556.04	75	6.8	6585.37	111	8.0 (6.0, 10.7)	11.0 (8.7, 13.7)
1–5	1862.25	66	23.5	23549.11	292	2.9 (2.2, 3.7)	2.8 (2.2, 3.6)
5–10	1506.39	46	20.0	21257.49	290	2.2 (1.6, 3.1)	2.3 (1.7, 3.0)
10–20	1352.45	42	18.1	22442.82	316	2.2 (1.6, 3.0)	2.3 (1.7, 3.1)
All	5277.13	229	68.4	73834.79	1009	3.5 (3.1, 4.1)	3.3 (2.9, 3.8)

[a]Expected deaths in AAV/PAN patients calculated from age, sex, calendar year matched Western Australian population mortality rates. [b]Mortality HR in AAV/PAN patients compared with controls. [c]SMR for observed and expected deaths in AAV/PAN patients compared with Western Australian population mortality rates. AAV: ANCA-associated vasculitis; HR: hazard ratio; SMR: standardized mortality ratio.

as the EMR, the difference between observed and expected mortality rates. Excess mortality for each subgroup analysis were compared using the EMR ratio (Table 2).

No difference in EMR was observed by sex. Excess mortality was, on average, almost 4-fold higher in patients aged 60 and over at diagnosis compared with patients under 60 years at diagnosis [EMR ratio 3.9 (95% CI: 2.6, 5.7)]. This effect was highest in the first year after diagnosis ($P = 0.038$), but EMR remained more than double in older patients throughout the remainder of follow-up [EMR ratio 2.6 (95% CI: 1.6, 4.4)].

AAV/PAN patients were subdivided based on ICD code structures (Supplementary Table S1, available at *Rheumatology* online): GPA/EGPA (61%) and MPA/PAN (39%). Patients with MPA/PAN were older than GPA/EGPA patients (mean age: 59 *vs* 55 years, $P = 0.01$, *t*-test) with an earlier temporal distribution of diagnosis year (median: 1998 *vs* 2003, $P < 0.001$, Wilcoxon rank sum test). Excess mortality was lower in GPA/EGPA patients compared with MPA/PAN patients in the first year after diagnosis [EMR ratio 0.45 (95% CI: 0.27, 0.76), Table 2]. However, there was no difference between these subgroups for the remainder of follow-up.

A period analysis was employed to evaluate whether AAV/PAN related mortality had improved. Excess mortality was lower in AAV/PAN patients diagnosed post-1997 compared with those diagnosed pre-1997 [EMR ratio 0.64 (95% CI: 0.43, 0.95)], indicating a reduction in excess mortality of ~40% for patients more recently

Table 2 AAV/PAN subgroup analyses

Subgroup comparison	Follow-up, years	EMR ratio (95% CI)
Female *vs* males	0–20	0.86 (0.60, 1.25)
	0–1	0.93 (0.57, 1.55)
	1–20	0.79 (0.46, 1.35)
Baseline age ≥60 *vs* <60 years	0–20	3.9 (2.6, 5.7)
	0–1	6.5 (3.3, 12.6)
	1–20	2.6 (1.6, 4.4)
GPA/EGPA *vs* MPA/PAN	0–20	0.64 (0.45, 0.94)
	0–1	0.45 (0.27, 0.76)
	1-20	0.95 (0.55, 1.64)
Period analysis: post-1997 *vs* pre-1997	0–15	0.64 (0.43, 0.95)
	0–1	0.59 (0.35, 0.97)
	1–15	0.73 (0.38, 1.4)

Results were compared with Western Australian population mortality rates and expressed as EMR ratios for each follow-up interval. EGPA: eosinophilic granulomatosis with polyangiitis; EMR: excess mortality rate; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis.

diagnosed. The effect size did not vary between short- and long-term follow-up ($P = 0.59$). Excess mortality in AAV/PAN patients after 1997 was 102 (95% CI: 73, 142) per 1000 patient-years in the first year following diagnosis, and 20 (95% CI: 14, 29) per 1000 patients-years thereafter.

Cause specific mortality in AAV/PAN patients compared with controls

Vasculitis, infection, ischaemic heart disease, malignancy, non-infective respiratory disease, acute or chronic renal impairment and stroke as a COD were extracted for AAV/PAN patients and controls who died during the study period. Collectively, these represented the underlying COD in the majority of AAV/PAN patients (171/229, 75%) and controls (735/1009, 73%).

Both cause-specific (HR) and competing risk [sub-distribution HR (SHR)] analyses for each underlying COD of interest were performed for AAV/PAN patients compared with controls. Contributory COD data were available from 1997 onwards, and therefore delayed entry was used to analyse a subset of the data for combined underlying/contributory COD. The subset of deaths with both underlying and contributory COD consisted of 382 AAV/PAN patients with 164 deaths, and 5928 controls with 804 deaths. Cause-specific HRs for underlying and combined underlying/contributory COD were comparable (Table 3).

Vasculitis was the most frequent COD in AAV/PAN patients, listed as underlying COD in 58/229 deaths, or underlying/contributory COD in 71/164 deaths. No vasculitis-related deaths were observed in controls. The contribution of vasculitis (as underlying/contributory COD) to overall mortality in AAV/PAN was further analysed in a competing risks analysis. The cumulative mortality incidence decomposed into vasculitis-related and non-vasculitis mortality demonstrates the overall impact of vasculitis on AAV/PAN mortality (Fig. 2A). The vasculitis-related, cause-specific mortality hazard rate was highest early after diagnosis (Fig. 2B). The proportion of deaths in AAV/PAN patients attributed to vasculitis was highest at the start of follow-up but persisted over long-term follow-up (Fig. 2C).

In cause-specific, time-invariant survival analyses, the risk of death attributed to renal impairment, IHD, infection, malignancy, non-infective respiratory disease and stroke were greater in AAV/PAN patients than hospitalized controls (Table 3). This interpretation was similar for competing risks analysis of the underlying COD, although it no longer reached statistical significance for malignancy and stroke.

Time-varying analyses of underlying/contributory COD cause-specific HRs indicated different temporal patterns of mortality risk in AAV/PAN (Fig. 3). The mortality HRs for infection (Fig. 3A), non-infective respiratory diseases (Fig. 3B) and renal impairment (Fig. 3C) were greatest early after diagnosis and remained persistently elevated over longer-term follow-up. The HR for IHD related deaths was constant over time (Fig. 3D), whereas the HRs for stroke (Fig. 3E) and malignancy related deaths (Fig. 3F) increased over long-term follow-up.

Discussion

This is the first study to determine mortality risk in Australian AAV/PAN patients. Excess mortality was demonstrated in AAV/PAN patients when compared with age- and sex-matched controls and matched WA population data, and this has reduced in patients more recently diagnosed. We additionally identified distinct temporal patterns in the contribution of vasculitis and comorbid conditions to mortality over long-term follow-up.

As expected, all-cause mortality was increased in incident AAV/PAN patients [SMR 3.3 (95% CI: 2.9, 3.8)], although with an estimate that is somewhat higher than reported in a 2017 meta-analysis [SMR 2.7 (95% CI:

Table 3 Cause specific mortality in AAV/PAN patients and controls

Cause of death	Underlying cause of death				Underlying and contributory cause of death[a]		
	Deaths, *n*		HR (95% CI)		Deaths, *n*		HR (95% CI)
	AAV/PAN	Controls	Cause-specific (HR)[b]	Competing risks (SHR)[c]	AAV/PAN	Controls	Cause-specific (HR)[b]
Vasculitis	58	0	—	—	71	0	—
Renal impairment[d]	8	<5[e]	37.8 (10.0, 142.7)	25.3 (6.5, 97.8)	37	37	13.1 (8.3, 20.8)
Ischaemic heart disease	30	188	2.2 (1.5, 3.3)	1.8 (1.2, 2.8)	38	185	2.7 (1.9, 3.9)
Infection	11	31	5.0 (2.5, 10.0)	4.2 (2.0, 9.2)	58	142	5.4 (4.0, 7.4)
Malignancy	42	402	1.5 (1.1, 2.0)	1.1 (0.80, 1.6)	43	359	1.6 (1.1, 2.2)
Respiratory disease	11	38	4.0 (2.0, 7.8)	3.2 (1.4, 7.0)	41	139	3.9 (2.7, 5.5)
Stroke	11	73	2.1 (1.1, 4.0)	1.9 (0.9, 4.0)	17	95	2.4 (1.4, 4.0)

[a]Data for both underlying and contributory COD available from 1997 to 2014. [b]Cause-specific HR, time invariant. [c]SHR: time invariant. Competing risk = any other underlying cause of death. [d]Renal impairment: acute kidney injury and chronic kidney disease. [e]In accordance with Western Australia data linkage policy, to minimize the risk of reidentification, cells with fewer than five individuals are reported as '<5'. AAV: ANCA-associated vasculitis; COD: cause of death; HR: hazard ratio; SHR: subdistribution hazard ratio.

2.3, 3.2)] [3]. However, average mortality ratios are difficult to interpret and compare when they are not constant over time. Higher mortality risk in the first year following diagnosis has been recognized in AAV [2, 4, 5, 8] and PAN [23]. We similarly found that mortality risk in AAV/PAN patients was highest in the first year following diagnosis [SMR 11.0 (95% CI: 8.7, 13.7)], but relatively stable, and comparable to previous studies [thereafter, SMR 2.5 (95% CI: 2.1, 2.9)]. Notably, AAV/PAN patients in this study were identified based on hospitalizations, which may skew towards patients with more severe disease and higher mortality.

In keeping with other studies, we observed a reduction in excess deaths for patients more recently diagnosed [2, 3, 9, 24, 25]. The improvement is likely multifactorial and due to combined effects of ongoing improvements in diagnosis, therapeutic and supportive care. Early mortality was increased in patients with MPA/PAN compared with those with a diagnosis of GPA/EGPA, which is consistent with known phenotypic and mortality risk differences for MPA compared with GPA. Limited available information for PAN suggests an increased mortality risk compared with the general population [14], though it is unclear how this compares with AAV related mortality.

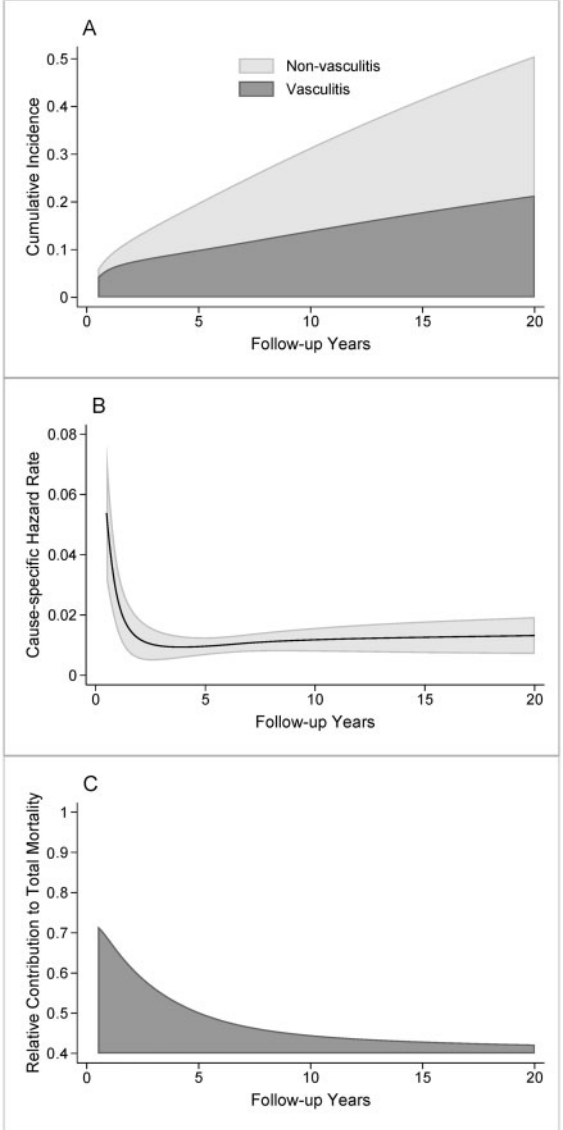
Despite significant advances in management, long-term studies have highlighted the relapsing nature of disease, often necessitating chronic immunosuppressive therapy, and the multimorbidity that these patients experience. Multiple COD analyses are often employed as assigning a single underlying COD in people who die with multiple life-limiting chronic conditions can be relatively arbitrary and the mortality burden of important conditions may be under-estimated [26, 27]. We analysed each COD of interest as both underlying and as a combination of underlying/contributory COD. We were able to do this because we had comparative data from matched controls, whose mortality risk was comparable to that of the WA population. Whilst we observed no substantive differences in interpretation, greater numbers for combined underlying/contributory COD contributed to a more robust analysis.

Vasculitis was the most important COD in AAV/PAN, particularly in the first year. In previous studies, although the risk of specific diseases contributing to death has been increased, they have accounted for relatively few deaths [1, 9]. Our observations support the findings of previous studies highlighting the impact of infection, IHD and malignancy as COD in AAV/PAN [1, 4, 8, 25]. In contrast to other population-based studies where underlying COD alone was evaluated, these comorbidities contributed to proportionally more deaths when considering underlying/contributory COD, further emphasizing the burden of these comorbid conditions in AAV/PAN patients.

The patterns observed for each condition's contribution to mortality was of interest. Infections are consistently identified as contributors to early mortality [1, 8]. This early peak followed by a persistent contribution to mortality coincides with the pattern observed in vasculitis, respiratory and renal related deaths, reiterating the difficult balance between treating severe disease and complications from treatment. Recent trials support the use of reduced dose glucocorticoids [28], which reduced infections, and the use of novel agents targeting complement pathways instead of oral glucocorticoids [29].

Previous studies postulating that later deaths may relate to vascular comorbidities and malignancy [4] are

Fig. 2 Vasculitis-related mortality in AAV/PAN over time



(**A**) Cumulative mortality incidence decomposed into vasculitis-related and non-vasculitis deaths. (**B**) Cause-specific hazard rate of vasculitis related deaths (shaded area represent 95% CI). (**C**) Relative contribution (proportion) of vasculitis-related deaths to total mortality.

supported in our study, where the risk of death related to stroke and malignancy increased late in the follow-up period. Notably, a persistently increased risk was observed for IHD, consistent with the pattern observed in AAV patients' long-term follow-up from RCTs and analyses of administrative data [1, 8].

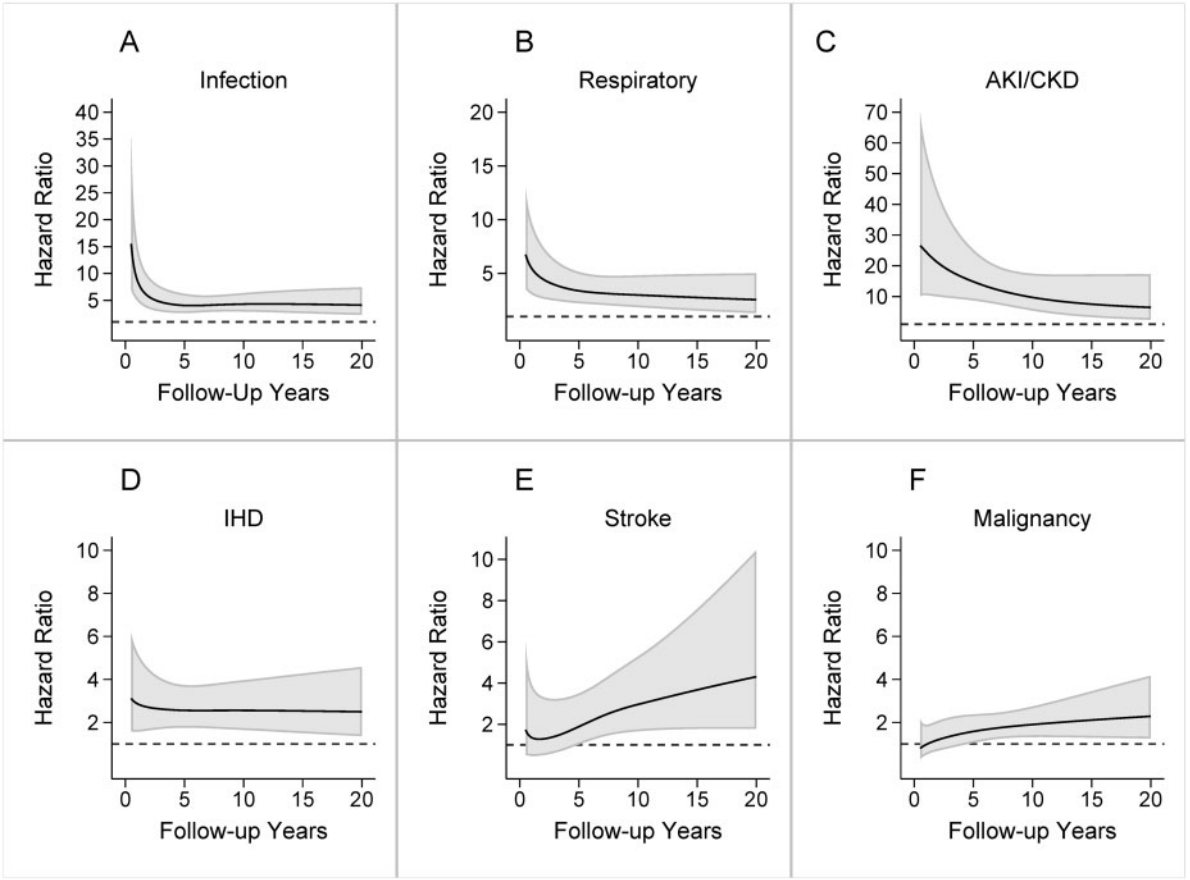
We also observed an increased risk of death related to non-infectious respiratory disease, highlighting the impact of respiratory manifestations and comorbid disease [30]. In this study we did not differentiate between respiratory manifestations and comorbidities. Few other studies have examined respiratory death in cause-specific mortality analyses in AAV/PAN. Where previously examined in AAV patients, the impact has been small [1, 8]. This discrepancy may relate to respiratory manifestations or comorbid respiratory disease being an under-recognized component of the multi-morbidity leading to death. Respiratory diseases are often considered contributory rather than an underlying COD. Thus, the mortality burden of respiratory disease may be under-represented in previous studies. A more complex interaction may also occur between comorbid chronic respiratory conditions and AAV/PAN, and treatment decisions.

Although respiratory manifestations can be wide ranging, in AAV patients they typically include tracheobronchial disease, nodules, pulmonary haemorrhage, interstitial lung disease (ILD), and asthma [31]. The burden of these respiratory manifestations presents at different time periods in long-term follow-up, with different management approaches for each. Variation also occurs between disease subtypes; for example, patients with MPO-positive AAV are more likely to experience pulmonary haemorrhage, increasing short-term mortality risk. As patients in this study were identified based on hospitalizations, deaths from pulmonary haemorrhage may explain some of the early higher risk of non-infective respiratory disease related death observed in our study. Notably, there is also increasing interest in the impact and clinical course of ILD in AAV, which can be independent of other vasculitis-related disease activity [32]. ILD itself is associated with increased mortality [33]; prior studies in AAV patients have noted ILD-related death, albeit in small numbers of patients [8, 32, 34]. Further evidence on the impact of comorbid respiratory disease and respiratory manifestations on patient outcomes is required.

There are strengths and limitations to this study. Linkage of public and private health system hospitalization data enabled identification of AAV/PAN patients across both systems. However, patients who were managed solely as outpatients would not have been identified. Therefore, there may have been a selection bias for patients with more severe disease. Furthermore, the diagnosis date were taken as the first hospitalization event with an AAV/PAN code. The use of diagnoses from hospitalization records for patient ascertainment has, however, allowed for inclusion of early deaths, which are less likely to be included in RCTs or observational cohorts for such analyses.

Diagnoses were clinician based rather than relying on classification criteria, which perhaps makes these results more generalizable to the patient population. Diagnoses were assigned ICD codes from clinician completed discharge summaries and case notes by trained medical coders, with regular auditing. In a prior study of AAV patients derived from the same region and identified using hospitalization ICD codes, 67/74 (91%) patients identified could be classified as AAV using European Medicines Agency classification algorithm, supporting

Fig. 3 Time-varying cause-specific hazard ratios for AAV/PAN patients compared with controls



Causes of death were either underlying or contributing from 1997 onwards. (**A**) Infection related deaths. (**B**) Respiratory disease related deaths. (**C**) Acute kidney injury/chronic kidney disease (AKI/CKD) related deaths. (**D**) Ischaemic heart disease (IHD) related deaths. (**E**) Stroke related deaths. (**F**) Malignancy related deaths. The shaded area represents 95% CI, and the dotted line represents a hazard ratio of 1.

the reliability of the ICD based diagnoses [35]. The same coding standards and auditing processes were used for the data in this study.

Despite the advantages of using linked de-identified data, AAV/PAN identification relied on ICD codes, which reflect historical classification groupings. Detailed clinical and laboratory findings including clinical manifestations and ANCA were not available. Therefore, it was not possible to compare subgroups based on more contemporary understandings of disease subtypes.

The large cohort, the use of both underlying and contributory COD and time-varying analyses over a long duration of follow-up are strengths of this study that help to improve our understanding of the burden of disease for AAV/PAN patients.

In conclusion, this data linkage study of Australian patients with AAV/PAN has shown that although survival has improved during the time period of this study, significant excess mortality remains. These data highlight the need to consider the time varying risk of mortality from primary disease and comorbidities. As we continue to advance therapeutics in controlling disease activity, ongoing research is also required to consider preventable COD in further reducing mortality in patients with AAV/PAN.

Acknowledgements

The authors wish to thank the staff at the Western Australian Data Linkage Branch and Hospital Morbidity Data Collection. The authors also wish to thank the State and Territory Registries of Births, Deaths and Marriages, the State and Territory Coroners, and the National Coronial Information System for enabling COD URF data to be used for this publication. W.D.R. is the recipient of the John Donald Stewart Scholarship from the Arthritis Foundation of Western Australia. J.T. is supported by a National Health and Medical Research Council postgraduate scholarship.

Funding: The establishment of WARDER was supported by an unrestricted grant from the Arthritis Foundation of Western Australia to J.C.N.

Disclosure statement: J.T. and C.L.H. report research grant funding from Vifor Pharma, outside of the submitted work. H.K. reports grants from Arthritis Australia during the conduct of the study; other funding from Abbvie, Sun Pharma, Emerald Pharma and Sanofi for clinical trials, personal fees and non-financial support from Roche, personal fees from Abbvie and personal fees from Novartis, outside the submitted work. The other authors have declared no conflicts of interest.

Data availability statement

The data underlying this article were provided by the Western Australia Data Linkage System. The data cannot be shared publicly to minimize reidentification of individuals. Data will be shared on request to the corresponding author with permission of the Western Australia Data Linkage System.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Wallace ZS, Fu X, Harkness T *et al.* All-cause and cause-specific mortality in ANCA-associated vasculitis: overall and according to ANCA type. Rheumatology (Oxford) 2020;59:2308–15.

2 Wallace ZS, Lu N, Unizony S *et al.* Improved survival in granulomatosis with polyangiitis: a general population-based study. Semin Arthritis Rheum 2016;45: 483–9.

3 Tan JA, Dehghan N, Chen W *et al.* Mortality in ANCA-associated vasculitis: a meta-analysis of observational studies. Ann Rheum Dis 2017;76:1566–74.

4 Luqmani R, Suppiah R, Edwards CJ *et al.* Mortality in Wegener's granulomatosis: a bimodal pattern. Rheumatology (Oxford) 2011;50:697–702.

5 Bourgarit A, Toumelin PL, Pagnoux C *et al.* Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: a retrospective analysis of causes and factors predictive of mortality based on 595 patients. Medicine (Baltimore) 2005;84:323–30.

6 Heijl C, Mohammad AJ, Westman K *et al.* Long-term patient survival in a Swedish population-based cohort of patients with ANCA-associated vasculitis. RMD Open 2017;3:e000435.

7 Mohammad AJ, Jacobsson LTH, Westman KWA *et al.* Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. Rheumatology (Oxford) 2009;48:1560–5.

8 Flossmann O, Berden A, de Groot K *et al.*; European Vasculitis Study Group. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 2011;70: 488–94.

9 Tan JA, Choi HK, Xie H *et al.* All-cause and cause-specific mortality in patients with granulomatosis with polyangiitis: a population-based study. Arthritis Care Res (Hoboken) 2019;71:155–63.

10 Wallace ZS, Fu X, Harkness T *et al.* All-cause and cause-specific mortality in ANCA-associated vasculitis: overall and according to ANCA type. Rheumatology 2020;59:2308–15.

11 Jennette JC, Falk RJ, Andrassy K *et al.* Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994;37:187–92.

12 Davson J, Ball J, Platt R. The kidney in periarteritis nodosa. Q J Med 1948;17:175–202.

13 Wohlwill F. Über die nur mikroskopisch erkennbare Form der Periarteriitis nodosa. Virchows Arch Pathol Anat Physiol Klin Med 1923;246: 377–411.

14 Gayraud M, Guillevin L, Le Toumelin P *et al.*; French Vasculitis Study Group. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum 2001;44: 666–75.

15 Sreih AG, Annapureddy N, Springer J *et al.*; Vasculitis Patient-Powered Research Network. Development and validation of case-finding algorithms for the identification of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis in large healthcare administrative databases. Pharmacoepidemiol Drug Saf 2016;25: 1368–74.

16 Mahr A, Guillevin L, Poissonnet M *et al.* Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate. Arthritis Rheum 2004;51:92–9.

17 Lynch C, Holman CD, Moorin RE. Use of Western Australian linked hospital morbidity and mortality data to explore theories of compression, expansion and dynamic equilibrium. Aust Health Rev 2007;31:571–81.

18 World Health Organization. International Statistical Classification of Diseases and Related Health Problems, 10th revision, edition 2010, Volume 2, Instruction Manual. Geneva: World Health Organization, 2010.

19 Royston P, Lambert PC. Flexible parametric survival analysis using Stata: beyond the Cox model. College Station, TX: StataPress, 2011.

20 Australian Bureau of Statistics. Deaths, Year of occurrence, Age at death, Age-specific death rates, Sex, States, Territories and Australia. http://stat.data.abs.gov.au/Index.aspx?DataSetCode=DEATHS_AGESPECIFIC_OCCURENCEYEAR# (March 2020, date last accessed).

21 Dickman PW, Coviello E. Estimating and modeling relative survival. Stata J 2015;15:186–215.

22 Mozumder SI, Rutherford MJ, Lambert PC. stpm2cr: a flexible parametric competing risks model using a direct likelihood approach for the cause-specific cumulative incidence function. Stata J 2017;17:462–89.

23 Pagnoux C, Seror R, Henegar C *et al.*; French Vasculitis Study Group. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. Arthritis Rheum 2010;62:616–26.

24 Holle JU, Gross WL, Latza U *et al.* Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades. Arthritis Rheum 2011;63:257–66.

25 Takala JH, Kautiainen H, Leirisalo-Repo M. Survival of patients with Wegener's granulomatosis diagnosed in Finland in 1981-2000. Scand J Rheumatol 2010;39:71–6.

26 Batty GD, Gale CR, Kivimäki M *et al.* Assessment of relative utility of underlying vs contributory causes of death. JAMA Netw Open 2019;2:e198024.

27 Redelings MD, Sorvillo F, Simon P. A comparison of underlying cause and multiple causes of death: US vital statistics, 2000-2001. Epidemiology 2006;17:100–3.

28 Walsh M, Merkel PA, Peh C-A *et al.* Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med 2020;382:622–31.

29 Jayne DRW, Merkel PA, Schall TJ *et al.* Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med 2021;384:599–609.

30 Mohammad AJ, Mortensen KH, Babar J *et al.* Pulmonary involvement in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: the influence of ANCA subtype. J Rheumatol 2017;44:1458–67.

31 Sacoto G, Boukhlal S, Specks U *et al.* Lung involvement in ANCA-associated vasculitis. Presse Med 2020;49: 104039.

32 Hervier B, Pagnoux C, Agard C *et al.*; French Vasculitis Study Group. Pulmonary fibrosis associated with ANCA-positive vasculitides. Retrospective study of 12 cases and review of the literature. Ann Rheum Dis 2009;68:404–7.

33 Araki T, Putman RK, Hatabu H *et al.* Development and progression of interstitial lung abnormalities in the Framingham heart study. Am J Respir Crit Care Med 2016;194:1514–22.

34 Schirmer JH, Wright MN, Herrmann K *et al.* Myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA)-positive granulomatosis with polyangiitis (Wegener's) is a clinically distinct subset of ANCA-associated vasculitis: a retrospective analysis of 315 patients from a German vasculitis referral center. Arthritis Rheumatol 2016;68:2953–63.

35 Paramalingam S, R W, Sharma C *et al.* Disease flares, damage accrual and survival in ANCA-associated vasculitis in Western Australia. Int J Clin Rheumatol 2019;14: 31–6.

Supplementary File

Supplementary Table S1: International Classification of Disease codes used for identifying patients with AAV/PAN

	ICD-9	**ICD-10**	
	1980 – 1999	*2000 – 2005*	*2006 - 2014*
AAV			
GPA	446.0	M31.3	M31.3
EGPA		M30.1	M30.1
MPA	446.4	M30.0	M31.7
PAN			M30.0

AAV: ANCA-associated vasculitis, GPA: granulomatosis with polyangiitis, EGPA: eosinophilic granulomatosis with polyangiitis, MPA: microscopic polyangiitis, PAN: polyarteritis nodosa

The Hospital Mortality Database Collection (HMDC) used ICD-9 until 1999, when ICD-10 was used for diagnosis classifications. The 5th edition was adopted in 2007.

GPA and EGPA shared a diagnosis code in ICD-9 and had separate diagnosis codes in ICD-10.

PAN and MPA shared a diagnosis code until the 5th edition ICD-10 update (adopted in HMDC in 2007) when separate codes were used.

Supplementary Table S2: International Classification of Disease codes used for cause of death

	ICD-9	ICD-10
Vasculitis	446.5, 446.0, 446.4	I77.6, M31.3, M31.7, M30.0, M30.8, M30.1, M30.9
Ischaemic heart disease	410 - 414	I21.0-I21.9, I22.0-I22.9, I23.0-I23.8, I24.0-I24.9, I25.0-I25.9
Renal impairment (acute and chronic)	584.9, 585.0 – 585.9	N17.0-N17.9, N18.0- N18.9
Stroke	430-438	I60-I69
Non-infective respiratory	467 – 511 (excluding infection codes: 480, 481, 482, 483, 484, 485, 486, 487, 487, 511.1), 786.3	J23 – J99 (excluding infection codes: J36, J39.0, J39.1, J41.1, J41.8, J44.0, J85.1-85.3, J86.0, J 86.9), R04.2, R04.8, R04.9
Malignancy	140 – 239	C0.0 – C97.9, D45 – D48
Infection	001–136, 320–326, 370.1, 370.3–370.5, 372.0-372.1, 373.4–373.6, 377.3, 380.1, 382, 383.0–383.2, 420–422, 447.7, 460-466, 480-487, 511.1, 513, 540.1, 567.0-567.2, 573.1-573.2, 577.0-577.1, 581.8, 583.8, 590, 595.4–595.8, 597, 598.0, 601.2, 601.4, 603.1, 604, 614.2–614.4, 616.0-616.1, 616.3-616.5, 681–686, 711, 727.0, 727.3, 728.0, 730, 785.4, 790.7-790.8	A00-A99, B00-B99, G00.0-G03.2, G04.1-G05.2, G06.0-G07, H03.0-H03.1, H06.0, H10.0, H13.0-H13.1, H60.0-H60.3, H62.0-H62.3, H66.0-H66.4, H67.0-67.1, H70.0 H73.0, H75.0, H94.0, I00-I01, I30.9, I32.0-32.1, I33.0, I40.0, J00-J22, J36, J39.0, J39.1, J41.1, J41.8, J44.0, J85.1-85.3, J86.0, J86.9, K04.6-K04.7, K11.3, K23.0/K23.1, K35.1, K57.0, K57.2, K57.4, K57.8, K67.0-67.3, K67.8, K75.0, K91.42, K93.0, K93.1, L00.0-03.9, L05.0, L08.0-L08.9, M00.0-01.9, M46.2-46.3, M49.0-49.2, M60.0, M63.0-63.2, M65.0-65.1, M71.0-71.1 M72.6, M73.0-73.1, M86.0-86.2, M86.5, N30.0, N30.9, N33.0, N34.0, N39.0, N45.0-45.9, N70.0-N71.0, N73.0-74.8, N75.1, R57.2, R65.0, R65.1, R75, T81.4, T82.6-T82.7,T83.5-T83.6,T85.7

Codes were chosen from International Classifications of Disease codes adapted for Australian use (Australian Modification, AM). Previously published ICD code groups were used where applicable for ischaemic heart disease [1], cerebrovascular disease [2], infection and malignancy [3]. All codes were reviewed and amended as required for Australian modification versions [4, 5].

Supplementary Table S3: Demographic details

	Controls	AAV/PAN
N	6672	614
Females (%)	2847 (43%)	276 (45%)
Age (years)[a]	57 ± 17	57 ± 17
Year of diagnosis/match[b]	2000 [1993, 2007]	2001 [1994, 2007]
Deaths	1009	229
Maximum follow-up (years)	20	20
Person-years at risk	73834.80	5277.12

a: age at diagnosis (AAV/PAN patients) or match date, mean ± standard deviation

b: median [interquartile range]

References (supplementary file)

1. Joshy, G., et al., *Categorising major cardiovascular disease hospitalisations from routinely collected data.* Public Health Research & Practice.
2. McCormick, N., et al., *Validity of Diagnostic Codes for Acute Stroke in Administrative Databases: A Systematic Review.* PLOS ONE, 2015. **10**(8): p. e0135834.
3. Rassekh, S.R., et al., *Reclassification of ICD-9 Codes into Meaningful Categories for Oncology Survivorship Research.* J Cancer Epidemiol, 2010. **2010**: p. 569517.
4. *Australian Version of The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)*. Vol. 1-3. National Coding Centre, Faculty of Health Sciences, University of Sydney.
5. *ICD-10-AM/ACHI/ACS Chronicle- First Edition to Eleventh Edition. Independent Hospital Pricing Authority.* 2019.

2.4 Manuscript: Cancer in anti-neutrophil cytoplasm antibody associated vasculitis and polyarteritis nodosa in Australia: a population-based study

Statement of Authorship

Title of Paper	Cancer in anti-neutrophil cytoplasm antibody associated vasculitis and polyarteritis nodosa in Australia: a population-based study
Publication Status	Accepted for publication
Publication Details	Tieu, J., S. Lester, W. Raymond, H. Keen, C. L. Hill and J. Nossent (2021). "Cancer in Anti-Neutrophil Cytoplasm Antibody-Associated Vasculitis and Polyarteritis Nodosa in Australia: A Population-Based Study." ACR Open Rheumatology.

Principal author

Candidate name	Joanna Tieu
Overall percentage	75%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signature Date 08/11/2021

Co-author contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Susan Lester
Contribution	Contributed to study design and analysis, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 09/12/2021

Name of Co-Author	Warren Raymond		
Contribution	Contributed to data acquisition, critical appraisal of draft manuscript and approval of manuscript for publication.		
Signature		Date	08/11/2021

Name of Co-Author	Helen Keen		
Contribution	Contributed to data acquisition, critical appraisal of draft manuscript and approval of manuscript for publication.		
Signature		Date	09/11/2021

Name of Co-Author	Catherine Hill		
Contribution	Contributed to study design and analysis, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.		
Signature		Date	07/12/2021

Name of Co-Author	Johannes Nossent		
Contribution	Contributed to data acquisition, study design, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.		
Signature		Date	08/11/2021

ACR Open Rheumatology
Vol. 0, No. 0, Month 2021, pp 1–8
DOI 10.1002/acr2.11378

American College of Rheumatology
Empowering Rheumatology Professionals

Cancer in Anti-Neutrophil Cytoplasm Antibody-Associated Vasculitis and Polyarteritis Nodosa in Australia: A Population-Based Study

Joanna Tieu,[1,2,3,4] Susan Lester,[1,2,3] Warren Raymond,[5] Helen Keen,[5,6] Catherine L. Hill,[1,2,3,7] and Johannes Nossent[5,8]

Objective. The study objective was to compare incident cancer rates among patients with anti-neutrophil cytoplasm antibody-associated vasculitis (AAV) and polyarteritis nodosa (PAN) in Western Australia (WA) with the general population and perform time-varying analyses to identify periods with greatest excess cancers.

Methods. Administrative health data from patients hospitalized with incident AAV/PAN from 1980 to 2014 were linked to the WA cancer registry, which holds compulsorily reported cancer data (excluding skin squamous cell and basal cell carcinomas). Incident cancer rates in patients with AAV/PAN were compared with age-, sex-, and calendar-year-matched WA population rates.

Results. Patients with AAV/PAN had higher overall rates of incident cancer compared with the matched population (standardized incidence ratio [SIR], 1.74; 95% confidence interval [CI], 1.42-2.10). In subgroup analyses, incident cancer rates in patients with granulomatosis with polyangiitis/eosinophilic granulomatosis with polyangiitis were approximately double the general population (SIR, 2.21; 95% CI, 1.73-2.78) but similar to the general population in patients with microscopic polyangiitis/PAN (SIR, 1.21; 95% CI, 0.85-1.68). Patients with AAV/PAN had higher rates of genitourinary, skin, hematological, and lung cancers. Excess rates of hematological and lung cancers peaked early after diagnosis, whereas excess skin and genitourinary cancer rates peaked at 5 and 10 years, respectively.

Conclusion. This study highlights the importance of long-term cancer surveillance in patients with AAV/PAN and defines time frames of excess risk for specific cancers, which may help inform guidance on cancer screening. Furthermore, it indicates the need for skin surveillance for melanoma in addition to nonmelanoma skin cancers in patients who have greater environmental ultraviolet exposure, such as in Australia.

INTRODUCTION

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a life- and organ-threatening systemic vasculitis encompassing the following three subtypes with overlapping features: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Early iterations of proposed classification criteria did not distinguish between the clinical presentations of the medium vessel vasculitis, polyarteritis nodosa (PAN), and MPA, which is reflected in International Classification of Diseases (ICD)

The establishment of WARDER was supported by an unrestricted grant from the Arthritis Foundation of Western Australia to Dr. Nossent. Mr. Raymond is the recipient of the John Donald Stewart Scholarship from the Arthritis Foundation of Western Australia. Ms. Tieu is supported by a National Health and Medical Research Council postgraduate scholarship.

[1]Joanna Tieu, MBBS, FRACP, Susan Lester, BSc, Catherine L. Hill, MBBS, FRACPS, MSc, MD: Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia; [2]Joanna Tieu, MBBS, FRACP, Susan Lester, BSc, Catherine L. Hill, MBBS, FRACP, MSc, MD: Rheumatology Research Group, Basil Hetzel Institute, Adelaide, Australia; [3]Joanna Tieu, MBBS, FRACP, Susan Lester BSc, Catherine L. Hill, MBBS, FRACP, MSc, MD: Rheumatology Unit, The Queen Elizabeth Hospital, Adelaide, Australia; [4]Joanna Tieu, MBBS, FRACP: Rheumatology Unit, Lyell McEwin Hospital, Adelaide, Australia; [5]Warren Raymond, BSc, Helen Keen, MBBS, FRACP, PhD, Johannes Nossent, MD, FRACP, PhD: Rheumatology Section, School of Medicine, University of Western Australia, Perth, Australia; [6]Helen Keen, MBBS, FRACP, PhD: Rheumatology Department, Fiona Stanley Hospital, Perth, Australia; [7]Catherine L. Hill, MBBS, FRACP, MSc, MD: Rheumatology Unit, Royal Adelaide Hospital, Adelaide, Australia; [8]Johannes Nossent, MD, FRACP, PhD: Rheumatology Department, Sir Charles Gairdner Hospital, Perth, Australia.

Dr. Tieu and Prof. Hill report research grant funding from Vifor Pharma outside of the submitted work. Outside the submitted work, Dr. Keen reports grants from Arthritis Australia during the conduct of the study; other funding from Abbvie, Sun Pharma, Emerald Pharma, and Sanofi for clinical trials; personal fees and nonfinancial support from Roche; personal fees from Abbvie; and personal fees from Novartis. No other disclosures relevant to this article were reported.

Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Facr2.11378&file=acr211378-sup-0001-Disclosureform.docx.

Address correspondence to Joanna Tieu, MBBS, FRACP, The Queen Elizabeth Hospital, Rheumatology Unit, 38 Woodville Road, Woodville South, 5011, Australia. Email: joanna.tieu@adelaide.edu.au.

Submitted for publication March 10, 2021; accepted in revised form June 10, 2021.

SIGNIFICANCE & INNOVATIONS

- Cancer rates are higher in patients with anti-neutrophil cytoplasm antibody-associated vasculitis (AAV)/polyarteritis nodosa (PAN) compared with the general population.
- In this study, patients with AAV/PAN had a peak in new cancer diagnoses early after diagnoses of AAV/PAN, which was explained by lung and hematological cancers.
- Excess skin cancer rates peaked approximately 5 years after diagnosis of AAV/PAN, and excess genitourinary cancers peaked approximately 10 years after diagnosis of AAV/PAN.

codes. Historic trials investigating treatment approaches for AAV subtypes have included PAN (1–4).

A link between systemic vasculitides and malignancy has been proposed in several observational studies. Studies have focused on cancers related to medicines commonly used to treat vasculitis, namely, bladder cancer with cyclophosphamide (5–7) and skin cancer with methotrexate and azathioprine (8,9). Other proposed mechanisms include chronic immune activation, which is a shared pathogenesis of immune dysfunction and paraneoplastic phenomena.

Notably, the published risk of common cancers in the general population, such as breast and colorectal cancer, have not been greater among patients with AAV compared with population rates (10–17). In studies of patients with AAV, increased nonmelanoma skin cancers (NMSCs) have been consistently reported (6,10–12,14,15,17). This has largely been driven by squamous cell carcinomas (SCCs) of the skin (10,13,14,17), with no increase in the risk of melanoma or other skin cancers (10,14,17). In the Australian setting, the impact of AAV and PAN on cancer risk has not been examined. Moreover, a higher background risk exists for skin cancer in Australia.

In this study, we examined overall and time-varying rates of incident cancer in patients with AAV/PAN compared with the general population in Western Australia (WA).

PATIENTS AND METHODS

Data source. Patients were identified in the Western Australia Rheumatic Disease Epidemiology Registry (WARDER), which collects compulsory reported hospitalization data from public and private hospitals in WA (from the Hospital Morbidity Data Collection [HMDC]) with emergency department data collection, WA cancer registry, and WA births, deaths and marriages registry and links the data via the WA Data Linkage System (WADLS). Linked emergency department data were not used in this analysis. This process is summarized in Figure 1. The high linkage accuracy (99.7%) of WADLS allows longitudinal follow-up for individuals across administrative health datasets (18).

The available HMDC dataset consists of data from 1980 to 2014, including demographic data, primary and up to 20 secondary diagnosis codes, and timing of hospitalization. Dates were provided as MM/YYYY to minimize the risk of reidentification of individuals. Data were available from the WA cancer registry from 1982 to 2014 and include diagnosis date, cancer topography, morphology, and behavior.

Study population. Patients were classified as having AAV/PAN using ICD-9 or ICD-10 codes from hospitalization or death diagnosis fields for AAV subtypes (Figure 1B). Patients with AAV/PAN were categorized into the following two subgroups using existing ICD code structures: GPA/EGPA or MPA/PAN, which reflect historic nomenclature and classification. Because of the nature of data linkage, additional clinical and laboratory data were not available to reclassify patients into alternative subgroup structures. Linked data for these patients in WARDER were used for analyses.

The date of first hospitalization listing ICD-9 or ICD-10 diagnosis codes for AAV/PAN was taken as the date of diagnosis. Patients were excluded if age at diagnosis was under 10 years. Patients were classified as having incident AAV/PAN if a prior hospitalization was identified without AAV/PAN, or if they were born after January 1980.

Outcome. The reporting of all cancers to state-based cancer registries is mandatory in Australia. All cancers are recorded in the WA cancer registry in accordance with World Health Organization ICD for Oncology codes, which are updated with each iteration of revisions. Solid organ malignancies were identified using topography codes and hematological malignancies using morphology codes. Where both were reported concurrently, morphology of the solid organ malignancy was reviewed to distinguish between concurrent cancers and occurrence of an extranodal or extra-medullary hematological malignancy. Reporting of recurrences is not mandatory, and because the objective of this study was to evaluate incident cancer, all recurrences in the same organ category or morphology for hematological malignancy were removed from analyses. The three most common skin cancers in Australia are melanoma, SCC, and basal cell carcinoma (BCC) (19). Both SCC and BCC of the skin are not included in Australian cancer registries, and skin cancers in Australian cancer registries are therefore predominantly melanoma, with other rare types such as Merkel cell included (19).

Statistical analysis. The study included patients who were diagnosed with AAV/PAN between January 1, 1983, and March 1, 2014, with an end date of December 31, 2014. Patients with a cancer diagnosis registered prior to AAV/PAN diagnosis or match date were excluded from analysis of incident cancer. The date of last linkage was used as the censor date (December

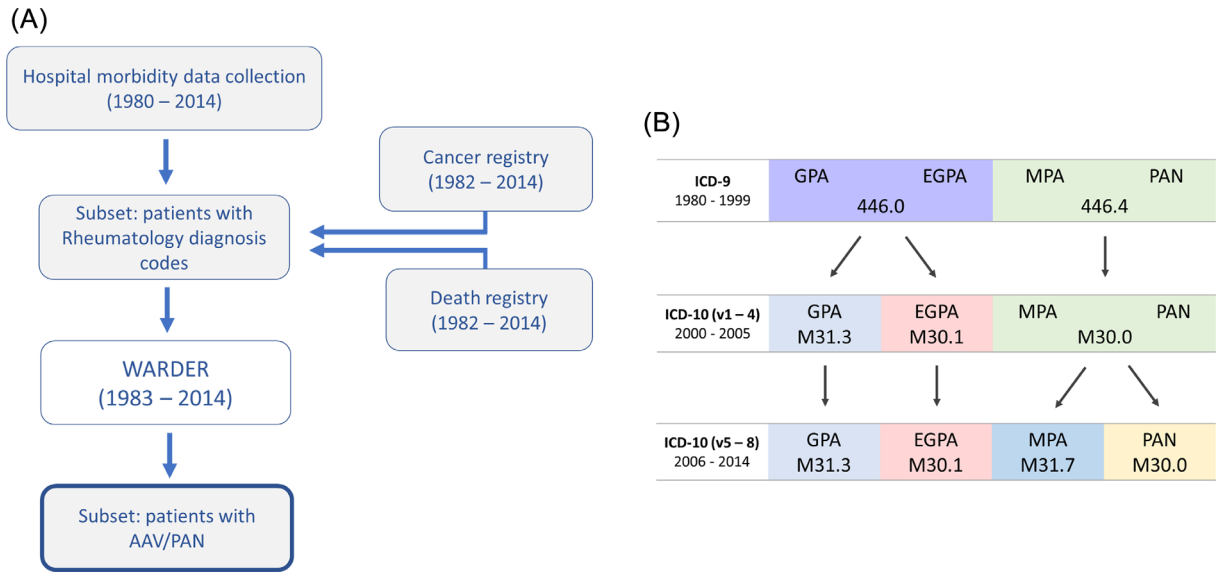


Figure 1. Data linkage flow chart and ICD codes for ANCA-associated vasculitis and PAN. **A**, Data linkage flowchart. **B**, ICD codes for ANCA-associated vasculitis and PAN. Patients with Rheumatological diagnoses from hospital admissions using ICD codes for the categories of chronic idiopathic arthritis, spondyloarthropathies, connective tissue disease, crystal induced arthritis, and osteoarthritis were identified from the HMDC. Data on all hospitalizations for these patients were linked to the WA Cancer registry and death registers from the Births, Deaths and Marriages registry to form the WARDER dataset. Patients with AAV/PAN were identified using ICD-9 and ICD-10 codes (Figure 1B), and linked WARDER data for these patients were used for analyses. The HMDC used ICD-9 until 1999, when ICD-10 was used for diagnosis classifications. The 5th edition was adopted in 2006. GPA and EGPA shared a diagnosis code in ICD-9 and had separate diagnosis codes in ICD-10. PAN and MPA shared a diagnosis code until the 5th edition ICD-10 update (adopted in HMDC in 2006) when separate codes were used. The distinction between PAN and the AAV subtypes (GPA, EGPA, and MPA) is therefore only possible from 2006 onward. AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasm antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; HMDC, Hospital Morbidity Data Collection; ICD, International Classification of Diseases; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa; WARDER, West Australian Rheumatic Disease Epidemiology Registry; WA, Western Australia.

31, 2014). Follow-up times for participants were right censored at 25 years of follow-up or an attained age of 89 years.

Demographic data have been summarized as proportion (percentage) and median (interquartile range). Comparisons of age and year of diagnosis were analyzed using Wilcoxon rank sum test. Cancer risk in AAV/PAN was analyzed using time to event analysis performed using Stata version 16 (StataCorp LLC).

Cancer types selected for specific cancer analyses were based on existing literature for cancer in patients with AAV/PAN and included the most common cancers in Australia (6,7,10,12,13). Both incident cancer (any) and specific cancer rates were analyzed. Crude cancer incidence rates were calculated from the observed number of cancers and follow-up (exposure time). For comparison with population cancer rates, the expected number of cancers were calculated from age-, gender-, and calendar-year-matched WA population cancer rates using the Ederer II method (20). Expected cancers, observed cancers, and person-years follow-up were tabulated at half-yearly intervals using the Stata ado program strs (20). The standardized incidence ratio (SIR) was calculated from the ratio of the total observed to expected cancers (over 25 years of follow-up), with exact mid-*P* confidence intervals (CIs).

Time-varying effects of AAV/PAN-related cancer risks were explored using the excess hazard rate (EHR), which is defined as the difference between the observed and expected cancer rates. This is an additive model of the effect of disease, is not confounded by an increase in the expected rates (the SIR denominator) that will occur during extended follow-up, and is not susceptible to distortions that may occur in the SIR with both small observed and expected rates. Spline-based modeling of the cancer EHR over follow-up time was performed using the Stata ado program stpm2 (21). The appropriate spline degrees of freedom were determined using the minimum Akaike information criterion, and knots were placed at default data centile positions determined by the degrees of freedom. The significance of differences in the time course of the excess hazards between AAV/PAN subgroups was determined by a multivariate Wald test of the time-varying regression coefficients.

Ethics. Ethical approval for linked data extraction was provided by the WA Health human research ethics committee (HREC) (WADOH HREC #2016.24).

RESULTS

In total, 564 incident patients with AAV/PAN were identified between 1980 and 2014. This included 342 (61%) patients with

Table 1. Demographics and incident cancer risk in patients with AAV/PAN

Characteristic	All AAV/PAN	GPA/EGPA	MPA/PAN
n	564	342	222
Females, *n* (%)	252 (45)	159 (46)	93 (42)
Age at Dx, median (IQR)	58 (45-69)	56 (44-67)	61 (58-65)
Year Dx, median (IQR)	2001 (1993-2007)	2002 (1996-2008)	1998 (1992-2005)
Maximum follow-up, y	25	25	25
Follow-up, person-years	4,882.249	2,836.339	2,045.91
Observed cancers	101	68	33
Expected cancers	58.13	30.84	27.29
Incident cancer rate[a] (95% CI)	2.07 (1.70-2.51)	2.40 (1.89-3.04)	1.61 (1.14-2.26)
SIR[b] (95% CI)	1.74 (1.42-2.10)	2.21 (1.73-2.78)	1.21 (0.85-1.68)

Abbreviations: AAV, antibody-associated vasculitis; CI, confidence interval; Dx, diagnosis; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IQR, interquartile range; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa; SIR, standardized incidence ratio.
[a]Crude incidence rate/100 person-years.
[b]SIR relative to age-, gender-, and calendar-year-matched West Australian population cancer rates.

GPA/EGPA and 222 (39%) with MPA/PAN. Demographic details are summarized in Table 1. Compared with patients with GPA/EGPA, patients with MPA/PAN were older at diagnosis ($P < 0.05$).

A total of 101 incident cancers were identified over 4,882 person-years of follow-up. Of the 101 incident cancers, 68 occurred in patients with GPA/EGPA and 33 in patients with MPA/PAN. Overall, the incident cancer rate observed in patients with AAV/PAN was greater than WA population rates (SIR, 1.74; 95% CI, 1.42-2.10).

When analyzed by disease subgroups, the rate of any type of cancer after the diagnosis of GPA/EGPA was double that of the general population (SIR, 2.21; 95% CI, 1.73-2.78). Patients with MPA/PAN, however, did not have an increased rate of incident cancer over the general population (SIR, 1.21; 95% CI, 0.85-1.68). The incidence rate ratio of cancers (derived from the crude incidence rates reported in Table 1) for the GPA/EGPA group compared with MPA/PAN was 1.49 (95% CI, 0.99-2.28; exact mid-*P*, 0.059).

However, the risk of cancer was not constant over time. The time frame for any incident cancer risk for the two subgroups is illustrated in Figure 2. Following an initial spike in excess cancers in both groups, the EHR for patients with MPA/PAN falls close to

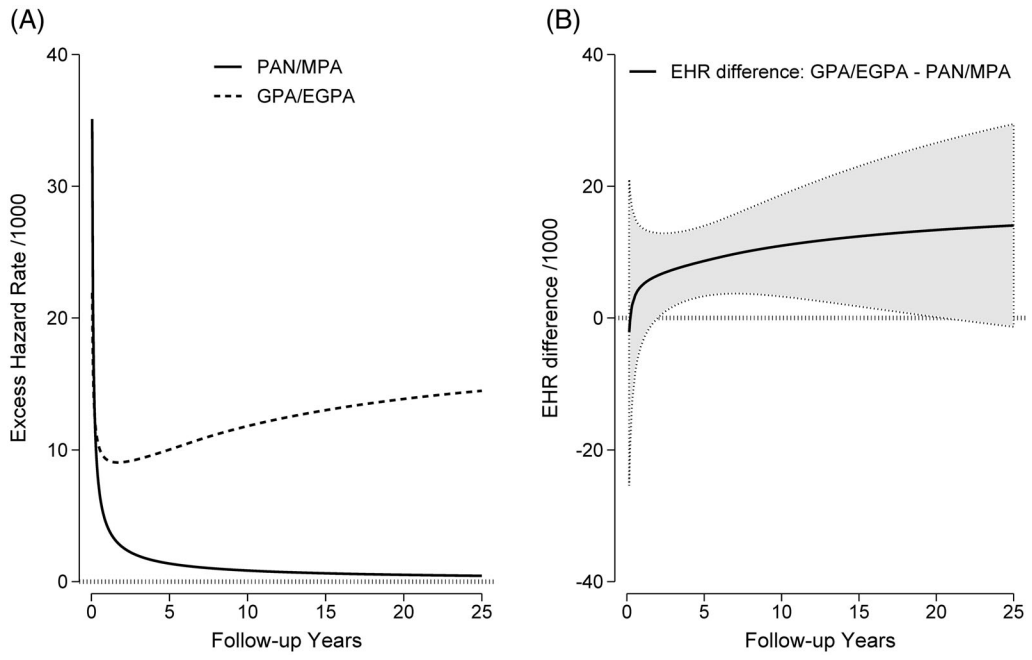


Figure 2. Spline based modelling of the cancer EHR, the difference between observed and expected rates, over follow-up time for both GPA/EGPA and MPA/PAN AAV subgroups. The EHR differed over time between the two AAV subgroups ($P = 0.011$). **A**, EHR for both GPA/EGPA and MPA/PAN subgroups. **B**, The difference in the EHR between AAV subgroups, with shaded areas representing 95% confidence interval. AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasm antibody; EGPA, eosinophilic granulomatosis with polyangiitis; EHR, excess hazard rate; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa.

Table 2. Specific cancer SIRs in patients with AAV/PAN and AAV/PAN subgroups

	AAV/PAN			GPA/EGPA			MPA/PAN		
Specific Cancer	Obs	Exp	SIR	Obs	Exp	SIR	Obs	Exp	SIR
Genitourinary	7	2.04	343 (1.50-6.79)	7	1.11	6.30 (2.76-12.47)	0	0.93	—
Breast	5	6.24	0.80 (0.29-1.78)	<5	3.97	0.76 (0.19-2.06)	<5	2.27	0.88 (0.15-2.91)
Lung	17	7.85	2.17 (1.30-3.40)	11	4.39	2.50 (1.32-4.35)	6	3.45	1.74 (0.71-3.62)
Colorectal	12	8.86	1.35 (0.73-2.30)	9	4.95	1.82 (0.89-3.34)	<5	3.92	0.77 (0.19-2.09)
Skin	22	6.56	3.35 (2.16-4.99)	15	3.73	4.02 (2.33-6.48)	7	2.83	2.48 (1.08-4.90)
Hematological	13	6.72	1.93 (1.08-3.22)	8	3.81	2.10 (0.98-4.00)	5	2.91	1.71 (0.63-3.80)
Prostate[a]	11	12.75	0.86 (0.45-1.50)	8	7.05	1.14 (0.53-2.16)	<5	5.70	0.52 (0.13-1.43)

Abbreviations: —, no data; AAV, antibody-associated vasculitis; EGPA, eosinophilic granulomatosis with polyangiitis; Exp, expected cancer rate; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; Obs, Observed cancer rate; PAN, polyarteritis nodosa; SIR, standardized incidence ratio; WA, Western Australia.
In accordance with WA Data Linkage policy, to minimize the risk of reidentification, cells with fewer than five individuals are reported as "<5."
[a]Men only.

zero, indicating that the cancer risk becomes similar to the population rate. For patients with GPA/EGPA, however, the EHR remains elevated and continues to increase over long-term follow-up.

Risk of specific cancer types in patients with AAV/PAN. Incident genitourinary, lung, skin (non-SCC/non-BCC), and hematological cancers were increased compared with age-, sex-, and calendar-year-matched population rates (Table 2). No increase in incident breast, prostate, or colorectal cancer was observed in patients with AAV/PAN compared with the population. Patients with GPA/EGPA had greater than expected rates of incident genitourinary cancer compared with matched population rates (Table 2), but no genitourinary cancers were observed in patients with MPA/-PAN. Skin cancer rates were increased in both GPA/EGPA and MPA/PAN subgroups of patients (Table 2). Incident lung cancer was increased in patients with GPA/EGPA compared with the general population, but not in patients with MPA/PAN (Table 2). Although the overall rate of hematological cancers was elevated, this was not statistically significantly in either subgroup.

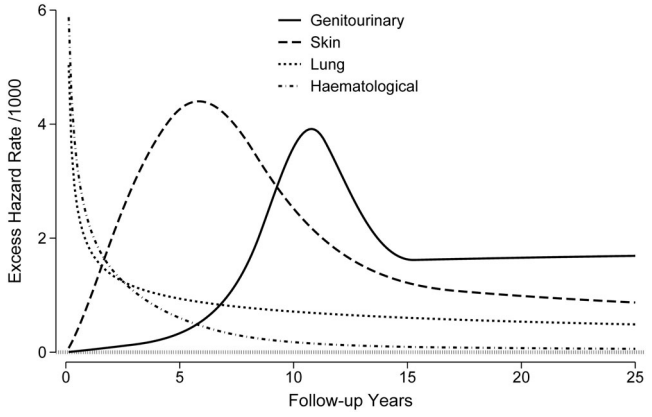


Figure 3. Spline based modelling of the excess hazard rate over time for specific cancers in patients with ANCA-associated vasculitis/polyarteritis nodosa. ANCA, anti-neutrophil cytoplasm antibody.

Timing of specific cancers after diagnosis. The EHR for cancers observed to be increased in patients with AAV/PAN (genitourinary, skin, lung, and hematological) in this dataset were modeled over time (Figure 3). A peak in EHR of skin and genitourinary cancers occurred at approximately 5 and 10 years, respectively, with a persistently increased rate observed thereafter. Lung and hematological cancer rates, however, peaked early after diagnosis and returned to rates similar to matched population rates in longer-term follow-up. Hematological cancers in the first 3 years included diagnoses of Hodgkin lymphoma, myelodysplastic syndrome, and myeloid sarcoma. Later hematological cancers included non-Hodgkin lymphomas, myeloma, and myelodysplastic syndrome.

DISCUSSION

With the success of induction therapy in the systemic vasculitides, longer-term outcomes have become an increasingly important focus in improving care. Treatment strategies to control disease activity and prevent relapses balance disease-related sequelae against treatment-related effects, including cancer. In this first study of cancer rates in Australian patients with AAV/-PAN, we observed higher rates of incident cancer in patients with AAV/PAN than the matched general population, explained by increased rates of genitourinary, skin, lung, and hematological cancers. We identified periods in the disease course with the greatest incidence of these cancers compared with the general population.

The estimated SIR for cancer in patients with AAV/PAN in this Australian cohort (1.74; 95% CI, 1.42-2.10) was comparable to a prior meta-analysis, which reported an overall SIR of 1.74 (95% CI, 1.37-2.21) (22). Cancer remains a significant contributor to mortality in patients with AAV and PAN (1,23,24). In a separate paper addressing mortality in the same cohort of patients with AAV/PAN included in this study, the risk of death related to malignancy was greater in patients with AAV/PAN than age-, sex-, and temporally matched hospitalized controls, increasing in longer-term follow-up (25).

Early observational studies of patients with GPA reported increased cancers compared with population rates, with estimated SIRs between 1.7 and 2.1 (6,10,17). Cancer studies including patients with MPA, EGPA, and PAN have produced mixed results. La Farage and colleagues reported no overall increase in malignancy in long-term follow-up of patients with AAV/PAN included in French vasculitis group studies (26). In contrast, Swedish, Dutch, United Kingdom, and Korean data suggest that an increased risk of cancer persists (13–16,27). Where cancer incidence has been compared among subgroups, rates were greater in patients with GPA compared with patients with MPA (13,15,16,27) and those with EGPA (16,27). In our subgroup analyses, patients with GPA/EGPA, but not MPA/PAN, also had increased rates of incident cancer compared with expected population rates. This may relate to the relapsing and refractory course of GPA and EGPA, resulting in repeated immune reactivation and consequently greater cumulative immunosuppressive therapy in these patients, and we note that increased cancer has been observed with greater cyclophosphamide (6,12,15,17) and methotrexate and azathioprine use (26,28). Disease activity and medication data were unfortunately not available in this linked dataset to address this hypothesis.

In analyses of specific cancer types in this study, the incidence of genitourinary, skin, lung, and hematological cancers were higher than general population rates. These cancers have been associated with AAV and PAN in prior studies (6,7,10–13,15–17,29), whereas rates of liver, pancreatic, and brain cancers identified in other studies were not increased (10,13). Whereas only patients with GPA/EGPA had increased rates of genitourinary and lung cancers, increased rates of skin cancer were identified in both patient groups. The long-term risk of genitourinary cancers is well recognized and attributed to the effects of cyclophosphamide, commonly used in treatment of AAV/PAN (5–7,10,11,17,27,30), with higher cumulative cyclophosphamide doses and with a diagnosis of GPA likely conferring greater risk (6,7). In this study, time-varying analyses of excess cancer rates revealed excess genitourinary cancer rates peaked approximately 10 years after diagnosis, consistent with the long latency periods noted in previous studies (6,7,10).

Prior studies have recognized the relatively common occurrence of skin SCCs and the substantial impact of SCCs on the overall risk of cancer (6,10–12,14,15). The association is most often attributed to azathioprine and methotrexate (6,26), which have been associated with NMSC in other settings (8,31–34). The high incidence of skin cancer in Australia is well-recognized, considering the high ultraviolet (UV) radiation exposure; although public health interventions have improved skin cancer rates, this effect has not changed skin cancer rates in the predominant age groups included in this study (35). The risk of skin cancers other than SCCs has not been significantly increased in European cohorts; whether patients with AAV/PAN with greater UV exposure in Australia were at greater risk of skin cancers has remained of interest. This study has confirmed the increased rate of incident skin cancer in Australian patients with AAV/PAN; importantly, this was predominantly driven by melanoma skin cancers as SCC and BCC are excluded from the cancer registry (19).

Few studies have evaluated the timing of cancer development in the follow-up of patients with AAV/PAN. Although not directly comparable, in contrast to the peak excess skin cancer rates observed in this study 5 years from diagnosis, a relatively stable SIR of NMSC was observed in two Scandinavian studies (6,10). Timing and behavior of melanoma compared with NMSC may explain this difference, or intensity and cumulative burden of immunosuppression may contribute. One study linking solid organ transplant with cancer registry data in the United States suggests a differing effect of short-term intense immunosuppression and longer-term immunosuppression; melanomas with regional or distant spread occurred early after transplantation, whereas in situ melanoma rates were consistently elevated over follow-up (36).

An early spike in excess cancers was observed soon after diagnosis in patients with AAV/PAN, with hematological and lung cancers contributing to this excess. This could be consistent with shared pathogenesis, short-term treatment effect or paraneoplastic effect. A paraneoplastic effect in AAV and PAN have been proposed by several reports [37-40]. Two case–control studies, however, have not identified an association between AAV diagnoses and preceding cancers (28,29). Patients with prior cancers were excluded from this study.

Although not significant in individual studies, a meta-analysis of early studies of cancer in patients with AAV identified increased lung cancer (22). Recent analyses of Korean health data have also identified an increased rate of lung cancer among patients with AAV (16,27). This has not, however, been found in recent European studies of patients enrolled in observational cohorts (13–15). Notably, this study and the Korean studies, both reporting increased lung cancer, have relied on administrative data for diagnoses, overcoming the difficulties in recruiting patients burdened with complex concurrent illnesses to observational cohorts.

The short latency to hematological cancers observed in this study is also congruent with the findings from data obtained from administrative data linkage studies from Korean and Sweden. Knight and colleagues report increased rates of both leukemias and lymphomas, with SIRs highest in the first year of follow-up (10). In the Korean studies, increased rates of hematological cancers were driven by increased non-Hodgkin lymphomas and myeloma in patients with AAV (16). These findings contrast with Faurschou and colleagues' report of myeloid leukemias in patients who received at least 36 g of cyclophosphamide, and after 5 years of follow-up (6).

Both AAV and PAN remain relatively uncommon, and collaboration among the vasculitis community has enabled recent large randomized controlled treatment trials (41–43). With the ability to better control initial disease activity, long-term and uncommon outcomes such as incident cancer, which can have a long

latency, need to be assessed by observational studies, including population-based studies. A population-based approach also enables the identification of outcomes for patients with early cancers and accounts for early deaths in patients who may not have the opportunity or ability to be included in observational cohorts and randomized controlled trials. The patients with AAV/PAN in this study were identified by ICD discharge codes. Although this represents real-world clinician-based diagnoses mandatorily audited by clinical coders, they are not validated against classification criteria through case-note review. A previous study from WA using the same discharge codes, however, reported a sensitivity of 91% for AAV diagnosis based on the European Medicines Agency classification algorithm (44).

Outpatient data are not included in WADLS, introducing possible bias because patients with AAV/PAN with less severe disease, never requiring hospitalization for AAV/PAN or complications, were not included. Moreover, because of the nature of data linkage in these patients, detailed clinical data and laboratory data including ANCA status were not available, limiting analyses on medication effects and analyses based on more contemporary understandings of patient subgroups.

Considering the early peak in excess cancers, including lung and hematological cancers, a degree of ascertainment bias was considered, owing to imaging and laboratory investigations required in the diagnosis of AAV/PAN. Rates of other commonly occurring cancers, including breast and colorectal cancers, were not increased, however. Moreover, the WA cancer registry consolidates mandatorily reported cancer data from pathology reports and radiation oncology records, which were available for all diagnosed lung and hematological cancers identified in this study. As highlighted earlier, the diagnosis of AAV/PAN is regularly and mandatorily audited. This study focused on incident cancer diagnoses because patients with prior cancer are more likely to have a second cancer and current standards in Australian cancer registries make the identification of recurrences unreliable. Larger scale studies may be helpful to study cancer outcomes in patients with a prior cancer, who may not have been included in clinical trials.

In conclusion, this study not only reiterates the importance of cancer monitoring in the follow-up of patients with AAV/PAN but also provides time frames for excess risk of specific cancers. These data help to inform future research as to whether, or when, cancer screening in patients with AAV/PAN is warranted, as skin and bladder cancers rates peaked at approximately 5 and 10 years, respectively. Furthermore, in addition to the increase in SCC skin cancers identified in European countries, this study has emphasized the need for vigilance for all skin cancers, including melanoma, in Australian patients.

ACKNOWLEDGMENTS

The authors wish to thank the staff at the Western Australia Data Linkage Branch, Western Australia cancer registry, and Hospital Morbidity Data Collection. The authors also wish to thank Richard Trevithick, in particular, from the WA cancer registry.

AUTHOR CONTRIBUTIONS

Dr. Tieu wrote the first draft of the manuscript. All authors contributed to article revisions and approved the submitted version.

Study conception and design. Tieu, Lester, Keen, Hill, Nossent.

Acquisition of data. Tieu, Lester, Raymond.

Analysis and interpretation of data. Tieu, Lester, Raymond, Keen, Hill, Nossent.

REFERENCES

1. Bourgarit A, Le Toumelin P, Pagnoux C, Cohen P, Mahr A, Le Guern V, et al. Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: a retrospective analysis of causes and factors predictive of mortality based on 595 patients. Medicine (Baltimore) 2005; 84:323–30.
2. Ribi C, Cohen P, Pagnoux C, Mahr A, Arène JP, Puèchal X, Carli, P, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: a prospective randomized study of one hundred twenty-four patients. Arthritis Rheum 2010; 62:1186–97.
3. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P, et al. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore) 2011; 90:19–27.
4. Gayraud M, Guillevin L, le Toumelin P, Cohen P, Lhote F, Cassassus P, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum 2001;44:666–75.
5. Talar-Williams C, Hijazi YM, Linehan WM, Hallahan CW, Lubensky I, Kerr GS, et al. Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. Ann Intern Med 1996; 124:477–84.
6. Faurschou M, Mellemkjaer L, Voss A, Krarup Keller K, Tonder Hansen I, Baslund B. Prolonged risk of specific malignancies following cyclophosphamide therapy among patients with granulomatosis with polyangiitis. Rheumatology (Oxford) 2015;54: 1345–50.
7. Le Guenno G, Mahr A, Pagnoux C, Dhote R, Guillevin L; French Vasculitis Study Group. Incidence and predictors of urotoxic adverse events in cyclophosphamide-treated patients with systemic necrotizing vasculitides. Arthritis Rheum 2011;63:1435–45.
8. Solomon DH, Kremer JM, Fisher M, Curtis JR, Furer V, Harrold LR, et al. Comparative cancer risk associated with methotrexate, other non-biologic and biologic disease-modifying anti-rheumatic drugs. Semin Arthritis Rheum 2014;43:489–97.
9. Coghill AE, Johnson LG, Berg D, Resler AJ, Leca N, Madeline MM. Immunosuppressive medications and squamous cell skin carcinoma: nested case-control study within the skin cancer after organ transplant (SCOT) cohort. Am J Transplant 2016;16: 565–73.
10. Knight A, Askling J, Ekbom A. Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis. Int J Cancer 2002;100:82–5.
11. Westman KW, Bygren PG, Olsson H, Ranstam J, Wieslander J. Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. J Am Soc Nephrol 1998;9:842–52.

12. Heijl C, Harper L, Flossmann O, Stücker I, Scott DGI, Watts RA, et al. Incidence of malignancy in patients treated for antineutrophil cytoplasm antibody-associated vasculitis: follow-up data from European Vasculitis Study Group clinical trials. Ann Rheum Dis 2011;70:1415–21.
13. Heijl C, Westman K, Höglund P, Mohammad AJ. Malignancies in patients with antineutrophil cytoplasmic antibody-associated vasculitis: a population-based cohort study. J Rheumatol 2020;47: 1229–37.
14. van Daalen EE, Rizzo R, Kronbichler A, Wolterbeek R, Bruin JA, Jayne DR, et al. Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis. Ann Rheum Dis 2017;76: 1064–69.
15. Rahmattulla C, Berden AE, Wakker SC, Reinders MEJ, Hagen EC, Wolterbeek R, et al. Incidence of malignancies in patients with antineutrophil cytoplasmic antibody-associated vasculitis diagnosed between 1991 and 2013. Arthritis Rheumatol 2015;67:3270–8.
16. Ahn SS, Han M, Yoo J, Jung SM, Song JJ, Park YB, et al. Risk of cancers in antineutrophil cytoplasmic antibody-associated vasculitis: results from the Korea National Health Insurance Claims Database 2010-2018. J Clin Med 2019;8:1871.
17. Faurschou M, Sorensen IJ, Mellemkjaer L, Rasmussen AG, Loft R, Thomsen BS, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol 2008;35:100–105.
18. Lynch C, Holman CD, Moorin RE. Use of Western Australian linked hospital morbidity and mortality data to explore theories of compression, expansion and dynamic equilibrium. Aust Health Rev 2007;31:571–81.
19. Australian Institute of Health and Welfare 2016. Skin Cancer in Australia. Cat. no. CAN 96. Canberra: AIHW.
20. Dickman PW, Coviello E. Estimating and modeling relative survival. Stata J 2015;15:186–215.
21. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. Stata J 2009;9:265–90.
22. Shang W, Ning Y, Xu X, Li M, Guo S, Han M, et al. Incidence of cancer in ANCA-associated vasculitis: a meta-analysis of observational studies. PLoS One 2015;10:e0126016.
23. Wallace ZS, Fu X, Harkness T, Stone JH, Zhang Y, Choi H. All-cause and cause-specific mortality in ANCA-associated vasculitis: overall and according to ANCA type. Rheumatology (Oxford) 2020;59: 2308–15.
24. Tan JA, Choi HK, Xie H, Sayre EC, Esdaile JM, Aviña-Zubieta, JA. All-cause and cause-specific mortality in patients with granulomatosis with polyangiitis: a population-based study. Arthritis Care Res (Hoboken) 2019;71:155–63.
25. Tieu J, Lester S, Raymond W, Keen HI, Hill CL, Nossent J. Mortality and cause of death in patients with AAV/PAN in Australia- a population-based study. Rheumatology (Oxford) 2021;keab469 [online ahead of print].
26. Lafarge A, Joseph A, Pagnoux C, Puechal X, Cohen P, Samson M, et al. Risk of malignancy in patients treated for systemic necrotising vasculitis. Ann Rheum Dis 2020;79:431–3.
27. Choi ST, Ahn SV, Lee PH, Moon CM. The cancer risk according to three subtypes of ANCA-associated vasculitis: a propensity score-matched analysis of a nationwide study. Semin Arthritis Rheum 2021;51:692–9.
28. Faurschou M, Mellemkjaer L, Sorensen IJ, Thomsen BS, Dreyer L, Baslund B. Cancer preceding Wegener's granulomatosis: a case-control study. Rheumatology (Oxford) 2009;48:421–4.
29. van Daalen EE, Rahmattulla C, Wolterbeek R, Bruijn JA, Bajema IM. Incidence of malignancy prior to antineutrophil cytoplasmic antibody-associated vasculitis compared to the general population. J Rheumatol 2017;44:314–8.
30. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488–98.
31. Long MD, Martin CF, Pipkin CA, Herfath HH, Sandler RS, Kappelman MD. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. Gastroenterology 2012;143:390–9e1.
32. Inman GJ, Wang J, Nagano A, Alexandrov LB, Purdie KJ, Taylor RG, et al. The genomic landscape of cutaneous SCC reveals drivers and a novel azathioprine associated mutational signature. Nat Commun 2018;9:3667.
33. Jiyad Z, Olsen CM, Burke MT, Ibsel NM, Green AC. Azathioprine and risk of skin cancer in organ transplant recipients: systematic review and meta-analysis. Am J Transplant 2016;16:3490–3503.
34. Vajdic CM, McDonald SP, McCredie MRE, van Leewen MT, Stewart JH, Law M, et al. Cancer incidence before and after kidney transplantation. JAMA 2006;296:2823–31.
35. Whiteman DC, Green AC, Olsen CM. The growing burden of invasive melanoma: projections of incidence rates and numbers of new cases in six susceptible populations through 2031. J Invest Dermatol 2016; 136:1161–71.
36. Robbins HA, Clarke CA, Arron ST, Tatalovich Z, Kahn AR, Hernandez BY, et al. Melanoma risk and survival among organ transplant recipients. J Invest Dermatol 2015;135:2657–65.
37. Hutson TE, Hoffman GS. Temporal concurrence of vasculitis and cancer: a report of 12 cases. Arthritis Care Res 2000;13:417–23.
38. Fain O, Hamidou M, Cacoub P, Godeau B, Wechsler B, Pariès J, et al. Vasculitides associated with malignancies: analysis of sixty patients. Arthritis Rheum 2007;57:1473–80.
39. Miyata KN, Siddiqi NA, Kiss LP, Harbord NB, Winchester, et al. Antineutrophil cytoplasmic antibody-positive pauci-immune glomerulonephritis associated with mantle cell lymphoma. Clin Nephrol Case Stud 2017;5:9–15.
40. Philipponnet C, Garrouste C, Le Guenno GL, Cartery C, Guillvein, Boffa JJ, et al. Antineutrophilic cytoplasmic antibody-associated vasculitis and malignant hemopathies, a retrospective study of 16 cases. Joint Bone Spine 2017;84:51–7.
41. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puèchal X, Fujimoto S, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med 2020;382:622–31.
42. Jayne DRW, Merkel PA, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis. N Engl J Med 2021;384:599–609.
43. Smith RM, Jones RB, Specks U, Bond S, Nodale M, Aljayyusi R, et al. Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. Ann Rheum Dis 2020;79:1243–9.
44. Paramalingam S, Raymond W, Sharma C, Dogra G, Mclean-Tooke A, Nossent J. Disease flares, damage accrual and survival in ANCA-associated vasculitis in Western Australia. Int J Clin Rheumatol 2019; 14:31–6.

Chapter 3 – Rituximab maintenance in ANCA-associated vasculitis

3.1 Introduction

This chapter presents consensus guidelines for the use of rituximab for maintenance of remission in AAV, that were developed through a Delphi exercise. The Delphi exercise included a literature review, included in Chapter 3.2, and the guidelines developed have been published as an executive summary [155] (Chapter 3.3) and full guidelines [155] (Chapter 3.4).

Treatment of AAV is separated into induction of remission and maintenance of remission. In the induction phase, potential adverse effects and a high burden of immunosuppression is often accepted in order to treat active disease effectively, particularly when life- and/or organ-threatening manifestations have developed. The maintenance phase aims to prevent relapse in patients who have achieved remission, with greater consideration of potential adverse effects.

The introduction of glucocorticoids and cyclophosphamide for remission induction in AAV was a significant step forward in successful treatment of AAV, transforming the disease from one of high mortality to high morbidity from disease and treatment related factors [53, 68]. The risk of relapse remains high. Over time, the need to reduce treatment-related adverse effects and the recognition of successful induction of remission with reduced intensity regimens has led to several trials evaluating alternatives for the maintenance of remission in AAV [52, 56, 146, 156, 157].

Rituximab, a monoclonal antibody targeting CD20, leads to peripheral B cell depletion and has been successfully trialled for the induction and maintenance of remission in AAV. Rituximab has been shown to be equivalent to cyclophosphamide for the induction of remission [58, 71, 158], and superior to azathioprine for the maintenance of remission [59, 61].

Prior to the publication of these clinical trials, there was growing use of rituximab for both induction and maintenance of remission, reported in several observational studies [76, 78-80, 82, 83, 85]. With increasing use, differing practices for rituximab use, and adjunctive and prophylactic therapies evolved such that variations exist between clinical practice, observational cohorts and the treatment regimens used in different randomised controlled trials [59, 61, 62, 76, 78-80, 82, 83, 85, 159].

Acknowledging differing practices, a Delphi exercise involving experts in AAV practising in the United Kingdom was undertaken to develop guidelines for the use of rituximab for the

maintenance of remission in AAV. A Delphi exercise is a commonly used technique to develop consensus using iterative rating exercises [160]. With each round of the Delphi exercise, all participants complete the same survey. Responses remain anonymous and de-identified responses to questions are provided to the group to allow for free expression of opinions. After each round, participants are able to compare their own responses to that of others and reflect on the responses before completing a subsequent survey. A pre-defined number of survey rounds are completed, and a pre-defined consensus threshold is either reached or not for each recommendation.

We invited leading vasculitis clinicians in the United Kingdom to complete a survey of their attitudes to patient management in AAV and highlight areas that they felt were important to include in a recommendation statement on rituximab use for maintenance of remission in AAV. After the first round, a literature review of the key questions raised was conducted and included below in Chapter 3.2. Three further rounds were conducted, including one combined face-to-face and virtual 'live' round before final voting was conducted. I served as the facilitator of the Delphi exercise, including literature review.

Through the early rounds of the Delphi exercise, the decision on when to use rituximab but also how it is used was important to the participants. Participants highlighted monitoring, concomitant therapies, adverse effects, and prophylactic therapies as issues relevant to the optimal use of rituximab. These adjunctive practices have been protocolised in clinical trials and observational cohorts in various ways owing to the nature of each research methodology and site-specific preferences. These have not been individually examined in RCTs. Moreover, the feasibility of this in a rare disease such as AAV remains a challenge.

These guidelines synthesise the existing evidence from observational studies and randomised controlled trials on rituximab use in the maintenance of remission in AAV, highlighting nuanced aspects of its use and adjunctive therapies, to develop a resource to assist physicians in treatment decisions. These guidelines have received a high level of attention when compared with similar papers published within three months of its publication from the Rheumatology (Oxford) journal, and from any source [161].

Included in Appendix 2 is the cumulative summary of participant responses that led to consensus on the guideline statements.

3.2 Literature review

Delphi exercise- rituximab/B cell depletion for the maintenance of remission in AAV [formulation of key questions and literature review]

Contents

Questions

1. When should rituximab be used for the maintenance of remission in AAV?
    a. GPA/MPA – new and relapsing patients
    b. EGPA patients
2. What rituximab maintenance regimen should be used for AAV?
    a. Dose and dosing intervals
    b. Management of relapse despite maintenance rituximab
        i. incomplete responders/early relapse on maintenance therapy (<6 months after induction)
        ii. late relapse on maintenance therapy (>6 months after induction)
    c. Duration of therapy
    d. Factors influencing duration of therapy
    e. Role of biomarkers in rituximab maintenance therapy
3. Concomitant therapy
    a. Concomitant immunosuppressive agents/disease modifying anti-rheumatic drugs
    b. glucocorticoids
4. Prophylaxis
    a. Co-trimoxazole
    b. Vaccination
5. Adverse effects with treatment
    a. Hypogammaglobulinaemia
        i. threshold for hypogammaglobulinaemia be investigated
        ii. further rituximab in the setting of hypogammaglobulinaemia
    b. Late onset neutropenia and further rituximab
6. Research agenda
    a. Rituximab alternatives e.g. for allergic/intolerant- biosimilars/ofatumumab
    b. Cost effectiveness analysis, particularly in view of the reducing cost of B cell depletion with the introduction of biosimilars
    c. Effects on health related quality of life
    d. B cell dysfunction in AAV
    e. Management of relapse during rituximab
    f. Paediatric patients with AAV

Introduction

ANCA associated vasculitis (AAV) is a multi-system disease which, untreated, leads to significant morbidity and mortality. The landscape of AAV management has dramatically altered with the introduction of agents successful in treating disease. However, despite the success of treatment to induce a remission, the disease course of AAV is often characterised by relapses and in some, incomplete disease control. The burden of disease on patient morbidity and quality of life, in addition to the health economic costs of relapsing disease necessitate adequate long-term maintenance of remission. Treatment is divided into induction of remission, maintenance of remission and long term follow-up.

Owing to the disease course of AAV, disease states have been variously defined. The Birmingham Vasculitis Activity Score (BVAS) and it's BVAS/Wegener's granulomatosis (BVAS/WG) version are used to quantify disease activity. Disease states are broadly identified as active disease, disease remission, refractory disease, and relapse.

Active disease: manifestations attributable to AAV, and not due to disease related damage

Disease remission: disease control (BVAS or BVAS/WG ≤1); glucocorticoid free remission refers to disease control (BVAS or BVAS/WG ≤ 1) off glucocorticoid therapy.

Refractory disease: despite treatment of disease, remission has not been established, with persistent or progressive disease activity.

Disease relapse: where disease activity has previously been well controlled, and has become active, defined by at least 1 point increase in BVAS.

- Major relapse: relapse with 1 new or recurrent major item on BVAS or BVAS/WG
- Minor relapse: relapse without a major item on BVAS or BVAS/WG

When should rituximab be used for the maintenance of remission in AAV?

GPA/MPA

Rituximab has been examined as a therapeutic strategy for the maintenance of remission in 3 randomised controlled trials (RCT) [1-3]. Two of these trials have been published and one presented in abstract form.

One RCT randomised 115 patients with new and relapsing GPA, MPA or renal limited vasculitis who had received induction therapy with cyclophosphamide and prednisolone, to receive rituximab or azathioprine for relapse prevention [1]. Patients in the rituximab arm received infusions on day 0, day 14, month 6, 12 and 18. Patients in the azathioprine arm continued azathioprine for a total of 22 months, at 2 mg/kg/d for 12 months and tapered over the subsequent 10 months. Both arms continued prednisolone until at least 18 months. Rituximab was superior to azathioprine at 28-month follow-up with relapse rates of 29% and 5% respectively (hazard ratio 6.61, 95% confidence interval 1.56 to 27.96, p = 0.002), and no difference in severe adverse effects. 60-month follow-up has been reported in abstract form, with the benefit of rituximab maintenance protocol persisting (relapse free survival 57.9% vs 37.2%, p = 0.012) [4].

One small trial randomised patients with refractory GPA to receive either infliximab or rituximab induction and maintenance regimens, with only 8 patients receiving rituximab [2]. An additional RCT has completed recruitment with follow-up ongoing [5]. Patients in this RCT enrolled patients with relapsing GPA or MPA and randomised them to receive either fixed 4 monthly rituximab infusions or azathioprine for the maintenance of remission.

A number of observational cohorts have reported on the efficacy and safety with the use of rituximab for the maintenance of remission in AAV; case series including at least 25 patients receiving at least 2 courses of rituximab have been summarised in table 1.

EGPA

There are no RCTs examining the role of rituximab for the maintenance of remission in AAV in EGPA. Patients with EGPA have excluded from major RCTs using rituximab for both induction and maintenance therapy in AAV due to a number of issues, including recognised differences in disease manifestations and diagnostic difficulties.

With increasing use of ANCA based classification, patients with EGPA who are ANCA positive can be included in observational cohorts. One large cohort included 239 patients using ANCA based classification. Results for patients meeting classification criteria for EGPA were not presented.

A multi-centre retrospective review of patients with EGPA receiving rituximab for induction and/or maintenance therapy reported a response to rituximab in 88%, and was associated with significant reductions in glucocorticoid therapy [6]. Greater responses rates were noted in patients with ANCA positive compared with ANCA negative disease.

Quality of life with treatment

Poor health related quality of life (HRQoL) and secondary effects on employment are well established in AAV, with effects driven by fatigue, severe disease damage, weight gain and depression [7, 8].

RCTs of treatment in AAV have not demonstrated superiority of specific treatment regimens based on HRQoL measures. One RCT, MAINRITSAN, demonstrated significant benefits of rituximab over azathioprine for maintenance of remission, mostly in patients treated after their initial presentation of AAV. Improvements in the physical component of the SF-36 were identified in patients in both groups [9]. Paradoxically, despite the benefit of rituximab in prevention of relapse and similar Physical Component Scores, Health Assessment Questionnaire (HAQ) scores only improved in patients in the azathioprine arm and improvements in the Mental Component Score of the SF-36 were greater in those receiving azathioprine for maintenance of remission [9]. Moreover, adverse events were similar in both groups and is not able to explain this inconsistency.

Health economic evaluations

Although a disease with significant health resource utilisation, the economic burden of AAV remains incompletely defined. The cost of treatment, potential toxicities and costs of managing uncontrolled disease and the sequelae of relapse are significant contributors. In a US claims database, it was observed that GPA patients who experience a major relapse incurred greater all-cause and GPA related health expenditure, compared with those without major relapse [10]. The analysis of MPA patients was restricted within this database, though greater health expenditure was seen with MPA. Cost-effectiveness has been assessed by one RCT, MAINRITSAN, demonstrated a cost benefit of rituximab over azathioprine for the maintenance of remission in AAV [11]. With the introduction of biosimilars and the introduction of alternative routes of administration, the cost of treatment will continue to reduce, further improving the health economic benefit of rituximab over azathioprine.

What rituximab maintenance regimen should be used for AAV?

Dose/timing of rituximab in maintenance therapy

Varied doses of rituximab have been used and trialled for the maintenance of remission in AAV. The dose of rituximab used in these RCTs have varied, with 2 trials using a ‘low dose’ regimen of 500 mg at 6 monthly intervals, or with evidence of impending relapse [1, 3], and one using 375 mg/m^2 at 4 monthly intervals [2]. One ongoing trial has used 1g at 4 monthly intervals [5]. There have been no direct comparisons between different doses of rituximab in maintenance of remission.

The frequency of infusion (fixed dose compared with evidence of impending relapse) has been examined in one trial, which has been presented in abstract form [3]. 162 patients with new or relapsing GPA or MPA following induction of remission were randomised to receive rituximab at fixed intervals (500 mg day 0, day 14, month 6, month 12 and month 18), or biomarker guided (500 mg 3 monthly if CD19 positive B cells were detected on peripheral blood, ANCA return or change in ANCA titre). Patients dosed by fixed interval received more rituximab infusions than those dosed on

biomarker guidance (median 5 vs 3), with no difference in relapse rate at 28 month follow up (9.9% vs 17.3%, p = 0.22) or severe adverse events (38.3% vs 32.1%). Importantly, although guided by ANCA and circulating CD19 positive B cells for dosing, there was no association between ANCA status or B cells and relapses.

Additional information is derived from observational cohorts. Notably, in contrast to the evidence currently available from randomised controlled trials, observational studies predominantly include patients with longstanding refractory or relapsing disease.

Dosing regimens in observational cohorts are variable, with the greatest experience being with 1g every 4 months, 1g every 6 months, 500 mg every 6 months, 375 mg/m^2 every 6 months and planned repeat induction on clinical or biochemical relapse with either 1g D0 and D14, or 375 mg/m^2 weekly for four weeks. All regimens are reported to be generally well tolerated.

One centre has examined outcomes across different treatment protocols, comparing patients with treatment on clinical relapse, with those treated with a fixed interval dosing regimen [12, 13]. Whilst recognising that the patient groups were treated over different time periods, patients with patients dosed on clinical relapse experiencing more relapses than those receiving fixed interval re-dosing every 6 months (73% vs 12%, p < 0.001), and 4 years (81% vs 26%, p <0.001) [13].

Other observational studies have not drawn comparisons between different treatment strategies or protocols. Key differences in the patient populations studied, duration of follow-up and assessment of relapse make direct comparison difficult. Data on disease related damage and mortality has been limited in reports from observational cohorts, which in addition to disease activity and treatment toxicities, would allow for greater assessment of the impact of these treatments and comparison between regimens.

Early relapse despite maintenance rituximab

Relapse in spite of continuing fixed interval rituximab treatment is reported in one RCT and several observational cohorts. In one RCT, 3 major relapses occurred in patients receiving rituximab maintenance, at months 8, 22 and 24, necessitating changes to their treatment [13]. Additional details were not reported on the management of these major relapses. A further 6 patients experienced minor relapses, all treated with a course of prednisolone.

Observational cohorts have reported success with various strategies in the setting of early relapse, although with no more than 9 patients each [13-18]. Treatment strategies have included short courses of prednisolone, earlier rituximab dosing or repeated induction therapy and the introduction of a concomitant conventional disease modifying anti-rheumatic drug (cDMARD) as add-on therapy. There are limited reports of unsuccessful strategies.

Duration of treatment

Longer duration of prednisolone use provides longer protection from relapse in AAV [19]. The benefit of prolonged maintenance treatment in AAV has been further demonstrated in an RCT comparing continuation and withdrawal of azathioprine and prednisolone after 18-24 months of

treatment in AAV [20]. Long term glucocorticoid therapy, however, is associated with well recognised toxicity and, in an AAV population, accumulation of disease damage [21].

Published and unpublished RCTs have all provided up to 2 years of rituximab for relapse prevention after successful induction of remission [1-3, 5]. In one RCT comparing rituximab and azathioprine maintenance therapy in new and relapsing patients with AAV, rituximab was superior to azathioprine in relapse prevention at 28 months, as mentioned above (MAINRITSAN) [22]. Notably, rituximab ceased after a dose at 18 months and azathioprine withdrawal began at 20 months, and progressive reduction in relapse free survival over time.

Progressive increase in relapse rates with longer term follow-up is common to long term rituximab maintenance cohorts. This is illustrated in time to event analyses of a number of observational cohorts, particularly after treatment is discontinued [1, 13, 16]. In contrast, although not directly comparable, in one observational cohort where maintenance therapy is initially administered 4 monthly and routinely extended to 6 monthly beyond 2 years, relapse free survival does not appear to follow the same pattern of decline [23]. Notably, data on cumulative adverse events over is not readily available for comparison.

One ongoing RCT, to be completed in 2018, aims to evaluate the effects of extended duration rituximab therapy (NCT02433522). Patients who have already completed 18 months of rituximab maintenance therapy by fixed interval or demand dosing as part of another RCT, randomised to receive a further 18 months of fixed interval rituximab or placebo.

Utility of biomarkers in rituximab maintenance therapy

The role of biomarkers in guiding therapy in AAV is contentious owing to, historically, poor reliability of these biomarkers, and forms the rationale for fixed interval dosing of rituximab maintenance therapy.

Relapses are commonly recorded during rituximab maintenance treatment in spite of ANCA negativity and ongoing B cell depletion [1, 13, 15, 16, 18, 24].

An ANCA binding level increase or return from negative to positive has been of interest, particularly after rituximab maintenance therapy has been discontinued. In post-hoc analyses of an RCT comparing the use of rituximab to cyclophosphamide for the induction of remission in GPA and MPA, in patients with PR3-ANCA positive disease, a two-fold PR3-ANCA titre increase or PR3-ANCA return predicted recurrence of severe disease within 12 months [25]. Interestingly, the association between ANCA and subsequent relapse was true for those who had received rituximab induction, but not those who had received cyclophosphamide with azathioprine maintenance therapy. PR3-ANCA rise and return was not predictive of relapse involving only granulomatous manifestations.

One rituximab maintenance cohort noted the potential significance of ANCA return in relapse after completion of 2 years of fixed interval rituximab [15]. In the follow-up of 54 patients who became ANCA negative, ANCA return was noted in 13, of which 10 subsequently relapsed. Again, ANCA return was noted to be associated with major relapse, but not minor relapse.

Persistent ANCA positivity has also been examined as a predictor for relapse. Post-hoc analyses (presented in abstract form) of patients randomised to receive 6 monthly rituximab in MAINRITSAN, found persistently positive ANCA at 12 months and PR3-ANCA positivity at diagnosis were predictive

of cumulative relapse rate at 50 months of follow-up [26]. Similarly, an RCT comparing continuation with withdrawal of azathioprine maintenance therapy beyond 18-24 months of treatment, ANCA positivity after 18-24 months of treatment was predictive of future relapse [20].

Concomitant therapy

Immunosuppressive agent

The additional impact of concomitant therapy on efficacy and adverse effects remains unclear. The effect of combination rituximab with cDMARDs has not been addressed in RCTs. Rituximab arms of randomised controlled trials have used rituximab with prednisolone, but no cDMARDs.

As discussed above, cDMARDs have been used in observational studies as add-on therapy in response to early relapse despite rituximab maintenance. Commencement of maintenance rituximab with concomitant therapy has been observed in a subgroup of patients in several observational cohorts, albeit in low numbers. This is often withdrawn with ongoing follow-up, or after disease stability is established [13, 16-18].

Where the impact of concomitant therapy on efficacy, or adverse effects have been assessed, no differences have been identified [16, 27, 28]. In a case series of a mixed group of patients with AAV, systemic lupus erythematosus and rheumatoid arthritis, the incidence of late onset neutropenia was no different between those receiving rituximab compared with concurrent rituximab and methotrexate [29].

Definitive conclusions on potential adverse effects of concomitant therapy are limited by small numbers in these observational studies. Furthermore, the potential for an additive increase in risk of infection including atypical infections, and hypogammaglobulinaemia from concomitant therapy remains poorly delineated in AAV. In a recent RCT examining the role of belimumab in addition to azathioprine and low dose glucocorticoids for maintenance of remission, a subgroup who had received rituximab induction followed by beliumumab and azathioprine with low dose glucocorticoids experienced greater infections than those receiving azathioprine and low dose glucocorticoids without belimumab [personal communication] [30].

Glucocorticoids

The relapse prevention benefit afforded by prolonged glucocorticoid use in AAV has been demonstrated in a systematic review of glucocorticoid therapy in studies using cDMARDs for the maintenance of remission [19]. The adverse effects from high dose and prolonged glucocorticoid use are well recognised, including predictable metabolic and infective risks. In AAV, cumulative glucocorticoid dose following rituximab has been associated with a reduction in immunoglobulin levels and severe infection [31]. Concerningly, in the long-term off-trial follow-up of patients included in European RCTs at 7 years, prolonged use of glucocorticoids was associated with greater disease damage, measured by the vasculitis damage index, after adjusting for number of relapses during follow-up, age, baseline disease activity and renal involvement [21]. Consistent with reports in other conditions, this study additionally demonstrated an association between prolonged

glucocorticoid use and development of cataract and hypertension in this AAV population. Thus, glucocorticoid-free remission remains optimal.

The effects of early and late glucocorticoid withdrawal in patients receiving rituximab maintenance therapy has not been investigated in clinical trials. In all arms of 2 completed RCTs, glucocorticoids have been progressively tapered, but maintained until at least 18 months after induction of remission [1, 3]. In an ongoing trial of maintenance rituximab therapy, prednisolone is continued until at least 24 months from induction [5]. In contrast, in uncontrolled settings, earlier prednisolone dose reduction and cessation is well documented [13, 15, 32].

Patients with an EGPA disease phenotype have greater difficulty with glucocorticoid withdrawal. A multi-centre observation cohort of patients receiving rituximab for induction and maintenance of remission, significant reductions in glucocorticoid therapy was achieved [6]. However, withdrawal of glucocorticoid was lower than is seen in GPA and MPA cohorts.

Prophylaxis

Co-trimoxazole in conjunction with rituximab as treatment and prophylaxis

The issue of co-trimoxazole use in rituximab revolves around two main issues- its use as prophylaxis for *Pneumocystis jirovecii/carinii* pneumonia (PJP/PCP), and its role in relapse prevention.

The use of co-trimoxazole in selected patients with limited GPA was first reported in the 1980s [33]. Though its exact mechanism of action has remained unclear, theories of efficacy involve suppression of staphylococcus triggering flares and its immunosuppressive effects.

Two RCTs have examined the use of co-trimoxazole for the maintenance of remission in AAV. One trial randomised 81 patients with AAV following induction of remission to receive co-trimoxazole 800mg/160mg twice daily or placebo for 24 months [34]. Notably, standard induction treatment in the Netherlands at the time included cyclophosphamide and prednisolone, with half the patients in each arm on cyclophosphamide and prednisolone respectively. A large proportion of patients in both groups remained ANCA positive at baseline despite having achieved remission (68% co-trimoxazole, 48% placebo). Patients receiving co-trimoxazole had greater relapse free survival compared with placebo (82% vs 60%, relative risk of relapse 0.40, confidence interval 0.17 to 0.98) and unsurprisingly, fewer infections (median 0 vs 1, $p<0.001$). It is noted by the trialists that relapses were associated with a preceding respiratory tract infection in half of the patients included in this trial, and therefore does not account for the relapse difference. Though generally well tolerated, 20% of patients ceased therapy as a result of generally mild adverse effects.

In a subsequent trial, 31 patients with GPA in remission following cyclophosphamide and prednisolone, to receive co-trimoxazole prophylaxis of 800mg/160mg three times a week or placebo [35]. At this lower dose of co-trimoxazole, a significant difference was still identified with 75% remaining in remission in the co-trimoxazole group compared with 55% in the placebo group (HR 0.8 CI 0.21-1.20). Again, fewer infections occurred in patients in the co-trimoxazole group than placebo over the study period (median 0 vs 4 $p <0.01$).

Importantly, neither trial used any alternative or additional therapy for maintenance of remission (other than co-trimoxazole/placebo). There were no trials identified examining the efficacy of co-

trimoxazole in conjunction with an additional agent, including rituximab, in the maintenance of remission.

One case series reporting on a French cohort of patients with refractory GPA treated with rituximab, 15 continued co-trimoxazole as a maintenance therapy agent in conjunction with rituximab [16]. Outcomes for these patients were not reported separately.

A proposed mechanism of action of co-trimoxazole is related to staphylococcus aureus clearance. One observational cohort of 29 patients receiving rituximab maintenance therapy, evaluated staphylococcus carriage and relapse in a small number of patients who relapsed [36]. A total of 8 patients experienced 9 relapses on rituximab maintenance, with no association identified between staphylococcus carriage and relapse in these patients.

The occurrence of PCP in the setting of immunosuppression in AAV has been well documented in early case series [37] and continues to be a recognised complication from immunosuppression in AAV, including with the use of rituximab [38]. Trials involving rituximab based regimens in AAV have included PCP prophylaxis [1, 39, 40]. In one RCT comparing rituximab or azathioprine after cyclophosphamide induction, one patient developed PCP despite a protocol for prophylaxis when CD4 count <250 mm^3. Therapy prior to and at the time of PCP diagnosis is unclear in this patient.

A Markov state-transition model for the cost-effectiveness of PCP prophylaxis in GPA has been examined by Chung and colleagues, comparing no prophylaxis, co-trimoxazole 800 mg/160 mg 3 times a week or co-trimoxazole at the same dose with pentamidine used if intolerant. An annual incidence of PCP in GPA was estimated from a separate retrospective cohort, at 0.85%. The effectiveness of co-trimoxazole in preventing PCP was estimated to be 90% and 87% for pentamidine. Based on a 35 year old with GPA, this model demonstrated that the use of co-trimoxazole at 800 mg/160 mg three times per week increased life expectancy and QALY, and reduces cost in GPA in patients receiving immunosuppressive therapy. This persists so long as the annual incidence of PCP remained greater than 0.2%.

The incidence of PCP in the setting of GPA is variably reported. A claims database analysis using data collected from 2006 to 2013 for 4606 patients with a diagnosis of GPA of whom 636 patients had received rituximab. 53% of the patients who had received rituximab had claims for PCP prophylaxis. The estimated annual incidence of PCP in GPA was 0.2% and 0.1% in those with GPA who had received rituximab. Furthermore, the mean age of patients with AAV is older, at 47 and 57 in cohorts and trials respectively, reducing the potential impact of co-trimoxazole prophylaxis in this model [41].

Vaccination

In the context of ongoing B cell depletion, the potential for infection and potential inefficacy of vaccinations are key considerations.

The protective benefit of influenza vaccination is well established and is widely implemented in public health strategies. The benefit of influenza vaccination in patients with autoimmune disease has also been reported. A retrospective analysis of a claims database in Taiwan demonstrated reduced morbidity, hospitalisation and mortality in patients with systemic lupus erythematosus who had received influenza vaccination compared with those who had not [42]. This is yet to be

replicated in an AAV population, though poor vaccine response in a cohort of 92 patients with vasculitis (88 with AAV) was associated with increased mortality [43].

Of note, case reports have speculated over the potential contribution of vaccination to disease activity, with ANCA, new disease or relapses occurring following vaccinations [44-47]. In AAV, the safety of influenza vaccination has been demonstrated in an RCT of 31 patients with AAV in remission, randomised to receive influenza vaccination or no vaccination [48] and observational cohort of 92 patients with vasculitis, including 88 with AAV [43].

Although the in vitro humoral response to influenza vaccination following B cell depletion has generally been impaired in patients with AAV and rheumatoid arthritis [48-55], a preserved in vitro cellular response has been demonstrated [56-58], which may contribute to clinical efficacy.

In a small retrospective analysis of patients followed for 1 year following rituximab administration for autoimmune disease, the risk of severe bacterial infection was significantly reduced in those who had received pneumococcal vaccination [59]. In a cohort of patients with rheumatoid arthritis on concomitant rituximab (68 patients) or methotrexate monotherapy (32 patients) receiving pneumococcal vaccination, vaccine response as measured by seroconversion was lower in those on concomitant therapy [60]. Importantly, 38% demonstrated protective antibody levels to 3 pneumococcal antigens despite a median CD19 count below the lower limit of normal. Sequential vaccination with conjugated and polysaccharide vaccines has been trialled in patients with rheumatoid arthritis [61], though with less than 5 patients on rituximab treatment. A sequential vaccination study in AAV patients with previous rituximab is planned.

Adverse effects

Hypogammaglobulinaemia following rituximab

Hypogammaglobulinaemia has been reported following immunosuppression with a variety of immunosuppressive agents. In the context of rituximab use in AAV, hypogammaglobulinaemia is observed in excess of that seen in other autoimmune conditions [62, 63]. Although reports vary, the results of registry data and observational cohorts suggest that the development of hypogammaglobulinaemia likely increases the risk of infection [63, 64].

In one RCT, there was no statistically significant difference in the incidence of hypogammaglobulinaemia in patients who received rituximab maintenance compared with azathioprine maintenance (MAINRITSAN). In the post-hoc analysis of another RCT comparing induction of remission using rituximab and cyclophosphamide, although the proportion of patients with IgG under the lower limit of normal was numerically greater in the rituximab arm after 18 months, the change in IgG from baseline was not statistically significantly different between the two groups [65].

With multiple possible definitions of hypogammaglobulinaemia, its reported incidence in observational cohorts of maintenance rituximab has varied significantly, between 10% and 67% [13-15, 66, 67].

There has been limited information on how this could be prevented and the long term outcomes of these patients. Interestingly, cumulative rituximab dose has not been associated with an increased

risk of hypogammaglobulinaemia. The impact of prior immunosuppression on the risk of hypogammaglobulinaemia following rituximab remains unclear, with conflicting evidence on the effect of prior cyclophosphamide [67-69].

Late onset neutropenia following rituximab

Late onset neutropenia (LON) is widely recognised as a complication of rituximab therapy, particularly in the setting of haematological malignancy. Regular routine evaluation for neutropenia is uncommon. Hence, periods of asymptomatic neutropenia are likely to be missed in autoimmune disease, and the incidence of LON is likely underestimated.

The mechanism of LON following rituximab is poorly understood. LON is associated with periods of complete B cell depletion and has been postulated to occur as a result of arrest of granulopoiesis, in favour of B cell lymphopoiesis [70]. In a lymphoma population LON is associated with a high affinity FCγR 158 V allele, which also correlates to better disease control [71]. A similar correlation between FCγR IIIa genotype and B cell depletion has been demonstrated in SLE [72].

LON has been identified in AAV patients in rituximab maintenance cohorts [14-16, 27, 67, 73]. Safe retreatment with rituximab in patients with autoimmune disease and a history of LON following rituximab has been described in the literature. A total of 74 patients (43 AAV) developing LON following rituximab have been reported [14-16, 27, 29, 67, 73-78]. 44 of these patients have been rechallenged with rituximab with recurrence of LON noted in 2 patients. Symptomatic patients were treated with antimicrobial therapy and G-CSF if appropriate.

Progressive multifocal leukoencephalopathy (PML)

PML results from reactivation of the John Cunningham virus (JCV), often resulting in a devastating neurological disease of the central nervous system and mortality. PML has been reported in immunocompromised patients with human immunodeficiency virus and those undergoing chemotherapy, particularly for haematological malignancies.

Importantly, cases of PML have been reported in the context of GPA in the absence of rituximab [79-83]. All of these patients were treated with glucocorticoids and cyclophosphamide, with individuals also on cyclosporin A, mycophenolate, azathioprine or IVIG at various points. Though remaining rare, PML has been reported following the use of rituximab based treatment regimens in malignancy and autoimmunity [84-92]. In AAV, there have been 4 cases reported, with no clear indication of a propensity in this patient population [personal communication] [93].

The utility of screening with JCV antibody testing has not been examined in this patient population, and the rarity of PML makes this less feasible.

Randomised controlled trials

Study	Population and treatment arms	Outcomes	Safety outcomes	Comments
MAINRITSAN [1]	115 patients with GPA/MPA/RLV (80% newly diagnosed) Induction regimen: cyclophosphamide + GC RTX arm (57 patients) Dose: 500 mg D0, D14, 6 monthly thereafter Duration: 18 months Prednisolone: at least 5 mg/d for 18 m Concomitant therapy: nil AZA arm (58 patients) Dose: 2 mg/kg/d, reducing from 12 months until 22 m Prednisolone: at least 5 mg/d for 18 m Concomitant therapy: nil	Relapse rate (28 m) RTX: 9/57 (3 major, 6 minor) AZA: 26/58 (17 major, 9 minor) Relapse free survival (60 m) RTX: 57.9% (95% CI 46.4 – 72.2) [major RFS: 71.9% (95% CI 61.2 – 84.6)] AZA: 37.2% (95% CI 26.5 – 52.2) [major RFS: 49.4% (95% CI 38.0 - 64.3)]	Hypogammaglobulinaemia RTX: 6.7 +/- 1.0 g/L AZA: 6.9 +/- 2.5 g/L (Mean +/- SD) No between group differences.	
MAINRITSAN II	162 patients with GPA/MPA (planned recruitment 66% newly diagnosed) Induction regimen: cyclophosphamide (100), rituximab (61), methotrexate (1) Experimental/on-demand arm (81) Dose: 500 mg D0, repeated every 3 monthly if B cells detected or ANCA reappears or is higher than previous Duration: 18 m Prednisolone: tapered over 18 m Concomitant therapy: nil Control/timed arm (81) Dose: 500 mg [D0, D14, 6 monthly] Duration: 18 m Prednisolone: tapered over 18 m Concomitant therapy: nil	Relapse rate (28 m) On-demand: 13/81 (14 relapses, 13 individuals) Timed: 8/81	Hypogammaglobulinaemia Not discussed	Presented as abstract only. Full results awaited.

IFX/RTX [2]	17 patients with refractory GPA <u>Rituximab arm</u> (8) Dose: 375 mg/m^2 x4 induction, 375 mg/m^2 at month 4, 8, 12 if disease response Duration: 12 m Prednisolone: according to response Concomitant therapy: nil <u>Infliximab arm</u> (9) Dose: 3 mg/kg x2 induction, 5 mg/kg/month if disease response Duration: 11 m Prednisolone: according to response Concomitant therapy: nil	<u>RTX arm</u> 4 'complete remission' 1 'partial remission' 2 treatment failures 0 relapses <u>IFX arm</u> 2 'complete remission' 1 'partial remission' 5 treatment failures 2 relapses		
RITAZAREM [5, 94]	170 patients with relapsing GPA/MPA (188 patients induced, 170 achieved remission at 4 m and randomised) Induction: RTX 375 mg/m^2 x 4 <u>Rituximab arm</u> Dose: 1g 4 monthly Duration: 20 m Prednisolone: withdrawn 20 m (from induction) Concomitant therapy: nil <u>Azathioprine arm</u> Dose: 2 mg/kg/d, tapered from 24 m to 27 m Duration: 27 m Prednisolone: withdrawn 20 m (from induction) Concomitant therapy: nil	-	<u>Hypogammaglobulinaemia</u> IgG < 5 g/L: 52/188 (28%)	Ongoing study.

GPA: granulomatosis with polyangiitis, MPA: microscopic polyangiitis, RLV: renal limited vasculitis, RTX: rituximab, AZA: azathioprine, GC: glucocorticoids, IFX: infliximab

Observational studies

Study location [reference(s)]	Patients enrolled	Treatment regimen	Relapse rate	Safety outcomes	Comments
Massachusetts General Hospital, US [Pendergraft 2014, Cortazar 2017, Pendergraft 2013, Rhee 2010]	New and relapsing disease BVAS ≥ 3 172 patients (April 2006 – March 2013) 239 patients (April 2006 – August 2015) Follow-up: median duration B cell depletion 2.4 yr (IQR 1.5, 4.0), longest 7.6 yr	Induction includes 2/12 oral cyclophosphamide Maintenance: RTX 1g (D0, D14, 4 monthly for 2 y, then 6 monthly); interval shortened if B cell return Rituximab 'add-on' therapy if transitioning from previous maintenance strategy- concomitant therapy weaned after BVAS/WG 0 achieved. Relapse on rituximab: concomitant immunosuppression added.	[Pendergraft 2014] Relapse with BVAS/WG ≥ 2: 35 patients (20%) Relapse with BVAS/WG ≥ 3: 9 patients (5%)	[Pendergraft 2014] <u>Hypogammaglobulinaemia</u> 17/172 (10%), 9 discontinued; 3 of these patients had fever with LON <u>Neutropenia</u> 17/172 (10%) 4 resolved without intervention, 13 required G-CSF. Rituximab not discontinued in any. [Cortazar 2017] <u>Hypogammaglobulinaemia</u> IgG < 400 mg/dL: 23/239 (5 commenced IVIG replacement)	Comparison of patients receiving concomitant therapy as subgroup not performed.
Mayo Clinic, US [Cartin-Ceba 2012]	GPA Refractory disease ≥ 2 RTX courses 53 patients (Jan 2000 – May 2010) Follow-up: median 4.4 y IQR 2.7-6.2; Median 4 courses (3-5)	Induction: 375 mg/m^2 x4 OR 1g D0/D14 Maintenance: 375 mg/m^2 x4 OR 1g D0/D14 Re-treated if: - Clinical relapse - ANCA rise following B cell reconstitution (no GC)	32/53 (60%) all occurred after first remission induction with RTX all occurred in context of reconstitution of B cells and associated with or preceded by ANCA rise from nadir	<u>Hypogammaglobulinaemia</u> Significant reduction in all IG post-rituximab. No comment re: thresholds for hypogamma or IG replacement.	Comparison of patients receiving concomitant therapy as subgroup not performed.

		- B cell reconstitution in ANCA neg pt (no GC) - B cell reconstitution w/o ANCA rise with prev relapse on B cell reconstitution (no GC) Any existing IS therapy except glucocorticoids was discontinued. (no comparison) Glucocorticoids: discontinued after 5 months if in remission. Not commenced if rituximab infusion provided in the absence of clinical relapse.			
Addenbrooke's Hospital, UK [Smith 2012]	GPA/MPA Refractory or relapsing disease Historically ANCA positive or histological confirmation of AAV 73 patients	Group A- on demand 2g or 375 mg/m^2 x4 induction and on clinical relapse (28 patients) - 1 concomitant (6 on IS at 2 y) Group B- timed 2g induction then 1g 6 monthly for 2 y (45 patients) - 2 concomitant (1 on IVIG at 2 y) Group C- Group A then Group B regimen (19 patients) - 0 concomitant (2 on AZA at 2 y & 1 on IVIG at 2 y)	Relapse at 2 yr A: 19/26 (73%) B: 5/43 (12%) C: 2/18 (11%) Relapse at 4 yr A: 21/26 (81%) B: 11/43 (26%) C: 7/18 (56%) At relapse 19/57 (31%) ANCA +ve; 12/57 (21%) were persistently ANCA +ve (i.e. 7 had seroconverted before relapse); no difference between the groups	Baseline IG< 7 identified in: A: 7/28 (25%) B: 8/45 (18%) C: 5/19 (26%) After 2 years; IgG <7 in: A: - B: 13/40 (33%) C: 8/18 (44%) After 3 years; IgG <7 in: A: - B: 10/28 (26%) C: 12/18 (67%)	

		Concomitant therapy generally withdrawn prior to RTX (numbers above- those who continued); (no comparisons)			
[Alberici 2015]	69 patients (Overlap of 53 patients with Smith 2012) Duration: 2 yr Rx, median f/u 59.3 mth (44.5 – 73.3)	Induction: 1g D0 and D14 Maintenance: 1g 6 monthly for 2 years Concomitant therapy routinely withdrawn [no direct comparisons] Prednisolone provided according to disease severity at flare, reduced to <5 mg/d or withdrawn during follow-up	During maintenance treatment 9/69 (13%) - 3 steroid alone - 1 earlier RTX - 5 concomittant (2 MTX 1 IVIG 1 AZA 1 LEF) After 2 years 28/69 (41%) - 22 treated with RTX or RTX/GC - Others: alemtuzumab, AZA, MMF, CYC - After 6/12: 19/28 CR 6/28 PR 3/28 active At relapse: - 14/28 were ANCA positive - 20/28 had B cell return Of the 41 non-relapsing patients: - Median pred 0 mg - 14 (34%) ANCA positive - 28 (68%) had B cell return	<u>Hypogammaglobulinaemia</u> - IgG < 6 for ≥ 3m in 28/69 (41%) - 2 required immunoglobulin replacement <u>Neutropenia</u> 2/69 (3%), 1 admitted with febrile neutropenia, neither required G-CSF	In the post-treatment follow-up: 54 ANCA negative after 2 yr RTX - 13 subsequently became ANCA positive, of which 10/13 (77%) relapsed at a median of 1.8 months following ANCA switch - ANCA switch was associated with major but not minor relapse Patients who had B cells detectable within 12/12 of last RTX maintenance infusion had a shorter time to relapse than those whose B cells returned after 12/12

[Jones 2010]	AAV (75% GPA) Relapsing or refractory disease 106 patients Duration: median follow-up 31m (4-56)	<u>Timed (fixed-interval) group</u> (72) Induction: 1g x2 Maintenance: 1g 6 monthly for 2 years <u>On-demand group</u> (34) Induction: 1g x2 or 375 mg/m^2 x4 Maintenance: 1g x2 OR 375 mg/m^2 x 4 on clinical relapse	<u>Relapse at 2 years</u> Timed: 16/72 (22%) On demand: 24/34 (71%) <u>Relapse at end follow-up</u> Timed: 21/72 (71%) On demand: 26/34 (76%)	Not discussed	Abstract only
[Martinez Del Pero 2009]	GPA with refractory head and neck involvement 34 patients (2002 – 2008) Duration: median follow-up 33 months	Induction: 1g x2 or 375 mg/m^2 x4 Maintenance: re-dosed on clinical relapse or with persistent disease (19 patients), or fixed interval 1g 6 monthly (15 patients) Concomitant therapy - 30 (88%) prior to RTX - 5 (15%) after 6/12 - 25% at 12/12 - 14% at 18/12	7/28 (25%) [4 patients failed to respond to treatment] 16 retreated owing to incomplete response or early sx but not meeting definition for “true relapse”	Neutropenia: 2/34 (6%)	
[Roberts 2015]	243 patients (160 with AAV receiving rituximab-median total 6 g IQR 3-8 g)			Hypogammaglobulinaemia 34/223 (15%) IgG 5-7 13/223 (6%) IgG 3-5 2/223 (1%) IgG <3 12 patients initiated on IG Replacement	

Cochin Hospital, France [Calich 2014]	GPA Refractory disease 60 patients (2002 – 2013) Duration: 18 m; follow-up 34.2+/- 26.2 months	Induction: 375 mg/m^2 x4 OR 1g D0/D14 Maintenance: 375 mg/m^2 or 500 mg 6 monthly for 18 months Concomitant treatment generally ceased; continued in 16 pts (AZA: 4, MTX: 3, CYC: 6, MMF: 3). No difference in comparisons. 62.1% received co-trimoxazole - 26 (39.4%) PCP prophylaxis - 15 (22.7%) as maintenance	8/66 (12.1%) relapsed - 5 relapses occurred in the first 2 years - 2 occurred without B cell reconstitution 2 relapses without ANCA rise	Hypogammaglobulinaemia IgG <7 in 1/66 Late onset neutropenia 1/66	
Cochin Hospital, France [Roubaud-Baudron 2012]	GPA or MPA Newly diagnosed or relapsing disease 28 patients (2003-2010) Duration: median courses 4 (IQR 2-10), median follow-up 38 m (IQR 21-97)	Induction: RTX 1g x2 or 375 mg/m^2 x4 (21), or CYC (5), IVIG (1), MTX (1) Maintenance: RTX 375 mg/m^2 6 monthly (13), 1g 6 monthly (4), 1g annually (3), other (8) Concomitant IS in 14/28 AZA 6, MMF 5, LEF 1, MTX 4; subsequently ceased in 7) (no comparison) Concomitant steroids in 23 at baseline, reduced to 16 thereafter	2/28 (7%)	Not discussed	Comparison of patients receiving concomitant therapy as subgroup not performed.
France- FVSG [Charles 2014]	GPA/MPA/EGPA Newly diagnosed and relapsing disease	Induction: RTX 375 mg/m^2 x4 (54), 1g x2 (16), other (3)	18/80 (23%) relapsed (inclusive of patients who received induction but not maintenance)	<u>Neutropenia</u> 1 (febrile neutropenia)	

	64 patients (Jan 2002 – Jan 2011) Duration: follow-up median 18/12 (IQR 12- 37)	Maintenance: 375 mg/m^2 6 monthly (18), 500 mg 6 monthly (10), 1g 6 monthly (8), annual infusion (3), other (3) Concomitant therapy 9/70 (AZA 4, MTX 2, MMF 1, MMF + MTX 1, chlorambucil 1, IVIG 1, MTX + IVIG 1) (no difference in outcomes)	- 2 relapses occurred within 6 months of last rituximab infusion - 11/17 ANCA positive at time of relapse		
Leeds, UK [Md Yusof 2015] [Md Yusof 2013]	37 patients	Induction: RTX 1g x2 Maintenance: 1g x2 on clinical relapse (BVAS ≥ 1) Concomitant: 18/37 (MTX 7, AZA 7, MMF 5). No difference in outcomes. Glucocorticoid: per treating clinician	31 relapses in 35 patients	[Md Yusof 2013] Hypogammaglobulinaemia 4/29 at baseline 1/30 IgG <6 newly identified Difference in IgG level after repeat cycles of rituximab compared with baseline non-significant.	With each cycle/course, VDI increased in- 2/35 (6%) cycle 1, 3/27 (11%) cycle 2, 0/17 cycle 3, 1/11 (9%) cycle 4, 0/6 (0%) C5 by 1 point.
RAVE follow-up [Miloslavsky 2014]	GPA or MPA, included in RAVE trial 6-18 m after initial rituximab 99 patients Duration: 18 m of follow-up	Induction: RTX 375 mg/m^2 x4 Maintenance: 375 mg/m^2 x4 on clinical relapse (BVAS/WG > 3 or 1 major item) Concomitant IS: nil. Glucocorticoid taper: protocol per RAVE, aim for withdrawal by 20 weeks	15 relapsed (receiving 2nd cycle) At severe relapse, ANCA was increasing in 77% and B cells detectable or reconstituted in 85%. 1 patient was negative for ANCA and had depleted B cells. [NB: 2/3 of patients in RTX arm of this trial had detectable B cells without relapse]		

Tromso, Norway [Besada 2013, Besada 2014, Besada 2016]	GPA Newly diagnosed and relapsing disease 35 GPA (April 2004 – September 2011) (6 new, 28 relapsing) Duration: median courses 5 (1-10) cumulative dose 8 (2-13), f/u 47 (2-88)	Induction: Maintenance: 1 g 6 monthly (or 1g x2 yearly) Concomitant IS agent, not reported which. - In report of 29 pts, AZA/MMF/MTX/CYC At completion of follow-up only 3/22 still on rtx had concomitant therapy [no comparison]	8/35 relapsed (9 relapses in total) 2- no B cells detected 6- no ANCA rise (2 patients retreated for grumbling disease, both B cell deplete and ANCA negative)	<u>Hypogammaglobulinaemia</u> 8/35 patients, 5 commenced on IG replacement. 2 patients who received IVIG retreated with RTX. <u>Neutropenia</u> 1/35 pts	
EGPA					
Multi-centre [Mohammad 2016]	EGPA 41 patients; 22 received >1 RTX course	Induction: 375 mg/m^2 x4 or 1g x2 Maintenance: 375 mg/m^2 x4, 1g x2, 1g, or 600 mg (protocol for re-treatment variable) Concomitant IS: 16/41 (no comparisons)	34/41 (83%) response at 6 months with only 1 true non-responder after repeated treatment. 4/34 patients who had improved at 6 m experienced relapse at 12 m.	<u>Hypogammaglobulinaemia</u> - Baseline: 6/35 (17%) - 6 m: 9/27 (33%) - 12 m: 8/22 (36%)	

RTX: rituximab, CYC: cyclophosphamide, AZA: azathioprine, MMF: mycophenolate mofetil, MTX: methotrexate, LEF: leflunomide, IG: immunoglobulin,

Search strategy

Initial search

Pubmed

(Systemic vasculitis [MH] OR Systemic vasculiti* [TIAB] OR Pauci-Immune Vasculiti* [TIAB] OR Churg Strauss [tiab] OR Eosinophilic Granulomato* [TIAB] OR Wegener* [TIAB] OR Granulomatosis with Polyangiiti* [TIAB] OR Microscopic Polyangiiti* [TiAB] OR Periarteritis Nodosa [TIAB] OR Polyarteritis nodosa [TIAB] OR necrotising vasculiti* [TIAB] OR necrotizing vasculiti* [TIAB] OR Antibodies, antineutrophil cytoplasmic [MH] OR Anti Neutrophil Cytoplasmic Antibod* [TIAB] OR Anti Neutrophil Cytoplasm Antibod* [TIAB] OR AntiNeutrophil Cytoplasm Antibod* [TIAB] OR AntiNeutrophil Cytoplasmic Antibod* [TIAB] OR ANCA* [TIAB] OR cANCA [TIAB] OR pANCA [TIAB] OR pANCAs [TIAB]) AND (Rituximab [MH] OR Rituximab [TIAB] OR Mabthera [TIAB] OR Rituxan [TIAB] OR B-Lymphocytes/drug effects [MH])

Pubmed central

(Systemic vasculitis [MH] OR Systemic vasculiti* [all] OR Pauci-Immune Vasculiti* [all] OR Churg Strauss [all] OR Eosinophilic Granulomato* [all] OR Wegener* [all] OR Granulomatosis with Polyangiiti* [all] OR Microscopic Polyangiiti* [all] OR Periarteritis Nodosa [all] OR Polyarteritis nodosa [all] OR necrotising vasculiti* [all] OR Antibodies, antineutrophil cytoplasmic [MH] OR Anti Neutrophil Cytoplasmic Antibod* [all] OR Anti Neutrophil Cytoplasm Antibod* [all] OR AntiNeutrophil Cytoplasm Antibod* [all] OR AntiNeutrophil Cytoplasmic Antibod* [all] OR ANCA* [all] OR cANCA [all] OR pANCA [all] OR pANCAs [all]) AND (Rituximab [MH] OR Rituximab [all] OR Mabthera [all] OR Rituxan [all] OR B-Lymphocytes/drug effects [MH])

Medline

Systemic vasculiti$.tw. OR Pauci-Immune Vasculiti$.tw. OR Churg Strauss.tw. OR Eosinophilic Granulomato$.tw. OR Wegener$.tw. OR Granulomatosis with Polyangiiti$.tw. OR Granulomatosis ADJ3 Polyangiiti$.tw. OR Microscopic Polyangiiti$.tw. OR necrotising vasculiti$.tw. OR Antibodies, antineutrophil cytoplasmic [MH] OR Anti Neutrophil Cytoplasmic Antibod$.tw. OR Anti Neutrophil Cytoplasm Antibod$.tw. OR AntiNeutrophil Cytoplasm Antibod$.tw. OR AntiNeutrophil Cytoplasmic Antibod$.tw. OR ANCA$.tw. OR cANCA.tw. OR pANCA.tw. OR pANCAs.tw.) AND (Rituximab [MH] OR Rituximab.tw. OR Mabthera.tw. OR Rituxan.tw. OR B-Lymphocytes/drug effects [MH])

Embase

(systemic NEXT/1 vasculiti* OR 'Pauci-Immune Vasculitis' OR 'Pauci-Immune Vasculitides' OR 'Churg Strauss' OR eosinophilic next/5 granulomato* OR wegener*:ti,ab OR granulomatosis NEAR/5 polyangiitis OR microscopic NEXT/1 polyangiiti* OR "periarteritis nodosa" OR "polyarteritis nodosa" OR necrotising NEXT/1 vasculiti* OR necrotizing NEXT/1 vasculiti* OR "neutrophil cytoplasmic antibody"/syn OR neutrophil NEXT/1 cytoplasm* next/1 antibod* oR AntiNeutrophil NEXT/1 Cytoplasm* NEXT/1 Antibod* OR "ANCA associated vasculitis"/syn OR ANCA OR cANCA OR pANCA OR pANCAs) AND ("rituximab"/syn OR "CD20 antibody"/syn)

Additional pubmed searches for sub-topics

Co-trimoxazole

(("antibodies, antineutrophil cytoplasmic"[MeSH Terms] OR ("antibodies"[All Fields] AND "antineutrophil"[All Fields] AND "cytoplasmic"[All Fields]) OR "antineutrophil cytoplasmic antibodies"[All Fields] OR "anca"[All Fields])) AND (("trimethoprim, sulfamethoxazole drug combination"[MeSH Terms] OR ("trimethoprim"[All Fields] AND "sulfamethoxazole"[All Fields] AND "drug"[All Fields] AND "combination"[All Fields]) OR "sulfamethoxazole drug combination trimethoprim"[All Fields] OR ("co"[All Fields] AND "trimoxazole"[All Fields]) OR "co trimoxazole"[All Fields])) OR ((("pneumonia, pneumocystis"[MeSH Terms] OR ("pneumonia"[All Fields] AND "pneumocystis"[All Fields]) OR "pneumocystis pneumonia"[All Fields] OR "pneumocystis"[All Fields] OR "pneumocystis"[MeSH Terms])))

Vaccination

((("vaccination"[MeSH Terms] OR "vaccination"[All Fields]))) AND (("anti-neutrophil cytoplasmic antibody-associated vasculitis"[MeSH Terms] OR ("anti-neutrophil"[All Fields] AND "cytoplasmic"[All Fields] AND "antibody-associated"[All Fields] AND "vasculitis"[All Fields]) OR "anti-neutrophil cytoplasmic antibody-associated vasculitis"[All Fields] OR ("anca"[All Fields] AND "associated"[All Fields] AND "vasculitis"[All Fields]) OR "anca associated vasculitis"[All Fields]) OR “anca” OR “rituximab”[MeSH Terms] OR “rituximab”[All Fields]))

Hypogammaglobulinaemia

((((("hypogammaglobulinaemia"[All Fields] OR "agammaglobulinemia"[MeSH Terms] OR "agammaglobulinemia"[All Fields] OR "hypogammaglobulinemia"[All Fields])) OR ((acquired[All Fields] AND ("immunologic deficiency syndromes"[MeSH Terms] OR ("immunologic"[All Fields] AND "deficiency"[All Fields] AND "syndromes"[All Fields]) OR "immunologic deficiency syndromes"[All Fields] OR "immunodeficiency"[All Fields])))))) AND (("rituximab"[MeSH Terms] OR "rituximab"[All Fields]))

Late onset neutropenia

("neutropenia"[MeSH Terms] OR "leukopenia"[MeSH Terms])) AND ("rituximab"[MeSH Terms] OR "rituximab"[All Fields])

Progressive multifocal leukoencephalopathy

(((((Systemic vasculitis [MH] OR Systemic vasculiti* [TIAB] OR Pauci-Immune Vasculiti* [TIAB] OR Churg Strauss [tiab] OR Eosinophilic Granulomato* [TIAB] OR Wegener* [TIAB] OR Granulomatosis with Polyangiiti* [TIAB] OR Microscopic Polyangiiti* [TiAB] OR Periarteritis Nodosa [TIAB] OR Polyarteritis nodosa [TIAB] OR necrotising vasculiti* [TIAB] OR necrotizing vasculiti* [TIAB] OR Antibodies, antineutrophil cytoplasmic [MH] OR Anti Neutrophil Cytoplasmic Antibod* [TIAB] OR Anti Neutrophil Cytoplasm Antibod* [TIAB] OR AntiNeutrophil Cytoplasm Antibod* [TIAB] OR AntiNeutrophil Cytoplasmic Antibod* [TIAB] OR ANCA* [TIAB] OR cANCA [TIAB] OR pANCA [TIAB] OR pANCAs [TIAB]))) OR ((Rituximab [MH] OR Rituximab [TIAB] OR Mabthera [TIAB] OR Rituxan [TIAB] OR B-Lymphocytes/drug effects [MH]))) AND (("leukoencephalopathy, progressive multifocal"[MeSH Terms] OR ("leukoencephalopathy"[All Fields] AND "progressive"[All Fields] AND "multifocal"[All Fields]) OR "progressive multifocal leukoencephalopathy"[All Fields] OR ("progressive"[All Fields] AND "multifocal"[All Fields] AND "leukoencephalopathy"[All Fields]))

References

1. Guillevin, L., et al., *Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis.* N Engl J Med, 2014. **371**(19): p. 1771-80.
2. de Menthon, M., et al., *Infliximab or rituximab for refractory Wegener's granulomatosis: long-term follow up. A prospective randomised multicentre study on 17 patients.* Clin Exp Rheumatol, 2011. **29**(1 Suppl 64): p. S63-71.
3. Charles, P., et al., *Comparison of systematic vs individually tailored rituximab regimen to maintain anca-associated-vasculitis remission: Results of a prospective, randomized-controlled, phase 3 trial.* Arthritis and Rheumatology, 2016. **68**: p. 4384-4386.
4. Terrier, B., et al. *Rituximab versus azathioprine to maintain remission of ANCA associated vasculitides (MAINRITSAN): follow-up at 60 months*. Arthritis and rheumatology. Conference: american college of rheumatology/association of rheumatology health professionals annual scientific meeting, ACR/ARHP 2016. United states. Conference start: 20161111. Conference end: 20161116, 2016. **68**, 2480-2481 DOI: 10.1002/art.39977.
5. Smith, R., et al. *Ritazarem: An international, open label, randomised controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing anca associated vasculitis*. Nephrology Dialysis Transplantation, 2013. **28**, i180-i181 DOI: 10.1093/ndt/gft113.
6. Mohammad, A.J., et al., *Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss).* Ann Rheum Dis, 2016. **75**(2): p. 396-401.
7. Basu, N., et al., *Fatigue: a principal contributor to impaired quality of life in ANCA-associated vasculitis.* Rheumatology (Oxford), 2010. **49**(7): p. 1383-90.
8. Basu, N., et al., *Markers for work disability in anti-neutrophil cytoplasmic antibody-associated vasculitis.* Rheumatology (Oxford), 2014. **53**(5): p. 953-6.
9. Pugnet, G., et al., *Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life.* Clin Exp Rheumatol, 2016. **34**(3 Suppl 97): p. S54-9.
10. Raimundo, K., et al., *Clinical and economic burden of antineutrophil cytoplasmic antibody-associated vasculitis in the United States.* Journal of Rheumatology, 2015. **42**(12): p. 2383-2391.
11. Montante A, et al., *Economic evaluation of rituximab versus azathioprine for maintenance treatment of ANCA-associated vasculitis. A prospective, multicenter study.* Arthritis & Rheumatology, 2017. **2017**(69 (suppl 10)).
12. Jones, R.B., et al., *A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis.* Arthritis Rheum, 2009. **60**(7): p. 2156-68.
13. Smith, R.M., et al., *Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis.* Arthritis Rheum, 2012. **64**(11): p. 3760-9.
14. Pendergraft, W.F., 3rd, et al., *Long-term maintenance therapy using rituximab-induced continuous B-cell depletion in patients with ANCA vasculitis.* Clin J Am Soc Nephrol, 2014. **9**(4): p. 736-44.
15. Alberici, F., et al., *Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis.* Rheumatology (Oxford), 2015. **54**(7): p. 1153-60.
16. Calich, A.L., et al., *Rituximab for induction and maintenance therapy in granulomatosis with polyangiitis (Wegener's). Results of a single-center cohort study on 66 patients.* J Autoimmun, 2014. **50**: p. 135-41.
17. Roubaud-Baudron, C., et al., *Rituximab maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis.* J Rheumatol, 2012. **39**(1): p. 125-30.
18. Besada, E., W. Koldingsnes, and J.C. Nossent, *Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre.* Rheumatology (Oxford), 2013. **52**(11): p. 2041-7.
19. Walsh, M., et al., *Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: A meta-analysis.* Arthritis Care Res (Hoboken), 2010. **62**(8): p. 1166-73.

20. Karras, A., et al., *Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis.* Ann Rheum Dis, 2017. **76**(10): p. 1662-1668.
21. Robson, J., et al., *Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials.* Rheumatology (Oxford), 2015. **54**(3): p. 471-81.
22. Terrier, B., et al. *Rituximab versus azathioprine for maintenance in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (mainritsan): Follow up at 34 months*. Annals of the rheumatic diseases, 2013. **72**, DOI: 10.1136/annrheumdis-2013-eular.418.
23. Pendergraft, W., et al., *Maintenance therapy using rituximab-induced continuous B cell depletion for ANCA vasculitis.* Presse Medicale, 2013. **42**(4): p. 774-775.
24. Cartin-Ceba, R., F.C. Fervenza, and U. Specks, *Treatment of antineutrophil cytoplasmic antibody-associated vasculitis with rituximab.* Curr Opin Rheumatol, 2012. **24**(1): p. 15-23.
25. Fussner, L.A., et al., *Factors Determining the Clinical Utility of Serial Measurements of Antineutrophil Cytoplasmic Antibodies Targeting Proteinase 3.* Arthritis Rheumatol, 2016. **68**(7): p. 1700-10.
26. Terrier, B., et al., *Factors predictive of ANCA-associated vasculitis relapse in patients given rituximab-maintenance therapy.* Arthritis and Rheumatology, 2014. **66**: p. S779.
27. Charles, P., et al., *Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients.* Rheumatology (Oxford), 2014. **53**(3): p. 532-9.
28. Md Yusof, M.Y., et al., *Repeat cycles of rituximab on clinical relapse in ANCA-associated vasculitis: identifying B cell biomarkers for relapse to guide retreatment decisions.* Ann Rheum Dis, 2015. **74**(9): p. 1734-8.
29. Tesfa, D., et al., *Late-onset neutropenia following rituximab therapy in rheumatic diseases: association with B lymphocyte depletion and infections.* Arthritis Rheum, 2011. **63**(8): p. 2209-14.
30. Jayne, D., et al., *Efficacy and safety of belimumab in combination with azathioprine for remission maintenance in granulomatosis with polyangiitis and microscopic polyangiitis: a multicenter randomized, placebo-controlled study.* Arthritis & Rheumatology, 2017. **69 (suppl 10)**.
31. Marco, H., et al., *The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease.* BMC Musculoskeletal Disorders, 2014. **15**(1).
32. Cartin-Ceba, R., et al., *Rituximab for remission induction and maintenance in ANCA-associated vasculitis: A single-center ten-year experience in 108 patients.* Arthritis and Rheumatism, 2010. **62**: p. 680.
33. DeRemee, R.A., T.J. McDonald, and L.H. Weiland, *Wegener's granulomatosis: observations on treatment with antimicrobial agents.* Mayo Clin Proc, 1985. **60**(1): p. 27-32.
34. Stegeman, C.A., et al., *Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group.* N Engl J Med, 1996. **335**(1): p. 16-20.
35. Zycinska, K., et al., *Co-trimoxazole and prevention of relapses of PR3-ANCA positive vasculitis with pulmonary involvement.* Eur J Med Res, 2009. **14 Suppl 4**: p. 265-7.
36. Besada, E., W. Koldingsnes, and J.C. Nossent, *Staphylococcus Aureus carriage and long-term Rituximab treatment for Granulomatosis with polyangiitis.* PeerJ, 2015. **3**: p. e1051.
37. Jarrousse, B., et al., *Increased risk of Pneumocystis carinii pneumonia in patients with Wegener's granulomatosis.* Clin Exp Rheumatol, 1993. **11**(6): p. 615-21.
38. Kronbichler, A., D.R. Jayne, and G. Mayer, *Frequency, risk factors and prophylaxis of infection in ANCA-associated vasculitis.* Eur J Clin Invest, 2015. **45**(3): p. 346-68.
39. Jones, R.B., et al., *Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis.* New England Journal of Medicine, 2010. **363**(3): p. 211-20.
40. Stone, J.H., et al., *Rituximab versus cyclophosphamide for ANCA-associated vasculitis.* N Engl J Med, 2010. **363**(3): p. 221-32.
41. Pagnoux, C., et al., *Comparability of patients with ANCA-associated vasculitis enrolled in clinical trials or in observational cohorts.* Clin Exp Rheumatol, 2015. **33**(2 Suppl 89): p. S-77-83.

42. Chang, C.C., et al., *Effects of annual influenza vaccination on morbidity and mortality in patients with Systemic Lupus Erythematosus: A Nationwide Cohort Study.* Sci Rep, 2016. **6**: p. 37817.
43. Morgan, M.D., et al., *Association of Low B Cell Count and IgG Levels with Infection, and Poor Vaccine Response with All-Cause Mortality in an Immunosuppressed Vasculitis Population.* Arthritis Care and Research, 2016. **68**(6): p. 853-860.
44. Jeffs, L.S., et al., *Viral RNA in the influenza vaccine may have contributed to the development of ANCA-associated vasculitis in a patient following immunisation.* Clin Rheumatol, 2016. **35**(4): p. 943-51.
45. Santos-Ocampo, A.S., *Elevated anti-neutrophil cytoplasmic antibodies without vasculitis after influenza vaccination.* J Clin Rheumatol, 2012. **18**(5): p. 276-7.
46. Watanabe, T., *Vasculitis following influenza vaccination: A review of the literature.* Curr Rheumatol Rev, 2017.
47. Spaetgens, B., P. van Paassen, and J.W. Tervaert, *Influenza vaccination in ANCA-associated vasculitis.* Nephrol Dial Transplant, 2009. **24**(10): p. 3258; author reply 3259.
48. Jeffs, L.S., et al., *Randomized trial investigating the safety and efficacy of influenza vaccination in patients with antineutrophil cytoplasmic antibody-associated vasculitis.* Nephrology (Carlton), 2015. **20**(5): p. 343-51.
49. Holvast, A., et al., *Wegener's granulomatosis patients show an adequate antibody response to influenza vaccination.* Ann Rheum Dis, 2009. **68**(6): p. 873-8.
50. Kapetanovic, M.C., et al., *Impact of anti-rheumatic treatment on immunogenicity of pandemic H1N1 influenza vaccine in patients with arthritis.* Arthritis Res Ther, 2014. **16**(1): p. R2.
51. Rehnberg, M., et al., *Vaccination response to protein and carbohydrate antigens in patients with rheumatoid arthritis after rituximab treatment.* Arthritis Res Ther, 2010. **12**(3): p. R111.
52. van Assen, S., et al., *Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab.* Arthritis Rheum, 2010. **62**(1): p. 75-81.
53. Hua, C., et al., *Effect of methotrexate, anti-tumor necrosis factor alpha, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis.* Arthritis Care Res (Hoboken), 2014. **66**(7): p. 1016-26.
54. Zycinska, K., et al., *Antibody response to inactivated subunit influenza vaccine in patients with Wegener's granulomatosis.* J Physiol Pharmacol, 2007. **58 Suppl 5**(Pt 2): p. 819-28.
55. Westra, J., et al., *Rituximab impairs immunoglobulin (Ig)M and IgG (subclass) responses after influenza vaccination in rheumatoid arthritis patients.* Clin Exp Immunol, 2014. **178**(1): p. 40-7.
56. Holvast, A., et al., *Cell-mediated immune responses to influenza vaccination in Wegener's granulomatosis.* Ann Rheum Dis, 2010. **69**(5): p. 924-7.
57. Muller, R.B., et al., *Efficient boosting of the antiviral T cell response in B cell-depleted patients with autoimmune rheumatic diseases following influenza vaccination.* Clin Exp Rheumatol, 2013. **31**(5): p. 723-30.
58. Arad, U., et al., *The cellular immune response to influenza vaccination is preserved in rheumatoid arthritis patients treated with rituximab.* Vaccine, 2011. **29**(8): p. 1643-8.
59. Heusele, M., et al., *Risk factors for severe bacterial infections in patients with systemic autoimmune diseases receiving rituximab.* Clinical Rheumatology, 2014. **33**(6): p. 799-805.
60. Bingham, C.O., 3rd, et al., *Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial.* Arthritis Rheum, 2010. **62**(1): p. 64-74.
61. Nguyen, M.T.T., et al., *Initial Serological Response after Prime-boost Pneumococcal Vaccination in Rheumatoid Arthritis Patients: Results of a Randomized Controlled Trial.* J Rheumatol, 2017.
62. Reddy, V., et al., *Pragmatic Treatment of Patients With Systemic Lupus Erythematosus With Rituximab: Long-Term Effects on Serum Immunoglobulins.* Arthritis Care Res (Hoboken), 2017. **69**(6): p. 857-866.

63. van Vollenhoven, R.F., et al., *Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials.* J Rheumatol, 2010. **37**(3): p. 558-67.
64. Besada, E., *Low immunoglobulin levels increase the risk of severe hypogammaglobulinemia in granulomatosis with polyangiitis patients receiving rituximab.* BMC Musculoskelet Disord, 2016. **17**: p. 6.
65. Specks, U., et al. *Immunoglobulin concentrations and infection risk among patients with ANCA-associated vasculitis treated with rituximab or cyclophosphamide*. Arthritis and rheumatism, 2011. **63**.
66. Cortazar, F.B., et al., *Effect of Continuous B Cell Depletion With Rituximab on Pathogenic Autoantibodies and Total IgG Levels in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis.* Arthritis Rheumatol, 2017. **69**(5): p. 1045-1053.
67. Besada, E., *Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis.* Rheumatology (Oxford, England), 2014. **53**(10): p. 1818-1824.
68. Roberts, D.M., et al., *Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease.* J Autoimmun, 2015. **57**: p. 60-5.
69. Venhoff, N., et al., *Impact of rituximab on immunoglobulin concentrations and B cell numbers after cyclophosphamide treatment in patients with ANCA-associated vasculitides.* PLoS One, 2012. **7**(5): p. e37626.
70. Tesfa, D., et al., *Late-onset neutropenia associated with rituximab therapy: evidence for a maturation arrest at the (pro)myelocyte stage of granulopoiesis.* Med Oncol, 2008. **25**(4): p. 374-9.
71. Keane, C., et al., *Homozygous FCGR3A-158V alleles predispose to late onset neutropenia after CHOP-R for diffuse large B-cell lymphoma.* Intern Med J, 2012. **42**(10): p. 1113-9.
72. Anolik, J.H., et al., *The relationship of FcgammaRIIIa genotype to degree of B cell depletion by rituximab in the treatment of systemic lupus erythematosus.* Arthritis Rheum, 2003. **48**(2): p. 455-9.
73. Knight, A., et al., *Late-onset neutropenia after rituximab in ANCA-associated vasculitis.* Scand J Rheumatol, 2016. **45**(5): p. 404-7.
74. Besada, E., W. Koldingsnes, and J. Nossent, *Characteristics of late onset neutropenia in rheumatologic patients treated with rituximab: a case review analysis from a single center.* Qjm, 2012. **105**(6): p. 545-50.
75. Monaco, W.E., J.D. Jones, and W.F. Rigby, *Rituximab associated late-onset neutropenia-a rheumatology case series and review of the literature.* Clin Rheumatol, 2016. **35**(10): p. 2457-62.
76. Breuer, G.S., et al., *Late-onset neutropenia following rituximab treatment for rheumatologic conditions.* Clin Rheumatol, 2014. **33**(9): p. 1337-40.
77. Reitblat, T., A. Wechsler, and O. Reitblat, *Rituximab-related late-onset neutropenia in patients with rheumatic diseases: successful re-challenge of the treatment.* Am J Case Rep, 2015. **16**: p. 211-4.
78. Marotte, H., et al., *Rituximab-related late-onset neutropenia in a patient with severe rheumatoid arthritis.* Ann Rheum Dis, 2008. **67**(6): p. 893-4.
79. Ettinger, J., et al., *[Progressive multifocal leukoencephalopathy in Wegener's granulomatosis in relation to therapy with cyclosporin A].* Klin Wochenschr, 1989. **67**(4): p. 260-4.
80. Choy, D.S., A. Weiss, and P.T. Lin, *Progressive multifocal leukoencephalopathy following treatment for Wegener's granulomatosis.* Jama, 1992. **268**(5): p. 600-1.
81. Morgenstern, L.B. and C.A. Pardo, *Progressive multifocal leukoencephalopathy complicating treatment for Wegener's granulomatosis.* J Rheumatol, 1995. **22**(8): p. 1593-5.
82. Pagnoux, C., et al., *JC virus leukoencephalopathy complicating Wegener's granulomatosis.* Joint Bone Spine, 2003. **70**(5): p. 376-9.
83. Pugnet, G., et al., *Progressive multifocal encephalopathy after cyclophosphamide in granulomatosis with polyangiitis (Wegener) patients: case report and review of literature.* Clin Exp Rheumatol, 2013. **31**(1 Suppl 75): p. S62-4.

84. Fleischmann, R.M., *Safety of Biologic Therapy in Rheumatoid Arthritis and Other Autoimmune Diseases: Focus on Rituximab.* Seminars in Arthritis and Rheumatism, 2009. **38**(4): p. 265-280.
85. Carson, K.R., et al., *Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project.* Blood, 2009. **113**(20): p. 4834-40.
86. Harris, H.E., *Progressive multifocal leucoencephalopathy in a patient with systemic lupus erythematosus treated with rituximab.* Rheumatology (Oxford), 2008. **47**(2): p. 224-5.
87. Marie, I., E. Guegan-Massardier, and H. Levesque, *Progressive multifocal leukoencephalopathy in refractory polymyositis treated with rituximab.* Eur J Intern Med, 2011. **22**(3): p. e13-4.
88. Min, L., et al., *Reversible posterior leukoencephalopathy in connective tissue diseases.* Semin Arthritis Rheum, 2006. **35**(6): p. 388-95.
89. Clifford, D.B., et al., *Rituximab-associated progressive multifocal leukoencephalopathy in rheumatoid arthritis.* Arch Neurol, 2011. **68**(9): p. 1156-64.
90. Berntsson, S.G., et al., *Progressive Multifocal Leukoencephalopathy and Systemic Lupus Erythematosus: Focus on Etiology.* Case Rep Neurol, 2016. **8**(1): p. 59-65.
91. Belhassen-Garcia, M., et al., *Atypical progressive multifocal leukoencephalopathy in a patient with antisynthetase syndrome.* Intern Med, 2015. **54**(5): p. 519-24.
92. Warnatz, K., et al., *Infectious CNS disease as a differential diagnosis in systemic rheumatic diseases: three case reports and a review of the literature.* Ann Rheum Dis, 2003. **62**(1): p. 50-7.
93. Brunetta, P., et al. *Two case reports of progressive multifocal leukoencephalopathy (PML) in granulomatosis polyangiitis (GPA) treated with rituximab*. in *17th International Vasculitis & ANCA Workshop*. 2015. London, UK.
94. Smith, R., et al., *Rituximab as re-induction therapy in relapsing ANCA-associated vasculitis.* Arthritis & Rheumatology, 2017. **69**(suppl 10).

3.3 Manuscript: Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines. Executive summary.

Statement of Authorship

Title of Paper	Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines
Publication Status	Published
Publication Details	Tieu, J., R. Smith, N. Basu, P. Brogan, D. D'Cruz, N. Dhaun, O. Flossmann, L. Harper, R. B. Jones, P. C. Lanyon, R. A. Luqmani, S. P. McAdoo, C. Mukhtyar, F. A. Pearce, C. D. Pusey, J. C. Robson, A. D. Salama, L. Smyth, R. A. Watts, L. C. Willcocks and D. R. W. Jayne (2020). "Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines." Rheumatology (Oxford) **59**(4): e24-e32.

Principal author

Candidate name	Joanna Tieu
Overall percentage	75%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signature Date 08/11/2021

Co-author contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Rona Smith
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature *for Rona Smith* Date 14/12/2021

Name of Co-Author	Neil Basu
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 08/11/2021

Name of Co-Author	Paul Brogan
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 26/11/2021

Name of Co-Author	David D'Cruz
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 09/11/2021

Name of Co-Author	Neeraj Dhaun
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 08/11/2021

Name of Co-Author	Oliver Flossmann
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 08/11/2021

Name of Co-Author	Lorraine Harper
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 08/11/2021

Name of Co-Author	Rachel Jones
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 09/12/2021

Name of Co-Author	Peter Lanyon
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 17/11/2021

Name of Co-Author	Raashid Luqmani
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 09/11/2021

Name of Co-Author	Stephen McAdoo
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 08/11/2021

Name of Co-Author	Chetan Mukhtyar
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 08/11/2021

Name of Co-Author	Fiona Pearce
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 17/11/2021

Name of Co-Author	Charles Pusey
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 08/11/2021

Name of Co-Author	Joanna Robson
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 29/11/2021

Name of Co-Author	Alan Salama
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 08/11/2021

Name of Co-Author	Richard Watts
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 10/11/2021

Name of Co-Author	Lisa Willcocks
Contribution	Contributed to data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature ate 10/11/2021

Name of Co-Author	David Jayne
Contribution	Contributed to study design, data acquisition, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 24/11/2021

RHEUMATOLOGY

Rheumatology 2020;59:727–731
doi:10.1093/rheumatology/kez632
Advance Access publication 24 February 2020

Guideline

British Society for Rheumatology

Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines—Executive summary

Joanna Tieu [1,2], Rona Smith[1], Neil Basu[3], Paul Brogan[4,5], David D'Cruz[6], Neeraj Dhaun [7,8], Oliver Flossmann[9], Lorraine Harper[10], Rachel B. Jones[1,11], Peter C. Lanyon[12,13], Raashid A. Luqmani[14], Stephen P. McAdoo[15], Chetan Mukhtyar [16,17], Fiona A. Pearce[18,19], Charles D. Pusey[15], Joanna C. Robson[20,21], Alan D. Salama[22,23], Lucy Smyth[24], Richard A. Watts[25,26], Lisa C. Willcocks[11] and David R. W. Jayne[1,27]

Key words: rituximab, ANCA-associated vasculitis, hypogammaglobulinaemia, *Pneumocystis jirovecii*, practise guideline

[This is the executive summary of Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines: full guideline, doi: 10.1093/rheumatology/kez640]

Background

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) encompasses three disease phenotypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Considerable improvements in therapy mean induction of remission occurs in most patients with AAV [1–4]. However, disease relapse continues to pose a burden to patients. Morbidity accrues with relapses through disease-related damage and adverse effects of therapies to manage these relapses, negatively impacting on quality of life [5].

Rituximab (RTX), a monoclonal antibody targeting CD20, leads to peripheral B cell depletion. This has been successfully trialled, and is licensed, for the induction and maintenance of remission in AAV [2, 3]. RTX is increasingly being used for the maintenance of remission in patients with AAV, to reduce the risk of relapse and its consequences [6]. Other commonly used agents that have been trialled for the maintenance of remission in AAV include azathioprine, methotrexate and mycophenolate [7–9]. The decision to select RTX for the maintenance of remission is multifactorial, including but not limited to, patient-related factors and preferences, previous treatment and response, consideration of the overall risk of relapse, and access to therapy. These guidelines have been developed by a group of physicians practising in the UK.

[1]Department of Medicine, University of Cambridge, Cambridge, UK, [2]Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia, [3]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, [4]University College London Great Ormond Institute of Child Health, [5]Great Ormond Street Hospital NHS Foundation Trust, [6]Guy's and St Thomas' NHS Foundation Trust, London, [7]British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, [8]Royal Infirmary of Edinburgh, Edinburgh, [9]Berkshire Kidney Unit, Royal Berkshire Hospital, Reading, [10]Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, [11]Department of Renal Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge, [12]Department of Rheumatology, Nottingham University Hospitals NHS Trust, [13]Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, [14]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Science, University of Oxford, Oxford, [15]Department of Medicine, Imperial College London, London, [16]Norfolk and Norwich University Hospital, [17]University of East Anglia, Norwich, [18]University of Nottingham, [19]Nottingham University Hospitals NHS Trust, Nottingham, [20]Faculty of Health and Applied Sciences, University of West of England, [21]Department of Rheumatology, University Hospitals Bristol NHS Trust, Bristol, [22]University College London, [23]Department of Renal Medicine, Royal Free Hospital, London, [24]Exeter Kidney Unit, Royal Devon and Exeter Hospital, Exeter, [25]Ipswich Hospital, Ipswich, [26]Norwich Medical School, University of East Anglia, Norwich and [27]Vasculitis and Lupus Unit, Cambridge University Hospitals NHS Trust, Cambridge, UK

Submitted 13 August 2019; accepted 31 October 2019

Correspondence to: David R. W. Jayne, Box 57, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, UK. E-mail: dj106@cam.ac.uk

Whilst guidelines on the management of AAV have proposed RTX as a treatment option in remission maintenance, there has been limited guidance on how this should be used [10, 11]. We present guidelines developed through a modified Delphi exercise on the use of RTX in the maintenance of remission in adult AAV patients, with additional focus on adjunct therapies, adverse effects and use of prophylaxis. These guidelines can be used to assist specialty physicians making treatment decisions in patients with AAV when RTX has been chosen for remission maintenance.

Methods

This modified Delphi exercise invited experts in the management of AAV practising in the UK to participate. The group of clinicians included 11 nephrologists, eight rheumatologists and one paediatric rheumatologist.

The modified Delphi exercise was planned with four rounds, including a face-to-face meeting. The first round sought to identify key areas for the scope of these guidelines and systematic literature review. These key areas form the basis for each statement and substatement. The literature search was conducted using key search strings of systemic vasculitis, GPA, MPA and EGPA, including eponymous names where applicable, combined with RTX, CD20 and/or B lymphocytes as appropriate for each database (see full guideline). Studies including at least 20 patients receiving at least two infusions of RTX were included. The literature review addressing the key issues identified from the first round was presented to each participant with a summary of responses.

Following a third round, an expanded literature review was produced to address important issues with limited evidence in AAV. An expanded literature search of studies on *Pneumocystis jirovecii* pneumonia prophylaxis, vaccination, late onset neutropenia and hypogammaglobulinaemia in autoimmune disease was conducted (see full guidelines).

A final vote determined the level of agreement; a level of 80% was prespecified for inclusion in these guidelines. No statement was excluded for this reason. Prior to the final voting round, the guidelines were distributed to clinicians not involved in guideline development and patient participants in order to assess their face validity and clinical utility.

The Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence was used to grade the level of evidence and recommendation for each statement [12].

The BVAS or GPA specific measure BVAS/WG is used for assessment of disease activity [13, 14]. In these guidelines, the disease states used are: active disease, disease remission, refractory disease, and relapse.

Active disease: manifestations attributable to AAV, and not due to disease-related damage.

Disease remission: disease control (BVAS or BVAS/WG $\leq$1); glucocorticoid-free remission refers to disease control (BVAS or BVAS/WG $\leq$ 1) off glucocorticoid therapy.

Refractory disease: despite treatment of disease, remission has not been established, with persistent or progressive disease activity.

Disease relapse: where disease activity has previously been controlled, and has become active, defined by at least 1 unit increase in BVAS or BVAS/WG. Major relapse: relapse with 1 new, recurrent or worsening major item on BVAS or BVAS/WG; minor relapse: relapse without a major item on BVAS or BVAS/WG.

Statements

1. When should RTX be used for the maintenance of remission in AAV?

1.1. GPA/MPA—new and relapsing patients

We recommend the use of RTX for the maintenance of remission in patients with GPA and MPA following RTX induction. RTX maintenance can also be considered after cyclophosphamide induction.

Level of evidence: 1b (following cyclophosphamide induction), 2b (following RTX induction).
Grade of recommendation: A (following cyclophosphamide induction), B (following RTX induction).
Vote: 18/18 (100%).

1.2. EGPA patients

Despite limited evidence regarding the use of RTX for the maintenance of remission in EGPA, we advise a similar approach to use in GPA and MPA. Overall treatment responses to RTX may differ from GPA and MPA, and steroid withdrawal may be more challenging.

Level of evidence: 4.
Grade of recommendation: C.
Vote: 15/18 (83%).

2. What RTX maintenance regimen should be used for AAV?

2.1. Dose and dosing intervals

We recommend fixed interval dosing with RTX, either 500 mg or 1000 mg administered every 6 months for a period of 2 years. There is ongoing relapse risk after RTX withdrawal and patients should be monitored accordingly.

Level of evidence: 1b.
Grade of recommendation: B.
Vote: 18/18 (100%).

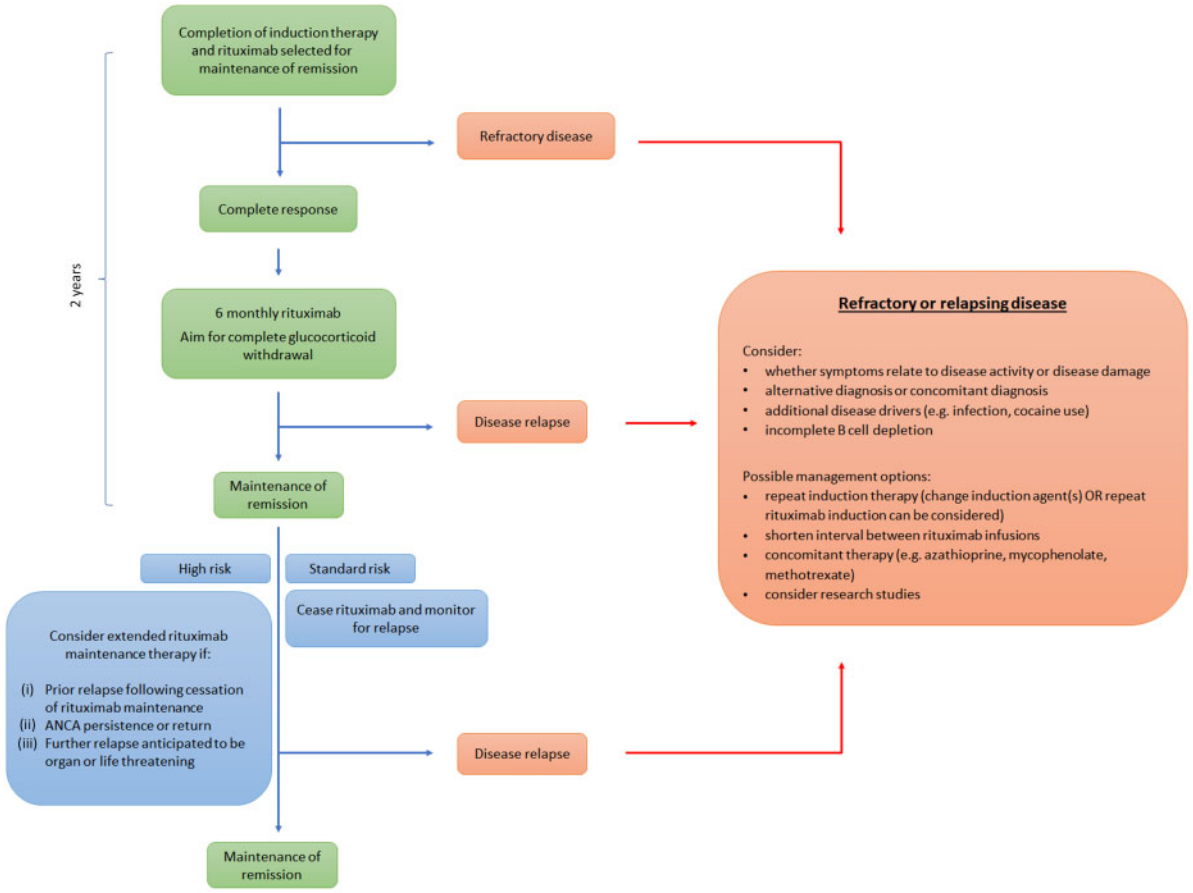
2.2. Management of relapse despite maintenance RTX

Changes to treatment in refractory disease or relapse despite induction and RTX maintenance therapy should be determined according to severity of disease activity and organ involvement.

A guide to treatment decisions is presented (Fig. 1).

Level of evidence: 4.
Grade of recommendation: C.
Vote: 18/18 (100%).

FIG. 1 RTX for the maintenance of remission in ANCA-associated vasculitis: guide to treatment decisions



2.3. Extended RTX maintenance therapy

In selected patients, relapse risk remains high after 2 years of maintenance therapy, and extended duration therapy could be considered. This includes patients who relapse after a prior course of RTX maintenance, with persistent elevation or return of ANCA, or where the consequence of relapse would be organ or life threatening.

Optimal treatment approaches beyond 2 years are yet to be determined in these patients. RTX 500-1000 mg every 6-12 months for up to 5 years could be considered. In patients with prior relapse after maintenance RTX cessation, this could be adjusted based on time from treatment cessation to disease relapse.

Level of evidence: 5.
Grade of recommendation: D.
Vote: 17/18 (94.4%).

2.4. Role of biomarkers in RTX maintenance therapy

Further research is needed to consider the role of biomarkers (e.g. ANCA and B cell return) in guiding RTX maintenance therapy in AAV.

Level of evidence: 2a.
Grade of recommendation: B.
Vote: 18/18 (100%).

3. Concomitant therapy

3.1. Concomitant immunosuppressive agents/disease modifying anti-rheumatic drugs (DMARD)

Where RTX is commenced in a patient already receiving a DMARD for remission maintenance (e.g. azathioprine, methotrexate or mycophenolate), we suggest that the existing DMARD(s) be withdrawn.

Level of evidence: 4.
Grade of recommendation: C.
Vote: 15/18 (83.3%).

3.2. Glucocorticoids

Glucocorticoid tapering strategies should aim for complete cessation 6–12 months after RTX commencement.

Level of evidence: 5.
Strength of recommendation: D.
Vote: 17/18 (94.4%).

4. Prophylaxis

4.1. Pneumocystis jirovecii *prophylaxis*

Pneumocystis jirovecii prophylaxis is suggested in all patients receiving RTX maintenance therapy.

Level of evidence: 4.
Grade of recommendation: C.
Vote: 16/18 (88.9%).

4.2. Vaccination

Influenza and pneumococcal vaccinations should be recommended to all patients. Live vaccinations should be avoided.

Although vaccinations are ideally provided at least 1 month prior to RTX infusion, timing should not preclude vaccination.

Level of evidence: 5.
Grade of recommendation: D.
Vote: 18/18 (100%).

5. Adverse effects

5.1. Hypogammaglobulinaemia

i. In the setting of RTX maintenance therapy:
   a. Immunoglobulins should be monitored in all patients.
   b. Further investigation is recommended if recurrent or atypical infections occur, or IgG <3 g/L (in paediatric age ranges, IgG less than age appropriate lower limit of normal should be used).

Level of evidence: 2a (part a), 5 (part b).
Grade of recommendation: B (part a), D (part b).
Vote: 18/18 (100%).

ii. Parallel administration of RTX and immunoglobulin replacement could be considered in patients with hypogammaglobulinaemia and a clinically important response to RTX is anticipated.

Level of evidence: 5.
Grade of recommendation: C.
Vote: 18/18 (100%).

5.2. Late onset neutropenia

Clinicians and patients should be aware of the possibility of late onset neutropenia with RTX use. A history of uncomplicated late onset neutropenia does not prohibit future RTX use.

Level of evidence: 4.
Grade of recommendation: C.
Vote: 16/18 (88.9%).

Research agenda

In addition to the areas discussed already, the following issues were identified as areas requiring further research and evidence.

i. Impact of maintenance therapy on health-related quality of life.
ii. The effects of extended RTX maintenance therapy.
   a. Adverse effects of treatment including neutropenia, progressive multifocal leukoencephalopathy and long term outcomes of hypogammaglobulinaemia.
   b. Longer term outcome of patients with RTX maintenance therapy including disease-related damage and cardiovascular risk.
   c. Health economics analysis of RTX maintenance therapy and extended RTX maintenance therapy.
iii. Prediction of relapse including the role of biomarkers (e.g. ANCA, CD19, CD27, serum calprotectin) for risk of relapse.
iv. Impact of RTX for the maintenance of remission in special populations and situations: paediatric patients, fertility and pregnancy.

Conclusion

Induction treatment for AAV is increasingly successful at achieving remission, and optimal maintenance of remission has become a key priority in the long-term management of these patients. The clinical efficacy of RTX in both the induction and the maintenance of remission has been demonstrated in clinical trials [2, 3, 15–17]. Developed through a modified Delphi exercise involving an expert group, we present guidelines that consider both the RCT and wealth of non-trial experience in the use of RTX for the maintenance of remission in AAV.

Acknowledgements

We thank Lesley Noblett, Catherine Hill, James Peters and Patrick Coleman for reviewing the guidelines. We acknowledge the support of the Cambridge Biomedical Research Centre.

Funding: nil for project.

Disclosure statement: J.T. has been supported by an Arthritis Australia grant funded by the Australian Rheumatology Association and Roche. N.B. has received consultancy/speaking fees from Roche, Vifor, Lilly and Pfizer, and research funding from GSK, Pfizer and Vifor. P.B. has received Institutional grants from SOBI, Roche, Novartis and Novimmune, and consultancy/speaker fees from Roche, Novartis, SOBI and UCB. D.C. has received consultancy fees from GSK and Eli Lilly and is a member of speakers' bureau for GSK and Eli Lilly. L.H. has received consultancy fees from Chemocentryx, research funding from Vifor, and honorarium from Roche for speaker fees. R.J. has received consultant fees from Chemocentryx and is chief investigator on a clinical trial for which grant funding has been provided by GSK. R.A.L. has received research or educational grants from AbbVie, Celgene, Chemocentryx, GSK, InflaRx and Vifor. S.P.M. has received honoraria (speaker fees) from Celltrion and Rigel and is an investigator on a clinical trial funded by GSK. C.P. has received research grants from GSK and is an investigator on a clinical trial funded by GSK. J.C.R. has received consultancy fees from Chemocentryx and honorarium from Roche for speaker fees. L.C.W. is an investigator in clinical trials sponsored by Chemocentryx, Rigel, Novartis and GSK. D.R.W.J. has received research or educational grants from Chemocentryx, GSK, InflaRx

and Sanofi, and received consulting fees from Celgene, Chemocentryx, GSK, InflaRX and Insmed.

The full guideline is available at *Rheumatology* online

Disclaimer statement: The opinions expressed in Rheumatology are those of the authors and contributors, and do not necessarily reflect those of the British Society for Rheumatology, the Editors, the Editorial Board, Oxford University Press or the organization to which the authors are affiliated.

References

1 de Groot K, Harper L, Jayne DR *et al*. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:670–80.

2 Jones RB, Tervaert JW, Hauser T *et al*. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211–20.

3 Stone JH, Merkel PA, Spiera R *et al*. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32.

4 Mukhtyar C, Flossmann O, Hellmich B *et al*. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. Ann Rheum Dis 2008;67:1004–10.

5 Robson JC, Dawson J, Cronholm PF, Milman N *et al*. Health-related quality of life in ANCA-associated vasculitis and item generation for a disease-specific patient-reported outcome measure. Patient Relat Outcome Meas 2018;9:17–34.

6 NHS England Specialised Services Clinical Reference Group for Specialised Rheumatology. Clinical Commissioning Policy: Rituximab for the treatment of ANCA-associated vasculitis in adults. London: NHS England, 2015.

7 Jayne D, Rasmussen N, Andrassy K *et al*. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36–44.

8 Pagnoux C, Mahr A, Hamidou MA *et al*. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008;359:2790–803.

9 Hiemstra TF, Walsh M, Mahr A *et al*. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. JAMA 2010;304:2381–8.

10 Yates M, Watts RA, Bajema IM, Cid MC *et al*. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75:1583–94.

11 Ntatsaki E, Carruthers D, Chakravarty K *et al*. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford) 2014;53:2306–9.

12 OCEBM Levels of Evidence Working Group. The oxford levels of evidence 2. Oxford: Centre for Evidence-Based Medicine. https://www.cebm.net/index.aspx?o=5653 (13 August 2019, date last accessed).

13 Stone JH, Hoffman GS, Merkel PA *et al*. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. Arthritis Rheum 2001;44:912–20.

14 Mukhtyar C, Lee R, Brown D *et al*. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009;68:1827–32.

15 Guillevin L, Pagnoux C, Karras A *et al*. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771–80.

16 Terrier B, Pagnoux C, Perrodeau E *et al*. Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. Ann Rheum Dis 2018;77:1150–6.

17 Charles P, Terrier B, Perrodeau E *et al*. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis 2018;77:1143–9.

3.4 Manuscript: Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines.

RHEUMATOLOGY

Rheumatology 2020;59:e24–e32
doi:10.1093/rheumatology/kez640

Guideline

British Society for Rheumatology

Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines

Joanna Tieu[1,2], Rona Smith[1], Neil Basu[3], Paul Brogan[4,5], David D'Cruz[6], Neeraj Dhaun[7,8], Oliver Flossmann[9], Lorraine Harper[10], Rachel B. Jones[1,11], Peter C. Lanyon[12,13], Raashid A. Luqmani[14], Stephen P. McAdoo[15], Chetan Mukhtyar[16,17], Fiona A. Pearce[18,19], Charles D. Pusey[15], Joanna C. Robson[20,21], Alan D. Salama[22,23], Lucy Smyth[24], Richard A. Watts[25,26], Lisa C. Willcocks[11] and David R. W. Jayne[1,27]

Key words: rituximab, ANCA-associated vasculitis, hypogammaglobulinaemia, *Pneumocystis jirovecii*, practise guideline

GUIDELINE

Background

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) encompasses three disease phenotypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Considerable improvements in therapy mean induction of remission occurs in most patients with AAV [1–4]. However, disease relapse continues to pose a burden to patients. Morbidity accrues with relapses through disease-related damage and adverse effects of therapies to manage these relapses, negatively impacting on quality of life [5].

Rituximab (RTX), a monoclonal antibody targeting CD20, leads to peripheral B cell depletion. This has been successfully trialled, and is licensed, for the induction and maintenance of remission in AAV [2, 3]. RTX is increasingly being used for the maintenance of remission in patients with AAV, to reduce the risk of relapse and its consequences [6]. Other commonly used agents that have been trialled for the maintenance of remission in AAV include azathioprine, methotrexate and mycophenolate [7–9]. The decision to select RTX for the maintenance of remission is multifactorial, including but not limited to, patient-related factors and preferences, previous treatment and response, consideration of the overall risk of relapse, and access to therapy. These guidelines have been developed by a group of physicians practising in the UK.

While guidelines on the management of AAV have proposed RTX as a treatment option in remission maintenance, there has been limited guidance on how this should be used [10, 11]. We present guidelines developed through a modified Delphi exercise on the use of RTX in the maintenance of remission in adult AAV patients, with additional focus on adjunct therapies,

[1]Department of Medicine, University of Cambridge, Cambridge, UK, [2]Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia, [3]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, [4]University College London Great Ormond Institute of Child Health, [5]Great Ormond Street Hospital NHS Foundation Trust, London, UK, [6]Guy's and St Thomas' NHS Foundation Trust, London, [7]British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, [8]Royal Infirmary of Edinburgh, Edinburgh, [9]Berkshire Kidney Unit, Royal Berkshire Hospital, Reading, [10]Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, [11]Department of Renal Medicine, Cambridge University Hospitals Trust, Cambridge, [12]Department of Rheumatology, Nottingham University Hospitals NHS Trust, [13]Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, [14]Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Science, University of Oxford, Oxford, [15]Department of Medicine, Imperial College London, London, [16]Norfolk and Norwich University Hospital, [17]University of East Anglia, Norwich, [18]University of Nottingham, [19]Nottingham University Hospitals NHS Trust, Nottingham, [20]Faculty of Health and Applied Sciences, University of West of England, [21]Department of Rheumatology, University Hospitals Bristol NHS Trust, Bristol, [22]University College London, [23]Department of Renal Medicine, Royal Free Hospital, London, [24]Exeter Kidney Unit, Royal Devon and Exeter Hospital, Exeter, [25]Ipswich Hospital, Ipswich, [26]Norwich Medical School, University of East Anglia, Norwich, UK and [27]Vasculitis and Lupus Unit, Cambridge University Hospitals NHS Trust, Cambridge, UK

Submitted 13 August 2019; accepted 31 October 2019

Correspondence to: David R. W. Jayne, Box 57, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, UK. E-mail: dj106@cam.ac.uk

adverse effects and use of prophylaxis. These guidelines can be used to assist specialty physicians making treatment decisions in patients with AAV when RTX has been chosen for remission maintenance.

Methods

This modified Delphi exercise invited experts in the management of AAV practising in the UK to participate. The group of clinicians included 11 nephrologists, eight rheumatologists and one paediatric rheumatologist.

The modified Delphi exercise was planned with four rounds, including a face-to-face meeting. The first round sought to identify key areas for the scope of these guidelines and systematic literature review. These key areas form the basis for each statement and sub-statement. The literature search was conducted using key search strings of systemic vasculitis, GPA, MPA and EGPA, including eponymous names where applicable, combined with RTX, CD20 and/or B lymphocytes as appropriate for each database (full search string in supplementary material, available at *Rheumatology* online). Studies including at least 20 patients receiving at least two infusions of RTX were included. The literature review addressing the key issues identified from the first round was presented to each participant with a summary of responses.

Following a third round, an expanded literature review was produced to address important issues with limited evidence in AAV. An expanded literature search of studies on *Pneumocystis jirovecii* pneumonia prophylaxis, vaccination, late onset neutropenia and hypogammaglobulinaemia in autoimmune disease was conducted (full search strategy provided in supplementary material, available at *Rheumatology* online).

A final vote determined the level of agreement; a level of 80% was prespecified for inclusion in these guidelines. No statement was excluded for this reason. Prior to the final voting round, the guidelines were distributed to clinicians not involved in guideline development and patient participants in order to assess their face validity and clinical utility.

The Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence were used to grade the level of evidence and recommendation for each statement [12].

The BVAS or GPA specific measure BVAS/WG are used for assessment of disease activity [13, 14]. In these guidelines, the disease states used are: active disease, disease remission, refractory disease and relapse.

Active disease: manifestations attributable to AAV, and not due to disease-related damage.

Disease remission: disease control (BVAS or BVAS/WG $\leq$1); glucocorticoid free remission refers to disease control (BVAS or BVAS/WG $\leq$ 1) off glucocorticoid therapy.

Refractory disease: despite treatment of disease, remission has not been established, with persistent or progressive disease activity.

Disease relapse: where disease activity has previously been controlled, and has become active, defined by at least 1 unit increase in BVAS or BVAS/WG. Major relapse: relapse with 1 new, recurrent or worsening major item on BVAS or BVAS/WG; minor relapse: relapse without a major item on BVAS or BVAS/WG

Statements

1. When should RTX be used for the maintenance of remission in AAV?

1.1. GPA/MPA—new and relapsing patients

We recommend the use of RTX for the maintenance of remission in patients with GPA and MPA following RTX induction. RTX maintenance can also be considered after cyclophosphamide induction.

Level of evidence: 1b (following cyclophosphamide induction), 2b (following RTX induction).
Grade of recommendation: A (following cyclophosphamide induction), B (following RTX induction).
Vote: 18/18 (100%).

Two randomized controlled trials (RCT) have evaluated the efficacy of RTX for the maintenance of remission in AAV [15, 16]. The MAINRITSAN trial randomized 115 patients with newly diagnosed (80%) or relapsing (20%) AAV (excluding EGPA) to receive a RTX or azathioprine based maintenance regimen following remission induction with cyclophosphamide [15]. The RTX regimen was two 500 mg doses of RTX a fortnight apart after remission induction followed by 500 mg every 6 months until month 18 (i.e. three further doses). After 28 months, fewer major relapses occurred in patients who received RTX compared with azathioprine (5% *vs* 29%, hazard ratio 6.61; 95% CI: 1.56, 27.96; $P = 0.002$), resulting in a number needed to treat of four patients to prevent one major relapse [15]. The superiority of RTX over azathioprine in relapse prevention persisted at 60 months' follow-up [17].

MAINRITSAN2 compared the fixed-schedule RTX dosing from the MAINRITSAN trial with an individually tailored RTX maintenance regimen, where after an initial maintenance infusion of 500 mg RTX $\times$2, further 500 mg doses were administered based on 3-monthly measures of ANCA and B cells [16]. In this trial, RTX induction was used in 37% of patients. At 28 months after the first maintenance RTX infusion, eight (9.9%) patients receiving fixed-schedule RTX had relapsed (three major) compared with 13 (16.0%) patients experiencing 14 relapses (six major) in the tailored infusion arm.

One ongoing RCT, RITAZAREM (NCT01697267), compares 4-monthly 1000 mg RTX dosing with azathioprine for the maintenance of remission following RTX induction in patients with a relapse of AAV [18].

Several observational studies, with follow-up to 7.6 years, provide further evidence on the safety and efficacy of RTX for the maintenance of remission in patients with new, relapsing and refractory AAV [19–26]. Reflecting current practice patterns, these studies have largely used RTX to maintain remission after successful RTX induction.

1.2. EGPA patients

Despite limited evidence regarding the use of RTX for the maintenance of remission in EGPA, we advise a similar approach to use in GPA and MPA. Overall treatment responses to RTX may differ from GPA and MPA, and steroid withdrawal may be more challenging.

Level of evidence: 4.
Grade of recommendation: C.
Vote: 15/18 (83%).

EGPA is a relatively understudied subgroup of AAV, owing to phenotypic differences from GPA and MPA, and relative rarity of disease. Published trials of RTX for induction and maintenance of remission in AAV have not included patients with EGPA. One multicentre retrospective case series of 41 patients with predominantly refractory or relapsing EGPA reported a clinical improvement in 83% by 6 months, with 34% achieving complete remission [27]. Prednisolone cessation was possible in only two patients at 12 months. In a single centre study including 69 patients with EGPA, similar remission rates were identified (34% at 6 months and 49% at 12 months) [28]. Median prednisolone doses were 7.25 mg/day at 12 months and 5 mg/day at 24 months. Relapse was common, with 54% of patients relapsing, predominantly due to uncontrolled asthma or other respiratory manifestations. In both studies, patients who were ANCA positive were more likely to achieve remission.

An ongoing RCT, MAINRITSEG (NCT02807103), is evaluating RTX in patients with EGPA for maintenance of remission [29].

2. What RTX maintenance regimen should be used for AAV?

2.1. Dose and dosing intervals

We recommend fixed interval dosing with RTX, either 500 mg or 1000 mg administered every 6 months for a period of 2 years. There is ongoing relapse risk after RTX withdrawal and patients should be monitored accordingly.

Level of evidence: 1b.
Grade of recommendation: B.
Vote: 18/18 (100%).

This regimen is recommended following the completion of induction therapy. The treatment regimen should be individualized, particularly in post-pubertal adolescents and older individuals with comorbidities where concerns regarding adverse effects exist. There are limited data for the use of RTX in children.

No direct comparisons have been made between the two most commonly used doses of RTX—500 and 1000 mg. Both published RCTs have used 500 mg doses of RTX while observational studies have largely used 1000 mg doses and this dose is being used in the ongoing RITAZAREM trial [15, 16, 19, 21–23]. While observational cohorts include a greater proportion of patients with relapsing or refractory disease than RCTs, it is unknown if the dose of RTX influences clinical outcomes in these patients.

There are two main approaches to RTX dosing intervals: fixed interval dosing and biomarker guided dosing. As detailed above, the MAINRITSAN2 trial compared fixed 6-monthly RTX infusions with dosing based on 3-monthly assessments for ANCA return or increase and B cell return [16]. At 28 months' follow-up, no difference in relapse rate was identified between the two groups ($P = 0.22$); 8/81 (9.9%) patients receiving fixed interval dosing had experienced eight relapses including three major relapses, whereas 13/81 (16.0%) patients with repeat dosing determined by biomarker changes had experienced 14 relapses including six major. No difference in serious adverse events related to infection was identified, with 16 individuals receiving fixed interval RTX having 18 infections and nine individuals with tailored dosing having 18 infections.

The role of biomarker guided RTX dosing has not been proven and requires further study, including the evaluation of long-term outcomes. Relapses in spite of ANCA negativity and B cell depletion have been observed in both RCTs and observational studies [15–17, 21–23, 26, 30]. Fixed interval dosing has therefore been recommended. As discussed below, in selected patients, biomarker fluctuations, comorbidities and adverse effects may necessitate a more individualized approach to RTX dose and dosing intervals.

2.2. Management of relapse despite maintenance RTX

Changes to treatment in refractory disease or relapse despite induction and RTX maintenance therapy should be determined according to severity of disease activity and organ involvement.

A guide to treatment decisions is presented (Fig. 1).

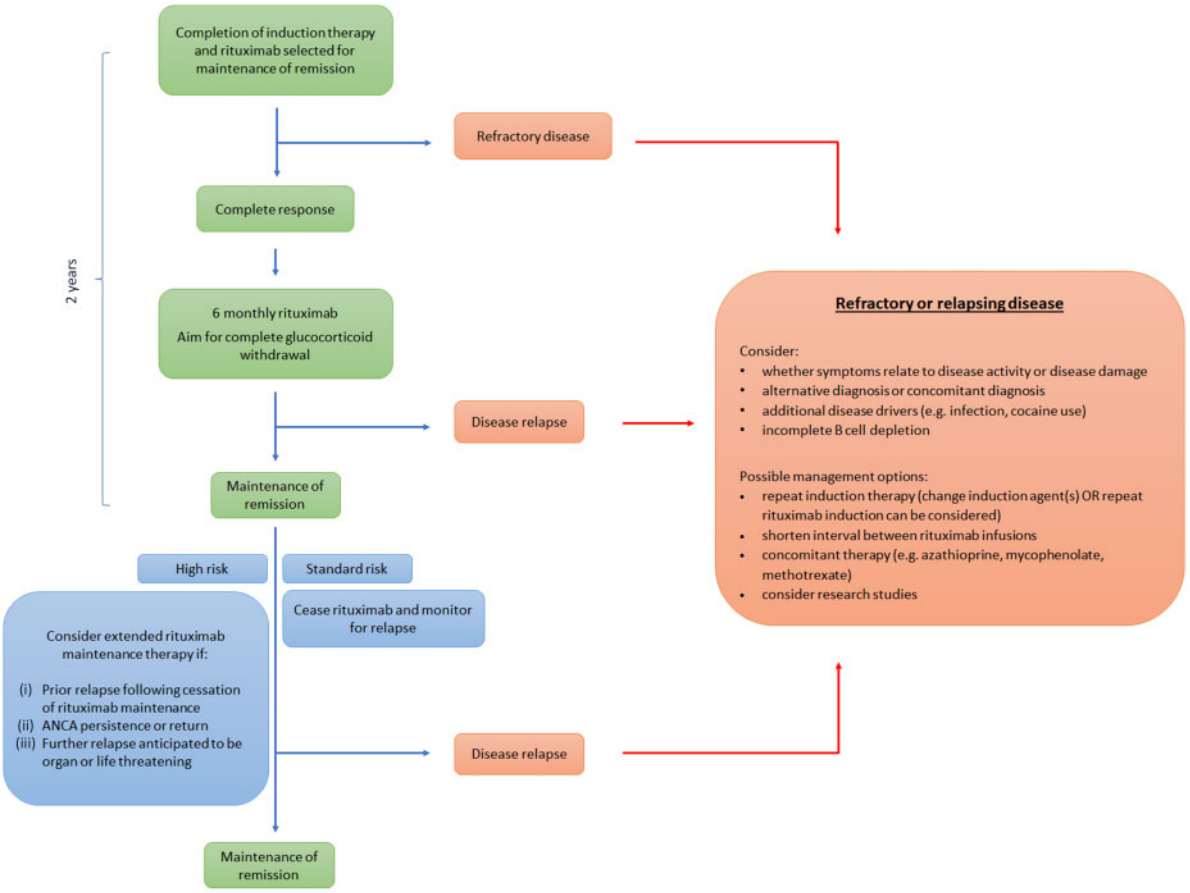
Level of evidence: 4.
Grade of recommendation: C.
Vote: 18/18 (100%).

In view of the rarity of refractory disease or relapse on RTX maintenance therapy, there are no studies specifically evaluating treatment approaches. Various strategies have been adopted in specialized centres and described in RCTs and observational studies [15, 16, 19, 21, 22].

Referral to a specialized centre is advised. Assessment requires careful consideration of the relative contribution of disease damage and activity to patient symptoms, alternative diagnoses, and potential disease drivers including infection, nasal carriage of *Staphylococcus aureus* and cocaine use.

Treatment of disease activity should depend on its severity, including consideration of major organ involvement and whether any benefit from RTX has been derived. For example, major organ involvement typically necessitates re-induction therapy. Shortened interval dosing is considered where disease activity emerges shortly prior to scheduled infusions, and the addition of concomitant immunosuppression could be considered where, despite a response to RTX, there is mild persistent disease activity without major organ manifestations. Concomitant therapy

Fig. 1 A guide to treatment decisions



includes traditional maintenance agents (e.g. azathioprine, methotrexate or mycophenolate), or low dose glucocorticoids (≤5 mg/day prednisolone, or equivalent). In the event of RTX failure, alternative maintenance strategies should be considered.

2.3. Extended RTX maintenance therapy

In selected patients, relapse risk remains high after 2 years of maintenance therapy, and extended duration therapy could be considered. This includes patients who relapse after a prior course of RTX maintenance, with persistent elevation or return of ANCA, or where the consequence of relapse would be organ or life threatening.

Optimal treatment approaches beyond 2 years are yet to be determined in these patients. RTX 500-1000 mg every 6-12 months for up to 5 years could be considered. In patients with prior relapse after maintenance RTX cessation, this could be adjusted based on time from treatment cessation to disease relapse.

Level of evidence: 5.
Grade of recommendation: D.
Vote: 17/18 (94.4%).

Long term follow-up data from the MAINRITSAN trial highlight the risk of relapse after RTX cessation [17]. Until 28 months' follow-up, 10 months after the last RTX infusion, only three (5%) patients experienced a major relapse. Over the subsequent 22 months, without further scheduled RTX infusions, an additional 13 (23%) patients experienced a major relapse. Consistent with this, RTX maintenance cohorts demonstrate a progressive reduction in relapse-free survival after RTX cessation [22, 23]. An ongoing RCT (MAINRITSAN3) compares the effects of extended RTX maintenance with standard duration therapy (NCT02433522) [31].

Optimal regimens for extended RTX maintenance require further study. Extended treatment to 5 years is proposed in patients at high risk of relapse or its consequences. The dosing strategy presented (Fig. 1) is a guide, derived by expert consensus. Individualization of any extended treatment regimen is emphasized, based on the patient's wishes, comorbidities, age, and the history of their AAV.

Identifying patients at greatest risk of relapse after RTX treatment remains challenging. Patients who have relapsed after a previous course of RTX are considered empirically to be at greater risk of further relapse.

Patients who are ANCA positive, either through persistent positivity or return, are likely to have a greater

risk of relapse. Notably, in the MAINRITSAN trial, the risk of relapse for patients who were ANCA positive at each follow-up visit increased over time [17]. Following RTX cessation, one cohort reported that switching from negative to positive ANCA status was predictive of subsequent relapse [22]. This is consistent with findings from the REMAIN trial, which randomized patients who had completed 18–24 months of treatment to continue or withdraw maintenance azathioprine and glucocorticoid [32]. The withdrawal of azathioprine maintenance therapy and ANCA positivity at randomization (i.e. 18–24 months after commencement of treatment) increased the risk of relapse.

The highlighted factors should be considered in each patient's individual context, and the risk of relapse must be balanced against potential adverse effects of ongoing RTX. Traditional risk factors for relapse such as PR3-ANCA-associated disease, GPA phenotype and the absence of renal involvement should also be considered in assessing the overall risk of relapse [15, 33, 34]. Observational cohorts of patients with AAV have not identified a clear association between cumulative RTX dose and infection or chronic hypogammaglobulinaemia [35, 36]. Long term prospective data are required, and ongoing vigilance is recommended.

2.4. Role of biomarkers in RTX maintenance therapy

Further research is needed to consider the role of biomarkers (e.g. ANCA and B cell return) in guiding RTX maintenance therapy in AAV.

Level of evidence: 2a.
Grade of recommendation: B.
Vote: 18/18 (100%).

The routine use of biomarkers, such as B cell counts and ANCA, in guiding therapy in AAV is historically contentious [37]. As discussed above, relapses continue to occur in the absence of such biomarkers [16, 17, 22]. Moreover, treatment regimens thus far have not incorporated measures of treatment related to toxicity, including infection rates and immunoglobulin levels, in guiding further therapy.

While these biomarkers should not determine treatment decisions in isolation, the results of long-term studies and the MAINRITSAN2 trial suggest that the use of ANCA and B cell return can be considered in guiding treatment decisions in association with other patient and disease-related factors [16, 17, 22].

The validation of alternative biomarkers for disease activity, disease-related damage and adverse effects of therapy is required.

3. Concomitant therapy

3.1. Concomitant immunosuppressive agents/disease disease modifying anti-rheumatic drugs (DMARD)

Where RTX is commenced in a patient already receiving a DMARD for remission maintenance (e.g. azathioprine, methotrexate or mycophenolate), we suggest that the existing DMARD(s) be withdrawn.

Level of evidence: 4.
Grade of recommendation: C.
Vote: 15/18 (83.3%).

Concomitant therapy refers to concurrent use of another non-glucocorticoid immunosuppressive or DMARD with RTX.

In clinical trials of RTX for the maintenance of remission in AAV, concomitant therapy has not been used. In observational cohorts, in which patients are already receiving a non-glucocorticoid immunosuppressive agent as maintenance therapy and RTX has been added, there has usually been withdrawal of this medication [19–22]. Owing to the potential for increased adverse effects, the routine use of concomitant therapy has not been recommended.

There is limited evidence from small numbers of patients receiving RTX maintenance treatment with refractory or relapsing disease described in observational studies, suggesting concomitant therapy may be efficacious in this setting [19, 22]. Rare cases of persistent disease activity despite ongoing RTX maintenance therapy may benefit from the addition of a concomitant immunosuppressive agent.

3.2. Glucocorticoids

Glucocorticoid tapering strategies should aim for complete cessation 6–12 months after RTX commencement.

Level of evidence: 5.
Strength of recommendation: D.
Vote: 17/18 (94.4%).

Glucocorticoid-free remission remains ideal in view of known, predictable adverse effects. In long term follow-up of patients enrolled in European RCTs, prolonged glucocorticoid use was associated with greater disease damage, after adjusting for number of relapses during follow-up, age, baseline disease activity and renal involvement [38].

Shorter glucocorticoid tapering strategies are possible in many patients with AAV. One RCT that randomized patients to RTX induction or cyclophosphamide followed by azathioprine maintenance provided a standardized glucocorticoid taper to cessation at 6 months to patients in both arms [39]. Glucocorticoid-free remission was achieved in 64% of the RTX treated patients and 53% of those who received cyclophosphamide. Completed RCTs of RTX for the maintenance of remission have used glucocorticoid protocols allowing for glucocorticoid reduction in the first 6–12 months, but typically continue at low dose until at least 18 months following induction therapy [15, 16]. In uncontrolled settings, earlier prednisolone dose reduction and cessation is well documented with RTX maintenance therapy [20–22].

In practice, patients with EGPA have greater difficulty with glucocorticoid withdrawal, often resulting in incomplete control of asthma symptoms [27]. Adrenal insufficiency may also prohibit complete cessation of glucocorticoids [40, 41].

4. Prophylaxis

4.1. Pneumocystis jirovecii *prophylaxis*

Pneumocystis jirovecii (PJP) prophylaxis is suggested in all patients receiving RTX maintenance therapy.

Level of evidence: 4.
Grade of recommendation: C.
Vote: 16/18 (88.9%).

PJP prophylaxis is encouraged for at least 6 months from commencement of induction therapy for AAV. In RCTs of RTX maintenance, two cases of PJP were identified in patients on RTX, neither of whom were on prophylactic therapy at the time of PJP diagnosis [17].

There is a paucity of information comparing PJP prophylaxis strategies in patients immunosuppressed for autoimmune disease including AAV. In trials of RTX in AAV, PJP prophylaxis strategies have varied, most commonly using combination trimethoprim and sulfamethoxazole [2, 3, 15, 16]. Data for the use of alternative agents, including pentamidine inhalation, dapsone and atovoquone are limited owing to the rarity of use.

Extended duration of prophylaxis is recommended in patients considered to be at high risk. The following factors influence the incidence of PJP: lymphopenia (especially low $CD4^+$ T cell counts), increased age, prolonged use of glucocorticoid or other immunosuppression, and structural lung disease including chronic obstructive pulmonary disease.

Similar to solid organ transplant, local clusters of patients with PJP have been identified in patients immunosuppressed for autoimmune disease, including AAV [42]. Recommencement of prophylaxis in individuals with ongoing immunosuppression should be considered when a local cluster of PJP is identified.

4.2. Vaccination

Influenza and pneumococcal vaccinations should be recommended to all patients. Live vaccinations should be avoided.

Although vaccinations are ideally provided at least 1 month prior to RTX infusion, timing should not preclude vaccination.

Level of evidence: 5.
Grade of recommendation: D.
Vote: 18/18 (100%).

Infections remain a significant source of morbidity and mortality in patients with AAV, with a predominance of respiratory tract infections [16, 17, 43, 44].

The protective benefit of influenza vaccination in the general population is well established. Despite previous reports on vaccinations precipitating disease activity in patients with AAV, a small RCT and observational cohort support the safety of influenza vaccination in patients with AAV [45, 46].

In patients receiving RTX maintenance therapy, inefficacy remains a concern, particularly where B cell depletion persists. The efficacy of vaccination in patients receiving RTX maintenance has not been evaluated for AAV. Vaccination response has been demonstrated in patients with rheumatoid arthritis 6 months post-RTX despite incomplete B cell repopulation in most patients [47]. Compared with patients receiving methotrexate alone, the response was blunted and occurred in a smaller proportion of individuals. Vaccination at least 1 month prior to RTX is recommended to maximize vaccination effect. However, given the practical implications of treatment timelines and seasonal nature of infections, vaccinations outside of the ideal timeframe in spite of potential inefficacy often remains appropriate.

5. Adverse effects

5.1. Hypogammaglobulinaemia

(i) In the setting of RTX maintenance therapy:

a. Immunoglobulins should be monitored in all patients
b. Further investigation is recommended if recurrent or atypical infections occur, or IgG <3 g/L (in paediatric age ranges, IgG less than age appropriate lower limit of normal should be used).

Level of evidence: 2a (part a), 5 (part b).
Grade of recommendation: B (part a), D (part b).
Vote: 18/18 (100%).

Despite stable IgG levels reported by RCTs of RTX maintenance therapy, hypogammaglobulinaemia has been consistently observed in observational cohorts of patients receiving RTX [15, 16, 35, 36]. Conflicting results are likely a result of multiple factors; observational cohorts include a greater proportion of patients with a higher burden of prior immunosuppression for refractory or relapsing disease, and hypogammaglobulinaemia is variably defined, is transient in some and can be a late complication. While long term data are limited, the primary concern with persistent hypogammaglobulinaemia is recurrent, chronic and/or atypical infections.

It is not known whether RTX should be withheld for low or falling IgG levels and in clinical trials a threshold of 3 g/l has been used [18]. The possibility that continued RTX will exacerbate hypogammaglobulinaemia should be considered.

Patients with an established pattern of recurrent or atypical infections and hypogammaglobulinaemia may benefit from interventions including prophylactic antimicrobial therapy and/or immunoglobulin replacement. This should be considered in these subgroups of patients in accordance with local guidelines.

Consistent with other recently published guidelines, while patients with persistent IgG <3 g/l without infections may not require further intervention, their infection profile and vaccination responses should be reviewed, in conjunction with Clinical Immunology services [48, 49]. For patients in paediatric age ranges, the long-term implications of hypogammaglobulinaemia are of greater concern and Clinical Immunology review should be sought when IgG levels fall below age-adjusted norms.

(ii) Parallel administration of RTX and immunoglobulin replacement could be considered in patients with

hypogammaglobulinaemia and a clinically important response to RTX is anticipated.

Level of evidence: 5.
Grade of recommendation: C.
Vote: 18/18 (100%).

In rare circumstances, relapse of AAV occurs in patients receiving immunoglobulin replacement therapy for hypogammaglobulinaemia. Uncontrolled disease typically necessitates further immunosuppression despite an established immunodeficient state. The additive effect of RTX associated hypogammaglobulinaemia with other immunosuppressive agents, thereby targeting multiple immune pathways, is unclear.

Decisions on co-administration of RTX and immunoglobulin replacement, and the timing of these agents should be in conjunction with Clinical Immunology.

5.2. Late onset neutropenia

Clinicians and patients should be aware of the possibility of late onset neutropenia with RTX use. A history of uncomplicated late onset neutropenia does not prohibit future RTX use.

Level of evidence: 4.
Grade of recommendation: C.
Vote: 16/18 (88.9%).

In patients with a history of late onset neutropenia, there should be greater clinician and patient vigilance of infective symptoms after future RTX administration.

Late onset neutropenia is incompletely understood but postulated to result from arrest of granulopoiesis in favour of B cell lymphopoiesis [50]. Late onset neutropenia has been identified in patients in RTX maintenance cohorts and RCTs [16, 19, 22, 23, 51, 52]. Owing to the unpredictable timing of late onset neutropenia, regular evaluation for neutropenia is not routine. The neutropenia is often asymptomatic, typically short-lived and, in the absence of routine testing, therefore likely underrecognized. Late onset neutropenia often recovers without therapy, with granulocyte colony stimulating factor (G-CSF) used in symptomatic patients with prolonged neutropenia, or with infective symptoms in conjunction with antimicrobial therapy. Moreover, reports of recurrence in patients treated for autoimmune disease, including AAV, are uncommon [53, 54]. In patients with a history of neutropenia complicated by severe infection, there is limited experience in repeat RTX administration.

Research agenda

In addition to the areas discussed already, the following issues were identified as areas requiring further research and evidence.

i. Impact of maintenance therapy on health-related quality of life.
ii. The effects of extended RTX maintenance therapy.
    a. Adverse effects of treatment including neutropenia, progressive multifocal leukoencephalopathy and long-term outcomes of hypogammaglobulinaemia.
    b. Longer term outcome of patients with RTX maintenance therapy including disease-related damage and cardiovascular risk.
    c. Health economics analysis of RTX maintenance therapy and extended RTX maintenance therapy.
iii. Prediction of relapse including the role of biomarkers (e.g. ANCA, CD19, CD27, serum calprotectin) for risk of relapse.
iv. Impact of RTX for the maintenance of remission in special populations and situations: paediatric patients, fertility and pregnancy.

Conclusion

Induction treatment for AAV is increasingly successful at achieving remission, and optimal maintenance of remission has become a key priority in the long-term management of these patients. The clinical efficacy of RTX in both the induction and the maintenance of remission has been demonstrated in clinical trials [2, 3, 15–17]. Developed through a modified Delphi exercise involving an expert group, we present guidelines that consider both the RCT and wealth of non-trial experience in the use of RTX for the maintenance of remission in AAV.

Acknowledgements

We thank Lesley Noblett, Catherine Hill, James Peters and Patrick Coleman for reviewing the guidelines. We acknowledge the support of the Cambridge Biomedical Research Centre.

Funding: nil for project.

Disclosure statement: J.T. has been supported by an Arthritis Australia grant funded by the Australian Rheumatology Association and Roche. N.B. has received consultancy/speaking fees from Roche, Vifor, Lilly and Pfizer, and research funding from GSK, Pfizer and Vifor. P.B. has received Institutional grants from SOBI, Roche, Novartis and Novimmune, and consultancy/speaker fees from Roche, Novartis, SOBI and UCB. D.C. has received consultancy fees from GSK and Eli Lilly and is a member of speakers' bureau for GSK and Eli Lilly. L.H. has received consultancy fees from Chemocentryx, research funding from Vifor, and honorarium from Roche for speaker fees. R.J. has received consultant fees from Chemocentryx and is chief investigator on a clinical trial for which grant funding has been provided by GSK. R.A.L. has received research or educational grants from AbbVie, Celgene, Chemocentryx, GSK, InflaRx and Vifor. S.P.M. has received honoraria (speaker fees) from Celltrion and Rigel and is an investigator on a clinical trial funded by GSK. C.P. has received research grants from GSK and is an investigator on a clinical trial funded by GSK. J.C.R. has received consultancy fees from Chemocentryx and honorarium

from Roche for speaker fees. L.C.W. is an investigator in clinical trials sponsored by Chemocentryx, Rigel, Novartis and GSK. D.R.W.J. has received research or educational grants from Chemocentryx, GSK, InflaRx, and Sanofi, and received consulting fees from Celgene, Chemocentryx, GSK, InflaRX and Insmed.

Disclaimer: The opinions expressed in Rheumatology are those of the authors and contributors, and do not necessarily reflect those of the British Society for Rheumatology, the Editors, the Editorial Board, Oxford University Press or the organization to which the authors are affiliated.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 de Groot K, Harper L, Jayne DR *et al*. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:670–80.

2 Jones RB, Tervaert JW, Hauser T *et al*. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211–20.

3 Stone JH, Merkel PA, Spiera R *et al*. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32.

4 Mukhtyar C, Flossmann O, Hellmich B *et al*. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. Ann Rheum Dis 2008;67:1004–10.

5 Robson JC, Dawson J, Cronholm PF, Milman N *et al*. Health-related quality of life in ANCA-associated vasculitis and item generation for a disease-specific patient-reported outcome measure. Patient Relat Outcome Meas 2018;9:17–34.

6 NHS England Specialised Services Clinical Reference Group for Specialised Rheumatology. Clinical Commissioning Policy: Rituximab for the treatment of ANCA-associated vasculitis in adults. London: NHS England, 2015.

7 Jayne D, Rasmussen N, Andrassy K *et al*. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36–44.

8 Pagnoux C, Mahr A, Hamidou MA *et al*. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008;359:2790–803.

9 Hiemstra TF, Walsh M, Mahr A *et al*. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. JAMA 2010;304:2381–8.

10 Yates M, Watts RA, Bajema IM, Cid MC *et al*. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75:1583–94.

11 Ntatsaki E, Carruthers D, Chakravarty K *et al*. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford) 2014;53:2306–9.

12 OCEBM Levels of Evidence Working Group. The oxford levels of evidence 2. Oxford: Centre for Evidence-Based Medicine. https://www.cebm.net/index.aspx?o=5653 (13 August 2019, date last accessed).

13 Stone JH, Hoffman GS, Merkel PA *et al*. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). Arthritis Rheum 2001;44:912–20.

14 Mukhtyar C, Lee R, Brown D *et al*. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009;68:1827–32.

15 Guillevin L, Pagnoux C, Karras A *et al*. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771–80.

16 Charles P, Terrier B, Perrodeau E *et al*. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis 2018;77:1143–9.

17 Terrier B, Pagnoux C, Perrodeau E *et al*. Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. Ann Rheum Dis 2018;77:1150–6.

18 Gopaluni S, Smith RM, Lewin M *et al*. Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis (RITAZAREM): study protocol for a randomized controlled trial. Trials 2017;18:112.

19 Pendergraft WF 3rd, Cortazar FB, Wenger J *et al*. Long-term maintenance therapy using rituximab-induced continuous B-cell depletion in patients with ANCA vasculitis. Clin J Am Soc Nephrol 2014;9:736–44.

20 Cartin-Ceba R, Golbin JM, Keogh KA *et al*. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. Arthritis Rheum 2012;64:3770–8.

21 Smith RM, Jones RB, Guerry MJ, Laurino S *et al*. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:3760–9.

22 Alberici F, Smith RM, Jones RB *et al*. Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis. Rheumatology (Oxford) 2015;54:1153–60.

23 Calich AL, Puechal X, Pugnet G *et al*. Rituximab for induction and maintenance therapy in granulomatosis with polyangiitis (Wegener's). Results of a single-center cohort study on 66 patients. J Autoimmun 2014;50:135–41.

24 Roubaud-Baudron C, Pagnoux C, Meaux-Ruault N *et al*. Rituximab maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis. J Rheumatol 2012;39:125–30.

25 Charles P, Neel A, Tieulie N *et al*. Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients. Rheumatology (Oxford) 2014;53:532–9.

26 Besada E, Koldingsnes W, Nossent JC. Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre. Rheumatology (Oxford) 2013;52:2041–7.

27 Mohammad AJ, Hot A, Arndt F *et al*. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Ann Rheum Dis 2016;75:396–401.

28 Teixeira V, Mohammad AJ, Jones RB, Smith R, Jayne D. Efficacy and safety of rituximab in the treatment of eosinophilic granulomatosis with polyangiitis. RMD Open 2019;5:e000905.

29 Rituximab in Eosinophilic Granulomatosis with Polyangiitis (REOVAS). 2018. https://ClinicalTrials.gov/show/NCT02807103.

30 Cartin-Ceba R, Fervenza FC, Specks U. Treatment of antineutrophil cytoplasmic antibody-associated vasculitis with rituximab. Curr Opin Rheumatol 2012;24:15–23.

31 Extended Follow Up of the Mainritsan 2 Study. Comparison between a long term and a conventional maintenance treatment with rituximab (MAINRITSAN3). https://clinicaltrials.gov/ct2/show/NCT02433522.

32 Karras A, Pagnoux C, Haubitz M *et al*. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. Ann Rheum Dis 2017;76:1662–8.

33 Mahr A, Katsahian S, Varet H *et al*. Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis. Ann Rheum Dis 2013;72:1003–10.

34 Walsh M, Flossmann O, Berden A *et al*. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:542–8.

35 Roberts DM, Jones RB, Smith RM *et al*. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun 2015;57:60–5.

36 Cortazar FB, Pendergraft WF 3rd, Wenger J *et al*. Effect of continuous B cell depletion with rituximab on pathogenic autoantibodies and total IgG levels in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol 2017;69:1045–53.

37 Tomasson G, Grayson PC, Mahr AD, Lavalley M, Merkel PA. Value of ANCA measurements during remission to predict a relapse of ANCA-associated vasculitis—a meta-analysis. Rheumatology (Oxford) 2012;51:100–9.

38 Robson J, Doll H, Suppiah R *et al*. Damage in the ANCA-associated vasculitides: long-term data from the European Vasculitis Study Group (EUVAS) therapeutic trials. Ann Rheum Dis 2015;74:177–84.

39 Stone JH. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. J Mineralstoffwechsel 2010;17:168.

40 Broersen LHA, Pereira AM, Jørgensen JOL, Dekkers OM. Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. J Clin Endocrinol Metab 2015;100:2171–80.

41 Karangizi AHK, Al-Shaghana M, Logan S *et al*. Glucocorticoid induced adrenal insufficiency is common in steroid treated glomerular diseases – proposed strategy for screening and management. BMC Nephrol 2019;20:154.

42 Jarrousse B, Guillevin L, Bindi P *et al*. Increased risk of Pneumocystis carinii pneumonia in patients with Wegener's granulomatosis. Clin Exp Rheumatol 1993;11:615–21.

43 Flossmann O, Berden A, de Groot K *et al*. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 2011;70:488–94.

44 Mohammad AJ, Segelmark M, Smith R *et al*. Severe Infection in Antineutrophil Cytoplasmic Antibody-associated Vasculitis. J Rheumatol 2017;44:1468–75.

45 Holvast A, Stegeman CA, Benne CA *et al*. Wegener's granulomatosis patients show an adequate antibody response to influenza vaccination. Ann Rheum Dis 2009;68:873–8.

46 Jeffs LS, Peh CA, Jose MD, Lange K, Hurtado PR. Randomized trial investigating the safety and efficacy of influenza vaccination in patients with antineutrophil cytoplasmic antibody-associated vasculitis. Nephrology (Carlton) 2015;20:343–51.

47 Bingham CO 3rd, Looney RJ, Deodhar A *et al*. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum 2010;62:64–74.

48 Wijetilleka S, Jayne DR, Mukhtyar C *et al*. Recommendations for the management of secondary hypogammaglobulinaemia due to B cell targeted therapies in autoimmune rheumatic diseases. Rheumatology (Oxford) 2019;58:889–96.

49 Wijetilleka S, Mukhtyar C, Jayne D *et al*. Immunoglobulin replacement for secondary immunodeficiency after B-cell targeted therapies in autoimmune rheumatic disease: systematic literature review. Autoimmun Rev 2019;18:535–41.

50 Tesfa D, Gelius T, Sander B *et al*. Late-onset neutropenia associated with rituximab therapy: evidence for a maturation arrest at the (pro)myelocyte stage of granulopoiesis. Med Oncol 2008;25:374–9.

51 Besada E, Koldingsnes W, Nossent JC. Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis. Rheumatology (Oxford) 2014;53:1818–24.

52 Knight A, Sundstrom Y, Borjesson O *et al*. Late-onset neutropenia after rituximab in ANCA-associated vasculitis. Scand J Rheumatol 2016;45:404–7.

53 Reitblat T, Wechsler A, Reitblat O. Rituximab-related late-onset neutropenia in patients with rheumatic diseases: successful re-challenge of the treatment. Am J Case Rep 2015;16:211–4.

54 Marotte H, Paintaud G, Watier H, Miossec P. Rituximab-related late-onset neutropenia in a patient with severe rheumatoid arthritis. Ann Rheum Dis 2008;67:893–4.

Search strategy

Initial search

Pubmed

(Systemic vasculitis [MH] OR Systemic vasculiti* [TIAB] OR Pauci-Immune Vasculiti* [TIAB] OR Churg Strauss [tiab] OR Eosinophilic Granulomato* [TIAB] OR Wegener* [TIAB] OR Granulomatosis with Polyangiiti* [TIAB] OR Microscopic Polyangiiti* [TiAB] OR Periarteritis Nodosa [TIAB] OR Polyarteritis nodosa [TIAB] OR necrotising vasculiti* [TIAB] OR necrotizing vasculiti* [TIAB] OR Antibodies, antineutrophil cytoplasmic [MH] OR Anti Neutrophil Cytoplasmic Antibod* [TIAB] OR Anti Neutrophil Cytoplasm Antibod* [TIAB] OR AntiNeutrophil Cytoplasm Antibod* [TIAB] OR AntiNeutrophil Cytoplasmic Antibod* [TIAB] OR ANCA* [TIAB] OR cANCA [TIAB] OR pANCA [TIAB] OR pANCAs [TIAB]) AND (Rituximab [MH] OR Rituximab [TIAB] OR Mabthera [TIAB] OR Rituxan [TIAB] OR B-Lymphocytes/drug effects [MH])

Pubmed central

(Systemic vasculitis [MH] OR Systemic vasculiti* [all] OR Pauci-Immune Vasculiti* [all] OR Churg Strauss [all] OR Eosinophilic Granulomato* [all] OR Wegener* [all] OR Granulomatosis with Polyangiiti* [all] OR Microscopic Polyangiiti* [all] OR Periarteritis Nodosa [all] OR Polyarteritis nodosa [all] OR necrotising vasculiti* [all] OR Antibodies, antineutrophil cytoplasmic [MH] OR Anti Neutrophil Cytoplasmic Antibod* [all] OR Anti Neutrophil Cytoplasm Antibod* [all] OR AntiNeutrophil Cytoplasm Antibod* [all] OR AntiNeutrophil Cytoplasmic Antibod* [all] OR ANCA* [all] OR cANCA [all] OR pANCA [all] OR pANCAs [all]) AND (Rituximab [MH] OR Rituximab [all] OR Mabthera [all] OR Rituxan [all] OR B-Lymphocytes/drug effects [MH])

Medline

Systemic vasculiti$.tw. OR Pauci-Immune Vasculiti$.tw. OR Churg Strauss.tw. OR Eosinophilic Granulomato$.tw. OR Wegener$.tw. OR Granulomatosis with Polyangiiti$.tw. OR Granulomatosis ADJ3 Polyangiiti$.tw. OR Microscopic Polyangiiti$.tw. OR necrotising vasculiti$.tw. OR Antibodies, antineutrophil cytoplasmic [MH] OR Anti Neutrophil Cytoplasmic Antibod$.tw. OR Anti Neutrophil Cytoplasm Antibod$.tw. OR AntiNeutrophil Cytoplasm Antibod$.tw. OR AntiNeutrophil Cytoplasmic Antibod$.tw. OR ANCA$.tw. OR cANCA.tw. OR pANCA.tw. OR pANCAs.tw.) AND (Rituximab [MH] OR Rituximab.tw. OR Mabthera.tw. OR Rituxan.tw. OR B-Lymphocytes/drug effects [MH])

Embase

(systemic NEXT/1 vasculiti* OR 'Pauci-Immune Vasculitis' OR 'Pauci-Immune Vasculitides' OR 'Churg Strauss' OR eosinophilic next/5 granulomato* OR wegener*:ti,ab OR granulomatosis NEAR/5 polyangiitis OR microscopic NEXT/1 polyangiiti* OR "periarteritis nodosa" OR "polyarteritis nodosa" OR necrotising NEXT/1 vasculiti* OR necrotizing NEXT/1 vasculiti* OR "neutrophil cytoplasmic antibody"/syn OR neutrophil NEXT/1 cytoplasm* next/1 antibod* oR AntiNeutrophil NEXT/1 Cytoplasm* NEXT/1 Antibod* OR "ANCA associated vasculitis"/syn OR ANCA OR cANCA OR pANCA OR pANCAs) AND ("rituximab"/syn OR "CD20 antibody"/syn)

Additional pubmed searches for sub-topics

Co-trimoxazole

(("antibodies, antineutrophil cytoplasmic"[MeSH Terms] OR ("antibodies"[All Fields] AND "antineutrophil"[All Fields] AND "cytoplasmic"[All Fields]) OR "antineutrophil cytoplasmic antibodies"[All Fields] OR "anca"[All Fields])) AND (("trimethoprim, sulfamethoxazole drug combination"[MeSH Terms] OR ("trimethoprim"[All Fields] AND "sulfamethoxazole"[All Fields] AND "drug"[All Fields] AND "combination"[All Fields]) OR "sulfamethoxazole drug combination trimethoprim"[All Fields] OR ("co"[All Fields] AND "trimoxazole"[All Fields]) OR "co trimoxazole"[All Fields])) OR ((("pneumonia, pneumocystis"[MeSH Terms] OR ("pneumonia"[All Fields] AND "pneumocystis"[All Fields]) OR "pneumocystis pneumonia"[All Fields] OR "pneumocystis"[All Fields] OR "pneumocystis"[MeSH Terms])))

Vaccination

((("vaccination"[MeSH Terms] OR "vaccination"[All Fields]))) AND (("anti-neutrophil cytoplasmic antibody-associated vasculitis"[MeSH Terms] OR ("anti-neutrophil"[All Fields] AND "cytoplasmic"[All Fields] AND "antibody-associated"[All Fields] AND "vasculitis"[All Fields]) OR "anti-neutrophil cytoplasmic antibody-associated vasculitis"[All Fields] OR ("anca"[All Fields] AND "associated"[All Fields] AND "vasculitis"[All Fields]) OR "anca associated vasculitis"[All Fields]) OR “anca” OR “rituximab”[MeSH Terms] OR “rituximab”[All Fields]))

Hypogammaglobulinaemia

((((("hypogammaglobulinaemia"[All Fields] OR "agammaglobulinemia"[MeSH Terms] OR "agammaglobulinemia"[All Fields] OR "hypogammaglobulinemia"[All Fields])) OR ((acquired[All Fields] AND ("immunologic deficiency syndromes"[MeSH Terms] OR ("immunologic"[All Fields] AND "deficiency"[All Fields] AND "syndromes"[All Fields]) OR "immunologic deficiency syndromes"[All Fields] OR "immunodeficiency"[All Fields])))))) AND (("rituximab"[MeSH Terms] OR "rituximab"[All Fields]))

Late onset neutropenia

("neutropenia"[MeSH Terms] OR "leukopenia"[MeSH Terms])) AND ("rituximab"[MeSH Terms] OR "rituximab"[All Fields])

Progressive multifocal leukoencephalopathy

(((((Systemic vasculitis [MH] OR Systemic vasculiti* [TIAB] OR Pauci-Immune Vasculiti* [TIAB] OR Churg Strauss [tiab] OR Eosinophilic Granulomato* [TIAB] OR Wegener* [TIAB] OR Granulomatosis with Polyangiiti* [TIAB] OR Microscopic Polyangiiti* [TiAB] OR Periarteritis Nodosa [TIAB] OR Polyarteritis nodosa [TIAB] OR necrotising vasculiti* [TIAB] OR necrotizing vasculiti* [TIAB] OR Antibodies, antineutrophil cytoplasmic [MH] OR Anti Neutrophil Cytoplasmic Antibod* [TIAB] OR Anti Neutrophil Cytoplasm Antibod* [TIAB] OR AntiNeutrophil Cytoplasm Antibod* [TIAB] OR AntiNeutrophil Cytoplasmic Antibod* [TIAB] OR ANCA* [TIAB] OR cANCA [TIAB] OR pANCA [TIAB] OR pANCAs [TIAB]))) OR ((Rituximab [MH] OR Rituximab [TIAB] OR Mabthera [TIAB] OR Rituxan [TIAB] OR B-Lymphocytes/drug effects [MH]))) AND ("leukoencephalopathy, progressive multifocal"[MeSH

Terms] OR ("leukoencephalopathy"[All Fields] AND "progressive"[All Fields] AND "multifocal"[All Fields]) OR "progressive multifocal leukoencephalopathy"[All Fields] OR ("progressive"[All Fields] AND "multifocal"[All Fields] AND "leukoencephalopathy"[All Fields]))

Chapter 4 – Rituximab associated hypogammaglobulinaemia in patients with autoimmune disease

4.1 Introduction

Rituximab is increasingly used for the treatment of systemic autoimmune conditions, including AAV. The efficacy of rituximab is well established in AAV, as discussed in previous chapters. Rituximab is licensed also for the treatment of rheumatoid arthritis (RA), and commonly used in other autoimmune conditions including systemic lupus erythematosus (SLE).

Despite its efficacy, concerns regarding the longer-term effects of rituximab on B-cell function have remained. Hypogammaglobulinaemia, defined as levels of gammaglobulin (immunoglobulin G, IgG) below the normal reference range. This has been consistently observed in observational studies although it has been uncommon in RCTs. Moreover, it is suggested that hypogammaglobulinaemia is observed in patients receiving rituximab for AAV in excess of that seen in other autoimmune conditions [162, 163].

Infection remains a serious and common adverse event in patients with autoimmune disease, particularly in the setting of glucocorticoid use or the combination of multiple disease modifying immunosuppressive agents. Symptomatic hypogammaglobulinaemia occurs when IgG levels are below normal levels and the patient experiences recurrent or severe infections. Although there are varied opinions on an IgG threshold of clinical concern, the presence of recurrent and/or severe infections is the main impact to patients.

A previous study examining immunoglobulin levels in patients attending the Vasculitis and Lupus clinic at Addenbrooke's Hospital, Cambridge, defined hypogammaglobulinaemia as an IgG < 7 g/L [117]. Hypogammaglobulinaemia was further broken into degrees of severity: mild (5 to <7 g/L), moderate (3 to <5 g/L), and severe (<3g/L). The manuscript included in this chapter identified hypogammaglobulinaemia in 56% of patients, and gammaglobulin (immunoglobulin G, IgG) levels at rituximab commencement correlated with nadir IgG levels following rituximab. It was noted that hypogammaglobulinaemia was transient in 50% of patients who developed severe hypogammaglobulinaemia (IgG < 3 g/L).

For this paper, follow-up of the patients who had hypogammaglobulinaemia from the original study was extended to explore longer-term outcomes in patients with autoimmune disease who develop rituximab associated hypogammaglobulinaemia. We found substantial change in IgG levels over time, with both decline and recovery of IgG levels. The study also highlighted a

complex relationship between immunosuppressive agents and IgG levels, and suggested a potential sex difference in longer-term hypogammaglobulinaemia, which requires further study.

Rituximab, a monoclonal antibody targeting to CD20 and therefore affecting circulating B-cells but not B-cell precursors and plasma cells, usually results in temporary peripheral B-cell depletion. Previous studies have hypothesised that rituximab associated hypogammaglobulinaemia in patients with autoimmune disease relates to underlying B-cell dysfunction [164, 165]. This is supported by the association of low baseline IgG levels with subsequent hypogammaglobulinaemia [117, 164], which may also be confounded by previous immunosuppression. Depletion in memory B cells, associated with disease response in patients with RA [164, 166]. Delayed B-cell repopulation has been observed in patients with AAV compared with those with RA or connective tissue disease [167] . One case series of 5 patients receiving immunoglobulin replacement therapy for rituximab associated hypogammaglobulinaemia demonstrated low switched and un-switched memory B-cells [165].

In this paper, we present further data supporting the presence of B-cell dysfunction observed in other studies. There was persistent B-cell depletion in most patients with symptomatic hypogammaglobulinaemia post-rituximab referred for Clinical Immunology assessment. However, in symptomatic hypogammaglobulinaemia patients with subsequent B-cell repopulation, a pattern of high naïve and low switched memory B-cells was observed. This finding suggests that future work to explore whether there is an underlying B-cell defect remains relevant to better understanding the pathogenesis of hypogammaglobulinaemia in these patients.

Parallels are drawn between patients with autoimmune disease and rituximab associated hypogammaglobulinaemia, with patients with common variable immunodeficiency (CVID), who typically have hypogammaglobulinaemia with recurrent sinopulmonary infections and have a greater risk of autoimmune disease and malignancy. Immunoglobulin replacement therapy is offered to patients with autoimmune disease with hypogammaglobulinaemia who develop severe or recurrent infections, extrapolated from practice in patients with CVID and patients with hypogammaglobulinaemia following treatment for haematologic malignancies. Although immunoglobulin replacement therapy is common practice, there is limited evidence supporting its use in patients with autoimmune disease [168, 169].

In this study, infections were a notable issue for these patients with hypogammaglobulinaemia, with 53/142 (37%) commencing antibiotic prophylaxis and 29/142 (20%) commencing

immunoglobulin replacement therapy. Importantly, immunoglobulin replacement therapy reduced infection rates, but not severe infection rates.

Data I collected for this paper including infections and treatment were included in additional papers Appendix 3 and Appendix 4. Additional contributions were made to the interpretation of results and manuscript review. The first paper further highlights the frequency of severe infections in patients with AAV who have received rituximab [170]. The rate of severe infection was 26 per 100 person years. In addition to patient and disease related factors, the use of trimethoprim-sulfamethoxazole for prophylaxis did reduce the risk of severe infections.

This chapter underscores the ongoing challenge in balancing the benefits of rituximab in controlling disease activity, with adverse effects. The paper expands current knowledge of longer-term outcomes in patients with hypogammaglobulinaemia associated with rituximab use. The data suggests a reduction in infections in patients receiving immunoglobulin replacement therapy, which has not been previously demonstrated in patients with autoimmune disease and rituximab associated hypogammaglobulinaemia. Importantly, whilst fewer overall infections were observed in patients with hypogammaglobulinaemia while on rituximab, severe infections did not, and remains a concern for long-term management of these patients.

4.2 Manuscript: Rituximab Associated Hypogammaglobulinemia in Autoimmune Disease

Statement of Authorship

Title of Paper	Rituximab Associated Hypogammaglobulinemia in Autoimmune Disease
Publication Status	Published
Publication Details	Tieu, J., R. M. Smith, S. Gopaluni, D. S. Kumararatne, M. McClure, A. Manson, S. Houghton and D. R. W. Jayne (2021). "Rituximab Associated Hypogammaglobulinemia in Autoimmune Disease."Frontiers in Immunology 12: 671503.

Principal author

Candidate name	Joanna Tieu
Overall percentage	75%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signature Date 08/11/2021

Co-author contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Rona Smith
Contribution	Contributed to study design, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature *or Rona Smith* Date 14/12/2021

Name of Co-Author	Seerapani Gopaluni		
Contribution	Contributed to data acquisition, analysis and interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.		
Signature		Date	09/11/2021

Name of Co-Author	Dinakantha Kumararatne		
Contribution	Contributed to study design, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.		
Signature		Date	08/11/2021

Name of Co-Author	Mark McClure		
Contribution	Contributed to study design, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.		
Signature		Date	08/11/2021

Name of Co-Author	Ania Manson		
Contribution	Contributed to interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.		
Signature		Date	11/11/2021

Name of Co-Author	Sally Houghton		
Contribution	Contributed to interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.		
Signature		Date	13/12/2021

Name of Co-Author	David Jayne
Contribution	Contributed to study design, interpretation of results, critical appraisal of draft manuscript and approval of manuscript for publication.

Signature Date 24/11/2021

frontiers in Immunology

ORIGINAL RESEARCH
published: 12 May 2021
doi: 10.3389/fimmu.2021.671503

Rituximab Associated Hypogammaglobulinemia in Autoimmune Disease

*Joanna Tieu[1,2,3], Rona M. Smith[1,2], Seerapani Gopaluni[1,2], Dinakantha S. Kumararatne[4], Mark McClure[1,2], Ania Manson[4], Sally Houghton[4] and David R. W. Jayne[1,2]**

[1] Department of Medicine, University of Cambridge, Cambridge, United Kingdom, [2] Vasculitis and Lupus Clinic, Cambridge University Hospitals National Health Service (NHS) Foundation Trust, Cambridge, United Kingdom, [3] Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia, [4] Clinical Immunology Unit, Cambridge University Hospitals NHS Trust, Cambridge, United Kingdom

OPEN ACCESS

Edited by:
Mohammed Yousuf Karim,
Weill Cornell Medicine-Qatar, Qatar

Reviewed by:
Ola Grimsholm,
University of Gothenburg, Sweden
Yu-Jih Su,
Kaohsiung Chang Gung Memorial Hospital, Taiwan

***Correspondence:**
David R. W. Jayne
dj106@cam.ac.uk

Specialty section:
This article was submitted to Autoimmune and Autoinflammatory Disorders, a section of the journal Frontiers in Immunology

Received: 23 February 2021
Accepted: 19 April 2021
Published: 12 May 2021

Citation:
Tieu J, Smith RM, Gopaluni S, Kumararatne DS, McClure M, Manson A, Houghton S and Jayne DRW (2021) Rituximab Associated Hypogammaglobulinemia in Autoimmune Disease. Front. Immunol. 12:671503. doi: 10.3389/fimmu.2021.671503

Objective: To evaluate the characteristics of patients with autoimmune disease with hypogammaglobulinemia following rituximab (RTX) and describe their long-term outcomes, including those who commenced immunoglobulin replacement therapy.

Methods: Patients received RTX for autoimmune disease between 2003 and 2012 with immunoglobulin G (IgG) <7g/L were included in this retrospective series. Hypogammaglobulinemia was classified by nadir IgG subgroups of 5 to <7g/L (mild), 3 to <5g/L (moderate) and <3g/L (severe). Characteristics of patients were compared across subgroups and examined for factors associated with greater likelihood of long term hypogammaglobulinemia or immunoglobulin replacement.

Results: 142 patients were included; 101 (71%) had anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis (AAV), 18 (13%) systemic lupus erythematosus (SLE) and 23 (16%) other conditions. Mean follow-up was 97.2 months from first RTX. Hypogammaglobulinemia continued to be identified during long-term follow-up. Median time to IgG <5g/L was 22.5 months. Greater likelihood of moderate hypogammaglobulinemia (IgG <5g/L) and/or use of immunoglobulin replacement therapy at 60 months was observed in patients with prior cyclophosphamide exposure (odds ratio (OR) 3.60 [95% confidence interval (CI) 1.03 – 12.53], glucocorticoid use at 12 months [OR 7.48 (95% CI 1.28 – 43.55], lower nadir IgG within 12 months of RTX commencement [OR 0.68 (95% CI 0.51 – 0.90)] and female sex [OR 8.57 (95% CI 2.07 – 35.43)]. Immunoglobulin replacement was commenced in 29/142 (20%) and associated with reduction in infection rates, but not severe infection rates.

Conclusion: Hypogammaglobulinemia continues to occur in long-term follow-up post-RTX. In patients with recurrent infections, immunoglobulin replacement reduced rates of non-severe infections.

Keywords: rituximab, hypogammaglobulinemia, autoimmune disease, immunoglobulin replacement therapy, B-cell

INTRODUCTION

B cell depletion plays a key role in the management of many autoimmune diseases. Rituximab (RTX) is licensed for use in rheumatoid arthritis (RA) and AAV, and clinical trials have evaluated RTX in other autoimmune conditions including SLE. Despite limited evidence of hypogammaglobulinemia in patients receiving RTX in these studies, it has been consistently identified in observational studies of patients with autoimmune disease (1–7).

Lower baseline immunoglobulin G (IgG) levels, including levels within population norms, have been associated with subsequent hypogammaglobulinemia (2, 4, 6, 7). An association between cumulative RTX exposure and hypogammaglobulinemia has not been demonstrated (2–4, 7).

Although there is no universal IgG threshold for hypogammaglobulinemia, the clinical significance of hypogammaglobulinemia lies in the resultant susceptibility to infection. Extrapolated from the treatment of patients with common variable immunodeficiency (CVID), prophylactic antibiotics and immunoglobulin replacement therapy are considered where there is a combination of hypogammaglobulinemia, poor vaccination responses, and recurrent and/or severe infection.

Although a proportion of patients with hypogammaglobulinemia have been identified following RTX therapy for autoimmune disease in several studies, their longer-term outcomes, including the effects of immunoglobulin replacement therapy, remain unclear.

In a previous study, from which this study cohort derives, 135/243 (56%) patients with systemic autoimmune disease treated with RTX developed hypogammaglobulinemia (4). This was classified as mild (5 to <7 g/L) in 72 (53%), moderate (3 to <5 g/L) in 53 (39%) and severe (<3 g/L) in 10 (7%). In this study, we sought to evaluate the long-term outcomes of patients with previously identified hypogammaglobulinemia.

OBJECTIVES

1. To explore the characteristics of patients with autoimmune disease who develop RTX associated hypogammaglobulinemia and their long-term outcomes.
2. To examine the outcomes of patients with autoimmune disease which develop RTX associated hypogammaglobulinemia requiring immunoglobulin replacement therapy.

METHODS

Patients with multi-system autoimmune disease who had received RTX between February 2003 and November 2012 and had an IgG <7 g/L on at least two occasions were included in this single center, retrospective cohort form the Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge, United Kingdom. Data were collected until August 2017 or last recorded follow-up. A previous report from this cohort described immunoglobulin outcomes in 243 patients who had received RTX for the treatment of multi-system autoimmune disease up to November 2012 (4). This report includes extended follow-up of 142 patients who met the above inclusion criteria.

Patients received a standard departmental dose of 2x1g a fortnight apart followed by 1g every 6 months for 2 years. Extension of RTX course and shortened treatment regimens occurred when clinically appropriate. At the time of treatment for these patients, biosimilar products were not available. Clinical assessments and laboratory data were typically obtained 6-monthly, prior to each dose of RTX. Interval data, where available, were also collected.

Patients were excluded if paraproteinemia was detected at any time during follow-up. All immunoglobulin results during periods of nephrotic range proteinuria and for 3 months following plasma exchange were excluded from analyses. Patients were categorized by absolute nadir IgG levels, as mild (5 to <7 g/L), moderate (3 to <5 g/L), and severe (<3 g/L). Infection was defined as any presumed or confirmed infection warranting the use of an oral antimicrobial agent. Severe infection was defined as a presumed or confirmed infection requiring an intravenously administered antimicrobial and/or hospital admission.

Data collected on each patient included age at diagnosis, gender, disease diagnosis and manifestations, age, date, and indication for first RTX prescription, cumulative RTX dose, use of immunosuppressive agent(s) pre-RTX, concurrently and post-RTX, prednisolone use at RTX commencement, and at 6 monthly intervals until 24 months post-RTX, infections, mortality, antibiotic prophylaxis and use and duration of immunoglobulin replacement therapy (intravenous or subcutaneous). Prednisolone was the standard oral glucocorticoid prescribed, with equivalent efficacy to prednisone. Laboratory data were collected for each patient from 1 month prior to rituximab to last follow-up, including IgG, IgM and IgA levels, lymphocyte, and neutrophil counts, and CD19, CD4 and CD8 counts. Flow cytometry for lymphocyte subsets were not routine prior to every RTX infusion. Where available, B cell subsets and antibody titers to pneumococcal, haemophilus, varicella, measles, mumps, rubella, and tetanus were collected.

Concurrent immunosuppression was defined as the use of an immunosuppressive agent for at least 6 weeks from RTX commencement, except for cyclophosphamide where any use within the first 6 weeks was included. Post-RTX immunosuppression was defined as use of an immunosuppressive agent at least 6 weeks after RTX commencement, for at least 3 months.

In the setting of hypogammaglobulinemia, immunoglobulin replacement therapy was typically commenced in patients with recurrent and/or severe infections following specialist clinical immunology evaluation. This generally included the assessment of infection rates, and laboratory parameters including lymphocyte subsets and vaccine responses to *Streptococcus pneumoniae* and *Haemophilus influenzae*, and a trial of prophylactic antibiotics. Prophylactic antibiotic choice was individualized where possible; azithromycin was typically used if not available microbiological or antibiotic sensitivity data was available. Intravenous immunoglobulin replacement therapy was commenced, and patients transitioned to self-administered subcutaneous administration where appropriate.

Intravenous immunoglobulin was not used for treatment of underlying autoimmune disease in these patients.

In accordance with the UK National Health Service Research Ethics Committee guidelines, ethics approval was not required as this work comprises anonymous retrospective data and all treatment decisions were made prior to our evaluation.

Dichotomous outcomes are summarized as proportions. Continuous outcomes are summarized as mean and standard deviation if normally distributed, otherwise as median and interquartile range. Comparisons of categorical variables across the immunoglobulin categories were analyzed using Somers' D to assess for the trend across nadir IgG subgroups. Nominal categorical variables were compared using Chi squared tests or Fisher's exact test as appropriate. Continuous variables have been compared using Kruskall-Wallis tests. In patients receiving immunoglobulin replacement therapy, infection and severe infection rates were compared by Wilcoxon sign ranked tests. Nadir IgG in the first 12 months were used to examine outcome at 60 and 100 months following the first dose of RTX. A multivariable logistic regression model was used to model outcome (IgG <5g/L or on immunoglobulin replacement therapy) at 60 months. Prespecified explanatory variables were included using a step-wise approach. Model fit was assessed using -2log likelihood, Cox & Snell R square and Nagelkerke R square values. Statistical analyses were performed in SPSS version 24 and figures were produced using Graphpad prism version 7 and R (ggalluvial package).

RESULTS

Long-term clinical and immunoglobulin data were available for 142 patients with hypogammaglobulinemia. Mild hypogammaglobulinemia was recorded in 40/142 (28.2%), moderate in 66/142 (46.5%) and severe in 36/142 (25.4%) patients. Mean follow-up was 97.2 months; and was longer in lower nadir IgG subgroups (**Table 1**). Patients with more severe hypogammaglobulinemia were younger at diagnosis and first RTX (**Table 1**). AAV was the most common indication for RTX (71%) and most patients received RTX for the management of relapsing (25%) or refractory (69%) disease (**Table 1**). There was no difference in indication for RTX (new, relapsing, or refractory disease), or by diagnosis ($p = 0.27$, data not shown) by subgroup. Seventy one percent were female, with a greater proportion in patients with moderate and severe hypogammaglobulinemia (**Table 1**).

Immunosuppression and Development of Hypogammaglobulinemia

Exposure to mycophenolate mofetil prior to RTX was more common in patients with moderate or severe hypogammaglobulinemia (**Table 2**). Prednisolone use at 12 and 24 months following RTX commencement were associated with lower nadir IgG (**Table 2**). Cumulative RTX dose and prior exposure to other immunosuppressive agents were not associated with a lower nadir IgG (**Table 2**).

Immunoglobulin Levels Over Long-Term Follow-Up

Baseline values were often collected after commencement of glucocorticoids; mean IgG at baseline was 7.45 (standard deviation (SD) 3.1), mean baseline IgM was 0.8 (SD0.5) and mean baseline IgA was 1.6 (0.8).

Moderate (IgG <5 g/L) and severe (IgG <3 g/L) hypogammaglobulinemia and use of immunoglobulin replacement therapy was increasingly observed with longer follow-up (**Figure 1**). Median time to moderate hypogammaglobulinemia was 22.5 months [IQR 3.0 to 61.5] and to severe hypogammaglobulinemia was 24.5 months [IQR 4.0 to 80.8].

Of the patients who were followed up to 60 months post-RTX (n=124), substantial change was observed in IgG levels over

TABLE 1 | Patient characteristics.

	All (n = 142)	Mild (n = 40)	Moderate (n = 66)	Severe (n = 36)
Total follow-up (months)	97.2 ± 36.4	87.5 ± 33.7	95.7 ± 34.1	110.6 ± 40.1
Age (years)	45.2 ± 17.6	47.9 ± 17.7	47.6 ± 16.7	37.4 ± 17.2
Age at first RTX (years)	51.4 ± 16.5	55.8 ± 15.8	52.4 ± 15.2	44.2 ± 17.7
Disease duration (months)	43.1 [13.2 – 101.7]	63.2 [10.8 – 159.2]	31.7 [11.7 – 76.8]	56.0 [19.4 – 97.7]
Female	101/142 (71)	21/40 (53)	50/66 (76)	30/36 (83)
Diagnosis				
AAV	101/142 (71)	30/40 (75)	48/66 (73)	23/36 (64)
GPA	69/101 (68)	21/30 (70)	34/48 (71)	14/23 (61)
MPA	15/101 (15)	4/30 (13)	6/48 (13)	5/23 (22)
EGPA	17/101 (17)	5/30 (17)	8/48 (17)	4/23 (17)
SLE	18/142 (13)	5/40 (13)	6/66 (9)	7/36 (19)
Other*	23/142 (16)	5/40 (13)	12/66 (18)	6/36 (17)
Disease state				
New	8/140 (6)	1/39 (3)	5/66 (8)	2/35 (6)
Relapse	35/140 (25)	10/39 (26)	16/66 (24)	9/35 (26)
Refractory	97/140 (69)	28/39 (72)	45/66 (68)	24/35 (69)

Mild: nadir IgG 5 to < 7 g/L, Moderate: nadir IgG 3 to < 5 g/L, Severe: nadir IgG < 3 g/L.

**other: Undifferentiated connective tissue disorder (4), Neuromyelitis optica (3), Undifferentiated vasculitis (2), Behcet's syndrome (2), polychondritis (2), mixed connective tissue disease (2), IgA vasculitis (1), cryoglobulinemic vasculitis (1), polyartertitis nodosa (1), Cogan's syndrome (1), Takayasu arteritis (1), myasthenia gravis (1), cryoglobulinemic vasculitis (1).*

AAV, ANCA-associated vasculitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; SLE, systemic lupus erythematosus.

Mean ± standard deviation, median [interquartile range].

TABLE 2 | Use of immunosuppressive agents in patients with hypogammaglobulinemia.

	All (n = 142)	Mild (n = 40)	Moderate (n = 66)	Severe (n = 36)	p
Cumulative RTX (g)	9.0 ± 5.1	8.5 ± 4.7	9.8 ± 5.6	8.1 ± 4.4	0.23
Pre-RTX immunosuppression					
Cyclophosphamide	107/142 (75)	29/40 (73)	49/65 (75)	28/36 (78)	0.79
Cumulative cyclophosphamide dose (g)	12.0 [6.0 – 26.0]	12.0 [5.8 – 27.8]	11.5 [6.0 – 17.3]	11.0 [5.7 – 27.0]	0.91
Azathioprine	88/141 (62)	27/40 (68)	39/65 (60)	22/36 (61)	0.54
Mycophenolate mofetil	94/141 (67)	25/40 (63)	39/65 (60)	30/36 (83)	0.05
Methotrexate	36/141 (26)	10/40 (25)	20/65 (31)	6/36 (17)	0.42
Intravenous immunoglobulin	22/141 (16)	7/40 (18)	8/65 (12)	7/36 (19)	0.86
Plasma exchange	16/141 (11)	4/40 (10)	5/65 (8)	7/36 (19)	0.27
No. immunosuppressive medications	3.0 [2.0 – 4.0]	3.0 [2.0 – 3.0]	3.0 [2.0 – 3.0]	3.0 [2.0 – 4.0]	0.49
Concurrent immunosuppression					
Cyclophosphamide	25/141 (18)	6/40 (15)	13/66 (20)	6/35 (17)	0.77
Mycophenolate mofetil	21/141 (15)	5/40 (13)	9/66 (14)	7/35 (20)	0.39
Plasma exchange	10/141 (7)	4/40 (10)	3/66 (5)	3/35 (9)	0.79
Post-RTX immunosuppression					
Cyclophosphamide	20/142 (14)	6/40 (15)	8/66 (12)	6/36 (17)	0.87
Mycophenolate mofetil	27/142 (19)	5/40 (13)	14/66 (21)	8/36 (22)	0.25
No. immunosuppressive medications	0.0 [0.0 – 1.0]	0.5 [0.0 – 1.0]	0.0 [0.0 – 1.0]	1.0 [0.0 – 1.8]	0.44
Prednisolone					
Baseline	115/121 (95)	36/38 (95)	53/55 (96)	26/28 (93)	0.82
6 months	120/133 (90)	31/39 (79)	61/63 (97)	28/31 (90)	0.15
12 months	113/137 (82)	27/39 (69)	56/64 (88)	30/34 (88)	0.04
24 months	98/133 (74)	22/37 (59)	48/62 (77)	28/34 (82)	0.03

Mild: nadir IgG 5 to < 7 g/L, Moderate: nadir IgG 3 to < 5 g/L, Severe: nadir IgG < 3 g/L.
RTX, rituximab. Proportion (%), median [interquartile range].

time (**Figure 2**). In patients with moderate hypogammaglobulinemia within the first 12 months of RTX administration, 17/37 (45%) patients recovered to an IgG ≥5 g/L without the need for immunoglobulin replacement therapy at 60 months. A further 8/37 (22%) had commenced immunoglobulin replacement therapy, and the remaining 12/37 (32%) remained hypogammaglobulinemia with an IgG <5 g/L at 60 months.

In a multivariable logistic regression model, cyclophosphamide use prior to RTX, lower nadir IgG in the first 12 months, prednisolone use at 12 months following RTX, and female sex were associated with an increased likelihood of moderate hypogammaglobulinemia and/or requiring immunoglobulin replacement 60 months after RTX commencement. This model was additionally adjusted for age at RTX commencement, mycophenolate use prior to RTX and total cumulative RTX (**Table 3**).

Cumulative RTX dose was not associated with a greater likelihood of moderate/severe hypogammaglobulinemia or requiring immunoglobulin replacement therapy 60 months after RTX commencement. The inclusion of disease duration prior to RTX and number of immunosuppressive agents used post-RTX did not improve model fit or alter overall interpretation. A model inclusive of nadir IgM values within the first 12 months improved model fit, with no change in interpretation (**Table 3**).

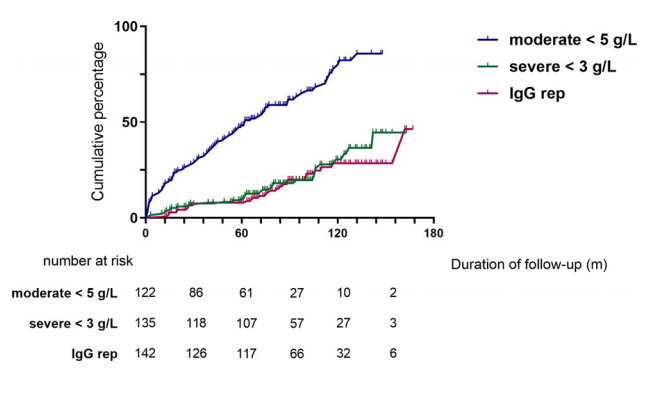


FIGURE 1 | Cumulative incidence of hypogammaglobulinemia and immunoglobulin replacement therapy commencement during follow-up.

Hypogammaglobulinemia and Infection

Overall, infection rates were low. Severe and non-severe infections predominantly involved the respiratory tract (65% and 58% respectively). There were no differences in infection rates between patients with mild, moderate, and severe hypogammaglobulinemia (**Figure 3A**). A subset of patients, however, were referred for further assessment and/or commenced prophylactic therapy due to recurrent infections.

Peripheral blood immunophenotyping was available in 30 patients at the time of Clinical Immunology assessment; CD19+ lymphocytes were detectable in 11 (37%). Where sufficient B cells were identified in 8 of these patients (7 with AAV and 1 with SLE), further B cell subset analyses were performed. This revealed a pattern of high naïve ($IgM^+IgD^+CD27^-$) and low switched memory ($IgM^-IgD^-CD27^+$) B cells in all patients (**Supplementary Table 1**).

Pneumococcal antibody titers were available in 28 patients with recurrent infection, with only 9 having protective antibody titers to at least 7 of the 13 serotypes tested. In those who went on

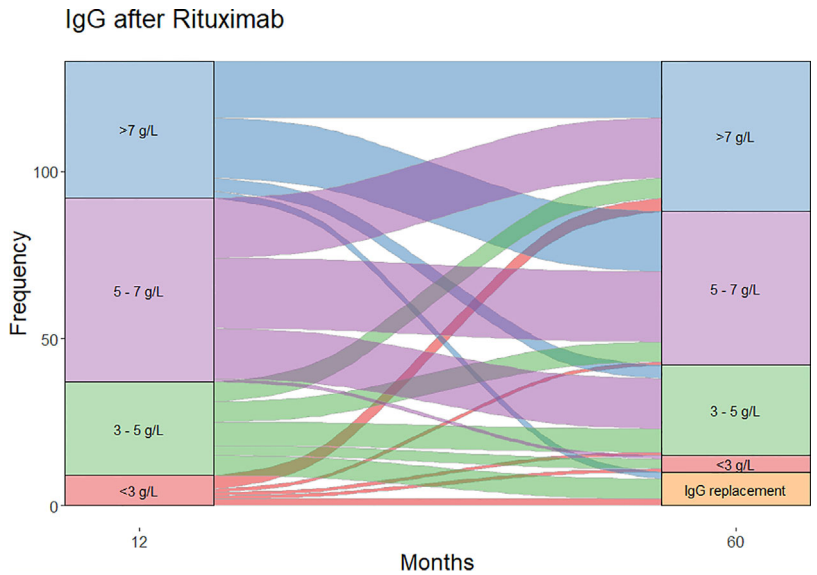


FIGURE 2 | Change in IgG strata between month 12 and month 60 of follow-up.

TABLE 3 | IgG < 5 g/L or immunoglobulin replacement at 60 months.

	Model 1 OR (95% CI)	p- value	Model 2 OR (95% CI)	p-value
Age at RTX commencement	0.98 (0.95 – 1.01)	0.21	0.97 (0.94 – 1.01)	0.10
Female	7.56 (1.88 – 30.48)	0.004	8.57 (2.07 – 35.43)	0.008
Pre-RTX cyclophosphamide	3.31 (1.00 – 10.96)	0.05	3.60 (1.03 – 12.53)	0.04
Pre-RTX mycophenolate	2.16 (0.75 – 6.26)	0.16	2.04 (0.70 – 5.95)	0.20
Nadir IgG (0 – 12 m)	0.67 (0.50 – 0.90)	0.008	0.68 (0.51 – 0.90)	0.008
Prednisolone use at 12 m	6.19 (1.12 – 33.31)	0.03	7.48 (1.28 – 43.55)	0.03
Total cumulative RTX	0.91 (0.81 – 1.02)	0.09	0.91 (0.81 – 1.02)	0.11
Nadir IgM (0 – 12 m)	–		0.12 (0.01 – 1.05)	0.06

RTX, rituximab; Ig immunoglobulin; m, month, OR, odds ratio, CI, confidence interval.

to receive immunoglobulin replacement therapy, only 4 of 18 patients tested (22%) had protective pneumococcal antibody levels, and a post-vaccination response was demonstrated in only 1/9 (11%) recorded.

Antibiotic Prophylaxis and Immunoglobulin Replacement Therapy

Antibiotic prophylaxis was initiated in 53 (37%) of patients; greater antibiotic prophylaxis use was observed in patients with moderate and severe hypogammaglobulinemia (**Figure 3B**). Of the patients who commenced antibiotic prophylaxis, 42 (79%) were AAV patients, 6 (11%) had SLE and 5 (9%) other autoimmune conditions. Immunoglobulin replacement therapy was initiated in 27/53 (51%) patients who had commenced antibiotic prophylaxis.

Immunoglobulin replacement therapy was commenced in 29 patients; with mild hypogammaglobulinemia in 1 (3%) patient, moderate hypogammaglobulinemia in 9 patients (31%) and severe hypogammaglobulinemia in 19 patients (66%). Of the patients commencing immunoglobulin replacement therapy, 21 (72%) had a diagnosis of AAV, 4 (14%) SLE and 4 (14%) other autoimmune diseases. Immunoglobulin replacement therapy was commenced a median of 71 months after first RTX. In patients commencing immunoglobulin replacement therapy, infections reduced (median [IQR] 1.02 infections/year [0.54 – 1.88] to 0.13 infections/year [0.00 – 0.35], p <0.001, **Figure 3C**). Annual severe infection rates were not reduced during immunoglobulin replacement therapy in these patients. After removal of two outliers with recurrent respiratory tract infections requiring antibiotics, there remained no difference in severe infection rates.

At the time of data collection or last recorded follow-up, 20 of 29 patients were continuing to receive immunoglobulin replacement therapy, 4 had died and 5 had ceased immunoglobulin replacement therapy. Of the four who died, the causes of death were respiratory sepsis in a patient with AAV, decompensated liver disease and pneumonia in a patient with IgA vasculitis, refractory vasculitis in a patient with AAV and was unknown in a patient with AAV. Of the five who had ceased immunoglobulin replacement therapy, 2 were intolerant and 3 were weaned off immunoglobulin replacement therapy without recurrent infection; 1 subsequently recommenced immunoglobulin replacement therapy owing to recurrent infection,

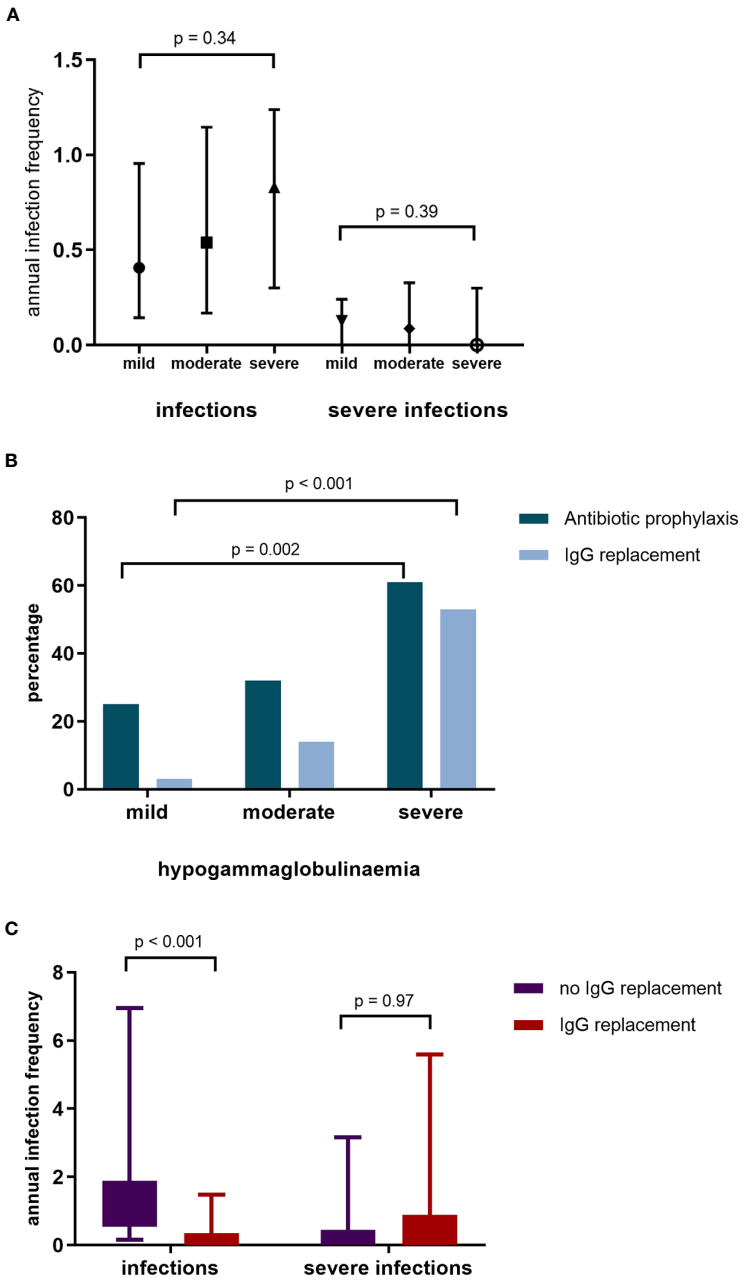


FIGURE 3 | **(A)** Annual infection and severe infection rate by IgG subgroup. **(B)** Commencement of antibiotic (Abx) prophylaxis and IgG replacement by IgG group. **(C)** Infection and severe infection rates in patients without IgG replacement and during IgG replacement.

1 has had IgG recovery to normal levels (>7 g/L), and 3 have remained off immunoglobulin replacement therapy with stable IgG levels <5 g/L.

DISCUSSION

We report on 142 patients with multi-system autoimmune disease with RTX associated hypogammaglobulinemia, their long-term outcomes and response to immunoglobulin replacement therapy. Overall, 102/142 (72%) had moderate hypogammaglobulinemia and 36/142 patients (25%) severe hypogammaglobulinemia. Factors associated with lower nadir IgG levels were prior mycophenolate use and prednisolone use 12 and 24 months after RTX initiation. Prior cyclophosphamide, prednisolone at 12 months after RTX initiation, nadir IgG in the first 12 months of RTX commencement and female sex were associated with an increased likelihood of moderate/severe hypogammaglobulinemia

and/or immunoglobulin replacement therapy use 60 months post-RTX commencement. Antibiotic prophylaxis was used in 53/142 (37%) patients and immunoglobulin replacement therapy commenced in 29/142 (20%) in whom infection rates but not severe infection rates were reduced.

The majority of patients included in this study had refractory SLE and AAV. There is substantial consistent evidence that RTX is beneficial in patients with AAV in both induction and maintenance of remission (8–10). Although data for RTX in SLE has been mixed, observational studies have demonstrated benefit (11, 12). Although hypogammaglobulinemia has been identified in multiple observational studies, the occurrence of hypogammaglobulinemia in this cohort is higher than previous estimates (7, 13–16). This cohort had a longer duration of follow-up, with nadir IgG levels occurring many months or years after commencing RTX therapy. Mean follow-up was 8 years, compared with up to an average follow-up of 4 years in other studies (2, 7, 13–18).

The rate of hypogammaglobulinemia may also be influenced by diagnosis. Although most patients in this study had AAV, other studies of hypogammaglobulinemia have included greater proportions of patients with RA (not included in this study) and SLE (13% of this cohort) (1, 16, 18). Thiel and colleagues have demonstrated delayed B cell recovery following RTX in patients with AAV compared with RA and SLE, suggesting a distinct underlying or acquired B cell dysfunction in these patients (19).

Notably, cumulative RTX doses are higher in this study than other reports (6, 7, 15, 17). This is likely influenced by multiple factors including the duration of follow-up and high proportion of patients with longstanding relapsing or refractory disease in this cohort. An association between cumulative RTX and hypogammaglobulinemia has previously been postulated (6), but not identified in other studies (2, 4, 7). In this study, there was no difference in cumulative RTX dose across the subgroups and was not associated with greater likelihood of moderate/severe hypogammaglobulinemia or requiring immunoglobulin replacement therapy at 60 months in an adjusted logistic regression model.

The impact of other immunosuppressive agents used prior to, in conjunction with or after RTX in the development of hypogammaglobulinemia has been difficult to delineate. Of note, mean baseline immunoglobulin levels were low-normal at baseline. In this study, mycophenolate and cyclophosphamide were the most common non-glucocorticoid immunosuppressive agents used. In the multivariable logistic regression model accounting for age, sex and prednisolone use post-RTX, prior cyclophosphamide, but not mycophenolate use increased the likelihood of moderate or severe hypogammaglobulinemia 60 months after RTX initiation. Venhoff and colleagues observed prolonged B cell depletion in patients who received RTX after previous cyclophosphamide use compared with RTX alone (20). In this study, 54% of patients who had received prior cyclophosphamide developed hypogammaglobulinemia, compared with 21% who received RTX alone.

Glucocorticoids alone have also been implicated in the development of hypogammaglobulinemia, and the impact of prolonged or greater glucocorticoid use in conjunction with RTX or other immunosuppressive agents on immunoglobulin levels requires further study (21). In this cohort, prednisolone use at 12 and 24 months were associated with lower nadir immunoglobulin levels. In the multivariable model examining outcomes at 5 years, prednisolone use at 12 months was associated with increased likelihood of moderate or severe hypogammaglobulinemia and/or immunoglobulin replacement. The use of prednisolone at 12 months was observed in 82.5% of patients, reflective of clinical practice in patients with historically more difficult to control, longstanding disease. Ongoing efforts to minimize glucocorticoid exposure remain important to the chronic management of these patients.

Of interest, there were more female patients were more likely to have more likely to have moderate/severe hypogammaglobulinemia and/or have commenced immunoglobulin replacement therapy at 60 months. Cross sectional studies suggest that immunoglobulin levels decline with age, with limited differences between males and females in adult age ranges (22–24). In post-hoc analyses of a trial evaluating induction therapy in AAV, female patients receiving RTX had higher serum RTX levels compared with males despite using body surface area dosing (25). Importantly, however, although higher serum levels of RTX were associated with a longer time to B cell repopulation, this was not associated with fewer relapses up to 18 months of follow-up. This association requires further assessment in larger cohorts and could have implications for dosing based on sex if confirmed.

Infections remain the key concern in patients with hypogammaglobulinemia. In a mixed cohort of patients receiving RTX for cancer (77.7%) and rheumatologic conditions (27.7%), severe infection rates were greater in patients with hypogammaglobulinemia (26). This was observed in early follow-up 12 months after RTX by MD Yusof and colleagues who in a mixed cohort of patients with autoimmune rheumatic diseases, identified an increased likelihood of severe infections in patients with hypogammaglobulinemia (16).

The use of immunoglobulin replacement therapy in patients with hypogammaglobulinemia associated with immunosuppression is extrapolated from experience in the management of the heterogenous group of patients with CVID. Both groups share a predisposition to infection, hypogammaglobulinemia, and impaired vaccination responses. In CVID, a reduction in respiratory tract infections has been demonstrated in small cohorts after commencement of immunoglobulin replacement therapy (27–29). The efficacy of immunoglobulin replacement therapy in patients with hypogammaglobulinemia and hematological malignancies has also been demonstrated in small cohorts (30). We observed a reduction in infection rates after initiation of immunoglobulin replacement therapy, supporting the efficacy of immunoglobulin replacement therapy in this population of patients with systemic autoimmune disease.

Importantly, despite the reduction in infections requiring antimicrobial therapy, the same benefit was not observed for severe infections. The majority of severe infections in these patients were respiratory tract infections; in this patient

population, disease related airways damage and colonization of the respiratory tract commonly contribute to chronic and recurrent infections, which may not be mitigated by immunoglobulin replacement. Age and other comorbidities may additionally influence infections in this cohort of patients with refractory and relapsing disease.

Given the patient and health care burdens of ongoing immunoglobulin replacement therapy, and increasing concerns regarding supply of this limited resource, trials of immunoglobulin replacement therapy cessation are considered. However, the most appropriate approach to this remains unknown. Recovery of immunoglobulin levels was observed in several individuals in longer term follow-up. In this single center study, of the 29 patients who commenced immunoglobulin replacement therapy, it was successfully ceased in 4 of the 5 patients in whom this was attempted. Although a very limited experience is presented in this study, it highlights the possibility of cessation of immunoglobulin replacement.

Again, albeit in small numbers, the pattern of high naïve and low switched memory B cells observed in a subset of these patients with hypogammaglobulinemia despite B cell repopulation warrants further investigation. Although a possible treatment effect, this could be representative of an associated underlying B cell dysfunction, which has been suggested in the associations between CVID and autoimmunity (31, 32).

Limitations of this study include the retrospective design, introducing selection bias in choice of treatments and total doses. Long-term follow-up in patients who have difficult to control rare autoimmune disease has inherent challenges. Though missing data, particularly for infection and severe infections, which were often not culture proven, is an important limitation, this group of patients typically have close clinical review focusing on infections, an important contributor to morbidity in this group of patients. The lack of control group for comparisons of infection and severe infection rates is a limitation to this study. Some studies have drawn comparisons between cyclophosphamide and rituximab treated patients. As refractory disease or disease relapse are common in long term follow-up, overlap of medications are common, and limit comparisons between groups.

In this study evaluating long-term outcomes of patients with RTX associated hypogammaglobulinemia, we have observed clinically significant hypogammaglobulinemia in a high proportion of patients, and an increasing incidence of hypogammaglobulinemia over time. The rates observed highlight the need for ongoing immunoglobulin monitoring in patients who have previously or continue to receive RTX. The use of prior immunosuppressive therapies, prolonged glucocorticoid use and female gender were associated with hypogammaglobulinemia long-term. Additionally, a reduction in infection in those receiving immunoglobulin replacement therapy for recurrent infection, provides evidence of its efficacy in this population of immunodeficient individuals. The risks and consequences of hypogammaglobulinemia should be considered with RTX therapy in multi-system autoimmune disease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation upon reasonable request.

ETHICS STATEMENT

In accordance with the UK National Health Service Research Ethics Committee guidelines, ethics approval was not required as this work comprises anonymous retrospective data and all treatment decisions were made prior to our evaluation.

AUTHOR CONTRIBUTIONS

JT, RS, DK, and DJ contributed to conception and design of the study. JT and SG extracted data. JT performed the statistical analysis. All authors contributed to interpretation of results. JT wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.671503/full#supplementary-material

REFERENCES

1. van Vollenhoven RF, Emery P, Bingham CO3rd, Keystone EC, Fleischmann R, Furst DE, et al. Longterm Safety of Patients Receiving Rituximab in Rheumatoid Arthritis Clinical Trials. *J Rheumatol* (2010) 37(3):558–67. doi: 10.3899/jrheum.090856
2. Boleto G, Avouac J, Wipff J, Forien M, Dougados M, Roux C, et al. Predictors of Hypogammaglobulinemia During Rituximab Maintenance Therapy in Rheumatoid Arthritis: A 12-Year Longitudinal Multi-Center Study. *Semin Arthritis Rheum* (2018) 48(2). doi: 10.1136/annrheumdis-2018-eular.1930
3. Aguiar R, Araujo C, Martins-Coelho G, Isenberg D. Use of Rituximab in Systemic Lupus Erythematosus: A Single Center Experience Over 14 Years. *Arthritis Care Res (Hoboken)* (2017) 69(2):257–62. doi: 10.1002/acr.22921
4. Roberts DM, Jones RB, Smith RM, Alberici F, Kumaratne DS, Burns S, et al. Rituximab-Associated Hypogammaglobulinemia: Incidence, Predictors and Outcomes in Patients With Multi-System Autoimmune Disease. *J Autoimmun* (2015) 57:60–5. doi: 10.1016/j.jaut.2014.11.009
5. Marco H, Smith RM, Jones RB, Guerry MJ, Catapano F, Burns S, et al. The Effect of Rituximab Therapy on Immunoglobulin Levels in Patients With Multisystem Autoimmune Disease. *BMC Musculoskelet Disord* (2014) 15 (178). doi: 10.1186/1471-2474-15-178
6. Besada E. Serum Immunoglobulin Levels and Risk Factors for Hypogammaglobulinaemia During Long-Term Maintenance Therapy With Rituximab in Patients With Granulomatosis With Polyangiitis. *Rheumatology (Oxford England)* (2014) 53(10):1818–24. doi: 10.1093/rheumatology/keu194

7. Cortazar FB, Pendergraft WF3rd, Wenger J, Owens CT, Laliberte K, Niles JL. Effect of Continuous B Cell Depletion With Rituximab on Pathogenic Autoantibodies and Total IgG Levels in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Arthritis Rheumatol* (2017) 69(5):1045–53. doi: 10.1002/art.40032
8. Jones RB, Cohen Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab Versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. *N Engl J Med* (2010) 363(3):211–20. doi: 10.1056/NEJMoa0909169
9. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab Versus Cyclophosphamide for ANCA-Associated Vasculitis. *N Engl J Med* (2010) 363(3):221–32. doi: 10.1056/NEJMoa0909905
10. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaître O, Cohen P, et al. Rituximab Versus Azathioprine for Maintenance in ANCA-associated Vasculitis. *N Engl J Med* (2014) 371(19):1771–80. doi: 10.1056/NEJMoa1404231
11. Cassia MA, Alberici F, Jones RB, Smith RM, Casazza G, Urban ML, et al. Rituximab as Maintenance Treatment for Systemic Lupus Erythematosus: A Multicenter Observational Study of 147 Patients. *Arthritis Rheumatol* (2019) 71(10):1670–80. doi: 10.1002/art.40932
12. McCarthy EM, Sutton E, Nesbit S, White J, Parker B, Jayne D, et al. Short-Term Efficacy and Safety of Rituximab Therapy in Refractory Systemic Lupus Erythematosus: Results From the British Isles Lupus Assessment Group Biologics Register. *Rheumatology (Oxford)* (2018) 57(3):470–9. doi: 10.1093/rheumatology/kex395
13. Besada E. Low Immunoglobulin Levels Increase the Risk of Severe Hypogammaglobulinemia in Granulomatosis With Polyangiitis Patients Receiving Rituximab. *BMC Musculoskelet Disord* (2016) 17:6. doi: 10.1186/s12891-015-0860-3
14. Md Yusof MY, Porto MI, Andrews J, Dass S, Savic S, Vital EM, et al. The Effect of Cyclophosphamide and Rituximab for Remission Induction and Maintenance in Severe ANCA-associated Vasculitis on Immunoglobulin Levels: Repeat Cycles on Clinical Relapse With Rituximab are Associated With Stable Iga and Igg. *Ann Rheum Dis* (2015) 74:161–2. doi: 10.1136/annrheumdis-2015-eular.5217
15. Calich AL, Puechal X, Pugnet G, London J, Terrier B, Charles P, et al. Rituximab for Induction and Maintenance Therapy in Granulomatosis With Polyangiitis (Wegener's). Results of a Single-Center Cohort Study on 66 Patients. *J Autoimmun* (2014) 50:135–41. doi: 10.1016/j.jaut.2014.03.002
16. Md Yusof MY, Vital EM, McElvenny DM, Hensor EMA, Das S, Dass S, et al. Predicting Severe Infection and Effects of Hypogammaglobulinemia During Therapy With Rituximab in Rheumatic and Musculoskeletal Diseases. *Arthritis Rheumatol* (2019) 71(11):1812–23. doi: 10.1002/art.40937
17. Cartin-Ceba R, Golbin J, Keogh KA, Peikert T, Fervenza FC, Ytterberg SR, et al. Rituximab for Remission Induction and Maintenance in ANCA-associated Vasculitis: A Single-Center Ten-Year Experience in 108 Patients. *Arthritis Rheum* (2010) 62:680. doi: 10.1002/art.34584
18. Reddy V, Martinez L, Isenberg DA, Leandro MJ, Cambridge G. Pragmatic Treatment of Patients With Systemic Lupus Erythematosus With Rituximab: Long-Term Effects on Serum Immunoglobulins. *Arthritis Care Res (Hoboken)* (2017) 69(6):857–66. doi: 10.1002/acr.22993
19. Thiel J, Rizzi M, Engesser M, Dufner AK, Troilo A, Lorenzetti R, et al. B Cell Repopulation Kinetics After Rituximab Treatment in ANCA-associated Vasculitides Compared to Rheumatoid Arthritis, and Connective Tissue Diseases: A Longitudinal Observational Study on 120 Patients. *Arthritis Res Ther* (2017) 19(1):101. doi: 10.1186/s13075-017-1306-0
20. Venhoff N, Effelsberg NM, Salzer U, Warnatz K, Peter HH, Lebrecht D, et al. Impact of Rituximab on Immunoglobulin Concentrations and B Cell Numbers After Cyclophosphamide Treatment in Patients With ANCA-associated Vasculitides. *PloS One* (2012) 7(5):e37626. doi: 10.1371/journal.pone.0037626
21. Settipane GA, Pudupakkam RK, McGowan JH. Corticosteroid Effect on Immunoglobulins. *J Allergy Clin Immunol* (1978) 62(3):162–6. doi: 10.1016/0091-6749(78)90101-X
22. Cassidy JT, Nordby GL, Dodge HJ. Biologic Variation of Human Serum Immunoglobulin Concentrations: Sex-age Specific Effects. *J Chronic Dis* (1974) 27(11):507–16. doi: 10.1016/0021-9681(74)90026-5
23. Butterworth M, McClellan B, Allansmith M. Influence of Sex in Immunoglobulin Levels. *Nature* (1967) 214(5094):1224–5. doi: 10.1038/2141224a0
24. Ritchie RF, Palomaki GE, Neveux LM, Navolotskaia O, Ledue TB, Craig WY. Reference Distributions for Immunoglobulins A, G, and M: A Practical, Simple, and Clinically Relevant Approach in a Large Cohort. *J Clin Lab Anal* (1998) 12(6):363–70. doi: 10.1002/(SICI)1098-2825(1998)12:6<363::AID-JCLA6>3.0.CO;2-X
25. Cornec D, Kabat BF, Mills JR, Cheu M, Hummel AM, Schroeder DR, et al. Pharmacokinetics of Rituximab and Clinical Outcomes in Patients With Anti-Neutrophil Cytoplasmic Antibody Associated Vasculitis. *Rheumatology (Oxford)* (2018) 57(4):639–50. doi: 10.1093/rheumatology/kex484
26. Barmettler S, Ong MS, Farmer JR, Choi H, Walter J. Association of Immunoglobulin Levels, Infectious Risk, and Mortality With Rituximab and Hypogammaglobulinemia. *JAMA Netw Open* (2018) 1(7):e184169. doi: 10.1001/jamanetworkopen.2018.4169
27. Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of Intravenous Immunoglobulin in the Prevention of Pneumonia in Patients With Common Variable Immunodeficiency. *J Allergy Clin Immunol* (2002) 109(6):1001–4. doi: 10.1067/mai.2002.124999
28. Martinez Garcia MA, de Rojas MD, Nauffal Manzur MD, Munoz Pamplona MP, Compte Torrero L, Macian V, et al. Respiratory Disorders in Common Variable Immunodeficiency. *Respir Med* (2001) 95(3):191–5. doi: 10.1053/rmed.2000.1020
29. Baris S, Ercan H, Cagan HH, Ozen A, Karakoc-Aydiner E, Ozdemir C, et al. Efficacy of Intravenous Immunoglobulin Treatment in Children With Common Variable Immunodeficiency. *J Investig Allergol Clin Immunol* (2011) 21(7):514–21.
30. Ueda M, Berger M, Gale RP, Lazarus HM. Immunoglobulin Therapy in Hematologic Neoplasms and After Hematopoietic Cell Transplantation. *Blood Rev* (2018) 32(2):106–15. doi: 10.1016/j.blre.2017.09.003
31. Gereige JD, Maglione PJ. Current Understanding and Recent Developments in Common Variable Immunodeficiency Associated Autoimmunity. *Front Immunol* (2019) 10:2753. doi: 10.3389/fimmu.2019.02753
32. Sánchez-Ramón S, Radigan L, Yu JE, Bard S, Cunningham-Rundles C. Memory B Cells in Common Variable Immunodeficiency: Clinical Associations and Sex Differences. *Clin Immunol* (2008) 128(3):314–21. doi: 10.1016/j.clim.2008.02.013

Conflict of Interest: JT reports grants from Arthritis Australia (funded by Australian Rheumatology Association and Roche) and National Health and Medical Research Council during the conduct of this study. DK reports other support from CSL Behring, Shire/Takeda, Charities Fund Addenbrookes Hospital Cambridge and Grifols outside the submitted work, and membership of Immunoglobulin Demand Management Assessment Panel for National Health Service UK, membership of Clinical Reference Group for Immunology and Allergy National Health Service, England since 2019. AM reports personal fees and other support from CSL Behring, and other support from Takeda outside submitted work. DJ reports grants from Roche/Genentech during the conduct of the study, personal fees from Astra-Zeneca, Aurinia, and Boehringer, grants and personal fees from Chemocentryx, grants and personal fees from GSK, and grants from Sanofi outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past co-authorship with one of the authors, DJ.

Supplementary Table 1

Patient	Diagnosis	Lymphocyte count ($x\ 10^9$/L)	CD19 ($x\ 10^9$/L)	Naïve B cells IgM+/IgD+/CD27- (42.6 – 82.3%)	Non-switched memory B cells IgM+/IgD+/CD27+	Switched memory B cells IgM-/IgD-/CD27+ (6.5 – 29.1%)
1	AAV	6.41	0.12	97.10	2.20	0.30
2	AAV	2.42	0.75	96.80	2.20	0.60
3	AAV	2.97	0.33	94.70	4.40	0.30
4	AAV	0.91	0.15	90.60	7.70	1.10
5	AAV	1.36	0.15	97.50	2.30	0.00
6	AAV	0.84	0.08	97.0	1.80	0.20
7	AAV	1.21	0.13	93.50	3.80	0.80
8	SLE	1.25	0.13	97.50	1.60	0.30

AAV ANCA associated vasculitis, SLE Systemic lupus erythematosus

Chapter 5 – Impacts of AAV to patients: a focus on health-related quality of life and glucocorticoids

5.1 Introduction

As highlighted in the preceding chapters, substantial progress has been made in the treatment of patients with AAV. Whilst mortality remains an important outcome, the management of patients in the longer-term is a key challenge in AAV. There has been substantial focus reducing morbidity, balancing disease- and treatment-related effects, and patients' HRQoL.

Key to exploring and optimising the management of AAV is assessing its impact from the patient's perspectives. HRQoL of patients with AAV is impaired [118-120]. Disease manifestations, damage, treatment related adverse effects and the emotional burden of these factors are possible contributors to the poor HRQoL of these patients.

In previous studies, this has been explored using generic HRQoL questionnaires, including the SF-36 and Eq-5D. More recently, the AAV-PRO has been developed using OMERACT methodology with both patient and clinician/research input [121, 122].

The link between fatigue and HRQoL in patients with AAV has been reported in previous observational studies [123-127, 171]. Emerging from this work is a complex interplay of disease activity, fatigue, pain, sleep disturbance, sex, age and mood disturbance influencing the HRQoL of patients with AAV. Moreover, the effects of treatments including glucocorticoids on factors such as sleep disturbance, mood disturbance and concerns about longer term outcomes has been highlighted in a qualitative study of patients in the United Kingdom, Canada and United States [121].

The unpublished manuscript included in this chapter explores the HRQoL of patients with a relapse of AAV during the initial 4-month induction phase of the RITAZAREM trial, during which patients received rituximab induction and either a higher- or lower-dose glucocorticoid regimen. In this study, physical function, as measured in the SF-36, remained impaired after induction therapy, despite the mental component score (MCS) returning to population norms. Using a propensity score weighted model to account for non-randomised allocation of glucocorticoid regimen, patients who received lower-dose glucocorticoid had less fatigue and better SF-36 physical component scores (PCS) compared with those who received higher dose glucocorticoid.

The findings of this study support ongoing international efforts to reduce glucocorticoid exposure in patients with AAV. In addition to the induction phase RITAZAREM findings of equivalent remission in both glucocorticoid groups [75], the recently reported PEXIVAS, LOVAS and ADVOCATE trials have demonstrated that less glucocorticoid can be used in the treatment of patients with AAV [57, 63, 107].

A major component of the work for this manuscript was data preparation including data cleaning and scoring of HRQoL questionnaires from the original data. The comparison of glucocorticoid arms was important in this phase of the study, where the majority of patients achieved remission and there were few other factors such as disease relapse, that could further influence this comparison. Endogenous treatment selection models and propensity score models to account for the probability of glucocorticoid group assignment based on baseline covariates were explored. This process is detailed further in Chapter 5.2.

I undertook the data preparation, analysis and write-up of this study in parallel with participation in the OMERACT glucocorticoid group as a fellow. This group aims to develop a set of outcome measures to be evaluated in clinical trials involving glucocorticoids. Included in the appendix are two papers. The first is a study evaluating patient perspectives on glucocorticoid use in patients with RA [172], which highlights patients' concerns around glucocorticoid use, Patients reported that in addition to treatment efficacy, adverse effects were a key consideration for glucocorticoid cessation (Appendix 5). This is in keeping with the theme of balancing treatment benefits and harms that has been highlighted in OMERACT glucocorticoid group work [173, 174]. The second paper summarises work from the OMERACT glucocorticoid group which saw the developed core domain set of outcome measures endorsed at the OMERACT 2020 virtual conference (Appendix 6) [175].

The work included in this chapter explores the HRQoL of patients with a relapse of AAV after a 4-month induction phase and explores the effects of glucocorticoids on patient HRQoL during this period. Whilst glucocorticoids undeniably, have made a substantial contribution to control of disease activity, adverse effects including fatigue are common and influential to patients' HRQoL. Lower-dose glucocorticoids, compared with higher-dose, have been demonstrated to have equivalent clinical outcomes in patients with AAV, but glucocorticoid dose has not been shown to have an impact on HRQoL (positive or negative) in these studies, except with the addition of avacopan [57, 63, 107]. In this paper, examining HRQoL in patients with a relapse of AAV after 4 months, physical function and fatigue were better in patients who had received lower-dose glucocorticoid.

5.2 Dataset description and methodological challenges

5.2.1 RITAZAREM

The RITuximab versus AZAthioprine as therapy for maintenance of REMission for AAV (RITAZAREM) trial is an international, multicentre, RCT that sought to demonstrate superiority of rituximab over azathioprine for the maintenance of remission in AAV. This trial has been described in further detail previously [75, 159]. The study involved three phases. During the induction phase (months 0 – 4), patients with AAV were enrolled into the study at the time of relapse and received rituximab (4 doses of 375 mg/m^2 at weekly intervals) and glucocorticoids (non-randomised allocation of higher and lower dose). This was followed by a maintenance phase (months 4 – 24) when patients who had achieved remission were randomized to receive rituximab or azathioprine maintenance therapy. Finally, the follow-up phase (months 24 - ≥ 36) continued for a minimum of 12 months.

The methodology described below and included in the draft paper pertain to the HRQoL outcomes for the induction phase of the RITAZAREM trial.

5.2.2 Data structure and HRQoL scoring

Appendix 5 includes the STATA do file for data preparation for analyses in this chapter. A brief description of the process is outlined below.

Data structure and cleaning

Data collected for the trial were organised according to the forms completed by participants and clinicians.

For forms completed at multiple time points, data for each timepoint were added end to end within the one spreadsheet for each form. Data were split by month, and variables from each form relevant to this analysis were merged and re-shaped to a long-form dataset for analysis.

In HRQoL questionnaires, a similar structure was used with wide-form data. However, some questions were grouped into categories of “sub-questions”, which were presented in long-form

for each group. The spreadsheets for each HRQoL questionnaires were therefore in a combined wide and long format. Each questionnaire spreadsheet was split according to the visit month, and then split into individual questions before being merged to form a complete set of responses for each HRQoL measure. These were re-shaped to a long-form dataset for analysis.

Health Related Quality of Life questionnaire scoring

Short form-36

For the SF-36, participants respond to 36 questions related to their general health, physical limitations due to health, emotional problems, pain interference, mental health and social impacts from physical or emotional issues. Version 1 of the SF-36 questionnaire was used in RITAZAREM. Two summary scores (physical component score (PCS) and mental component score (MCS)) and eight domain scores (physical function, role physical, general health, vitality, mental health, emotional role, social function and bodily pain) are obtained using an algorithm, which weights the responses to each question [176]. Data was structured according to instructions from the scoring manual, and the STATA SF-36 module was used to score the month 0 and month 4 data. Scores were standardised to the US general population.

EuroQoL Group 5-Dimension 5-Level Questionnaire

The Eq-5D is a two-part patient reported outcome measure. Patients record overall current health on a visual analogue scale (0 – 100) and responses to questions on 5 dimensions are summarised as an index value for health status. The Eq-5D stata command was used to derive Eq-5D index scores [177]. Scores were standardised to the US general population.

Patient-Reported Outcome Measurement Information System (PROMIS)

The PROMIS fatigue, pain interference and physical function questionnaires were collected at all time-points in the induction phase of RITAZAREM. The 4-question short forms were used for each. Fatigue and pain interference were negatively worded; higher scores indicated greater fatigue and pain interference. Physical function was positively worded; higher scores indicated better physical function. The scoring algorithm from Health Measures was used for each questionnaire to derive a T-score. Scores were standardised to the US general population, mean (centre) 50 and standard deviation 10.

5.2.3 Methodological considerations

Data structure

Longitudinal and panel-data modelling approaches were considered with the data. Participants were invited to complete all HRQoL questionnaires at month 0 and month 4 (table 5.1). Both PROMIS and patient global assessment measures were also recorded at month 1.5 and Month 3. These were also introduced after the study had begun enrolment and not translated for use at Japanese sites, and therefore the dataset included some missing data. Owing to the limited observation periods, for the induction phase HRQoL analysis, month 0 and month 4 data were used.

Table 5.1: Timepoints for collection of Health-Related Quality of Life data during the 4-month induction phase of RITAZAREM

	SF-36	Eq-5D	PROMIS	Patient global assessment
Month 0 (baseline)	✓	✓	✓	✓
Month 1.5			✓	✓
Month 3			✓	✓
Month 4	✓	✓	✓	✓

SF-36 *short form-36,* Eq-5D *EuroQoL Group 5-Dimensions 5-Level*, PROMIS *Patient-Reported Outcome Measurement Information System.*

Glucocorticoid regimen- accounting for confounders

One of the aims of this analysis was to compare the HRQoL after induction therapy in patients with relapsing AAV receiving higher-dose glucocorticoid with those receiving lower-dose glucocorticoid. The selection of higher- or lower- dose glucocorticoid was not randomly allocated but according to the physician judgement. Inherent biases are therefore introduced and in assessing the impact of glucocorticoid regimen, accounting for these confounders was important.

Treatment endogeneity was considered in addition to sample selection bias. Endogenous treatment effects models are used if the residuals of a treatment selection model (from

unobserved factors or variables) are correlated to the residuals of the outcome. Endogeneity was not observed and therefore a propensity score approach was used.

A propensity score represents the predicted probability of treatment assignment. A propensity score is derived from a logistic regression model using baseline characteristics to predict treatment assignment. The purpose of using propensity scores is to eliminate confounding bias, which occurs when risk factors for the outcome are non-randomly, and therefore potentially unequally, distributed among assigned treatment groups. Importantly therefore, the aim in deriving a propensity score is not to predict treatment as accurately as possible, but to balance baseline characteristics considered influential to the outcome of interest.

Thus, covariates selected for the propensity score are risk factors for the outcome of interest, not those that solely predict treatment assignment. The addition of variables that increase the accuracy of treatment selection do not provide additional advantage to the model [178, 179].

There are four main ways propensity scores have been used in the medical literature [179-182].

1. Matching

   In this approach, participants from the two groups with similar propensity scores are matched. The matched cohort is used for analysis and participants without a match from either group are excluded from the analysis.

2. Stratification

   Participants from both groups are stratified based on their propensity scores. Both groups are then compared within each stratum. Treatment effects for each stratum and overall treatment effect can be presented. In smaller studies, sample size can limit interpretation of treatment effects in each stratum.

3. Adjustment

   The propensity score is used as a covariate in the regression model of treatment outcome. This model allows all participants to be included.

4. Inverse probability weighting

   Participants are weighted based on their individual propensity score, resulting in balancing of covariates included in the propensity score model. Participants whose propensity scores are at extremes (0 or 1) can introduce inaccuracy Use of this method

can be inaccurate if participants have extremes of propensity score (0 or 1). “Trimming” of participants at these extremes is a proposed variation.

A “doubly robust” variation where balancing covariates are included in both the treatment selection and outcome models, can compensate for insufficient covariate balance between the groups, though with widening of confidence intervals of estimates [181].

Inverse probability weighting performs better than matching in participant populations between 60 and 1000 participants [183]. In the RITAZAREM induction phase dataset, inverse probability weighting model was therefore favoured. Using the STATA treatment effects modules (teffects), a doubly-robust model and inverse probability weighted model was used.

Covariate selection

Selection of covariates for propensity scores was based on background knowledge with considerations of imbalances in baseline characteristics (Table 5.2). Covariates considered for inclusion based on background knowledge were age, sex, disease severity and duration, combined disease assessment (CDA) score, disease manifestations and comorbidities.

The CDA was used to assess disease and treatment related damage in the RITAZAREM trial [184]. In previous studies otolaryngological (ENT) manifestations and neurological manifestations are impactful to patients’ HRQoL [118, 121, 123, 185]. Patients with chronic kidney disease, including those in the earlier stages, have impaired HRQoL [186, 187]; this has not been demonstrated in patients with AAV but was considered an important consideration for the model.

Covariates were added sequentially with assessment of overlap plots for propensity scores and balance of covariates. The final model included age, sex, relapse severity, baseline BVAS physician global assessment, baseline CDA score and neurological manifestations in the treatment selection model and the baseline value of the outcome assessed and BVAS physician global assessment at Month 4 were included in the outcome model. The results are detailed in the manuscript prepared for submission below.

Table 5.2: Covariate selection for propensity score (treatment selection) model

Covariate for treatment selection	Baseline imbalance	Background knowledge
Age		X
Sex	X	X
Relapse severity	X	X
BVAS score	X	X
CDA score		X
Previous rituximab	X	
Previous co-trimoxazole	X	
Region	X	
Specific manifestations (renal, ENT, neurological)		X
Individual and number of comorbidities		X
Disease duration		X

ENT Ear, nose, throat

Sensitivity analyses

A sensitivity analysis was performed using a model that combined inverse probability weighting and regression adjustment (IPWRA). This did not alter the conclusions and therefore the less complex doubly robust model was used in the final analysis.

Reflecting variations in clinical practice, geographic region was a strong determinant of glucocorticoid regimen selection. The HRQoL of patients with AAV has not been compared by region previously and whilst possible, was not thought to be a major determinant of HRQoL within the regions studied. This was included in the outcome model in a sensitivity analysis.

Summary of steps to compare HRQoL outcomes by glucocorticoid group

1. Base model constructed
    - Analysis of covariance (ANCOVA) used to compare Month-4 HRQoL scores between glucocorticoid groups, adjusted for baseline scores.

2. Investigation of treatment endogeneity
    - An endogenous treatment effect model was used to compare Month-4 HRQoL scores between glucocorticoid groups

- No endogeneity (residuals of the treatment selection model were not correlated with residuals of outcome model) was identified and therefore a propensity score model to account for sample selection was used

3. Using propensity scores to account for treatment selection bias
   - Month-4 HRQoL scores were compared between glucocorticoid groups using a doubly robust inverse probability weighted model

5.3 Manuscript: The Effect of Glucocorticoid Regimens on Patient-Reported Outcomes in ANCA-associated vasculitis.

Statement of Authorship

Title of Paper	The Effect of Different Glucocorticoid Regimens on Health-Related Quality of Life in ANCA-associated vasculitis.
Publication Status	Unsubmitted work written in manuscript style
Publication Details	Planned for submission

Principal author

Candidate name	Joanna Tieu
Overall percentage	75%
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signature Date 08/11/2021

Co-author contributions

By signing the Statement of Authorship, each author certifies that:

i. The candidate's stated contribution to the publication is accurate
ii. Permission is granted for the candidate to include the publication in the thesis; and
iii. The sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Rona Smith
Contribution	Contributed to main trial design, data acquisition, interpretation of results and critical appraisal of draft manuscript.

Signature *for Rona Smith* Date 12/12/2021

Name of Co-Author	Gunnar Tómasson
Contribution	Contributed to guiding analysis, interpretation of results and critical appraisal of draft manuscript.
Signature	Date 13/12/2021

Name of Co-Author	Catherine Hill
Contribution	Contributed to interpretation of results and critical appraisal of draft manuscript.
Signature	Date 07/12/2021

Name of Co-Author	David Jayne
Contribution	Contributed to main trial design, data acquisition, interpretation of results and critical appraisal of draft manuscript.
Signature	Date 24/11/2021

Name of Co-Author	Peter Merkel
Contribution	Contributed to main trial design, data acquisition, guiding analysis, interpretation of results and critical appraisal of draft manuscript.
Signature	Date 12/12/2021

Title

The Effect of Different Glucocorticoid Regimens on Health-Related Quality of Life in ANCA-Associated Vasculitis.

Authors

Joanna Tieu [1,2,3], Rona M Smith [4,5], Catherine L Hill [1,3], Gunnar Tómasson [6,7], David RW Jayne [4,5], Peter A Merkel [8,9] for the RITAZAREM Research group

Affiliations

1 Rheumatology Unit, The Queen Elizabeth Hospital, Adelaide, Australia

2 Rheumatology Unit, Lyell McEwin Hospital, Adelaide, Australia

3 Adelaide Medical School, University of Adelaide, Australia

4 Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust, Cambridge, United Kingdom

5 Department of Medicine, University of Cambridge, Cambridge, United Kingdom

6 Department of Epidemiology and Biostatistics, Faculty of Medicine, University of Iceland, Reykjavik, Iceland

7 Department of Rheumatology and Centre for Rheumatology Research, University Hospital, Reykjavik, Iceland

8 Division of Rheumatology, Department of Medicine, University of Pennsylvania, Philadelphia, USA

9 Division of Epidemiology, Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, USA

Conflicts of Interest

JT- Research grant, Vifor Pharma; CH- Research grant, Vifor Pharma; RS – Research support GlaxoSmithKline, Roche, Union Therpaeutics; PM: Consulting and Research Support: AbbVie, AstraZeneca, Boeringher-Ingelheim, Bristol-Myers Squibb, ChemoCentryx, Forbius, Genentech/Roche, Genzyme/Sanofi, GlaxoSmithKline, InflaRx, Takeda. Consulting only: CSL Behring, Dynacure, EMDSerono, Jannsen, Kiniksa, Kyverna, Magenta, MiroBio, Neutrolis, Novartis, Pfizer, Sparrow, Talaris. Royalties: UpToDate.

Abstract

Objectives

This study aimed to describe the health-related quality of life (HRQoL) in patients with a relapse of ANCA-associated vasculitis (AAV) treated with one of two different glucocorticoid regimens.

Methods

During the induction phase of RITAZAREM, all enrolled patients received rituximab and either lower- or higher-dose glucocorticoids, determined by the treating clinician. HRQoL was assessed using the short form-36 (SF-36), EuroQoL Group 5-Dimensions 5-Level, and Patient-Reported Outcome Measurement Information System (PROMIS) fatigue, pain interference, and physical function domains. All scores were standardized to United States population data. A propensity-score weighted model aimed to account for potential bias in selection of glucocorticoid regimen.

Results

Of the 188 patients with AAV in the induction phase of RITAZAREM, 134 (71%) received the lower-dose glucocorticoid regimen and 54 (29%) the higher-dose regimen. Average SF-36 physical and mental component scores (PCS, MCS) and all measured PROMIS domains were impaired at baseline compared with population norms. All group HRQoL scores improved during the induction phase ($p < 0.001$ for all).

At Month 4, patients who received lower-dose glucocorticoids, compared with higher-dose, had greater improvement in SF-36 PCS (mean difference (MD) 5.29 (95% confidence interval (CI) 1.10, 9.48) and fatigue MD -3.50 (95% CI -6.93, -0.06) in the propensity-score weighted model.

Conclusions

In patients with a relapse of AAV treated with rituximab and glucocorticoids for induction of remission, a lower-dose glucocorticoid regimen, compared to higher-dose, is associated with better physical HRQoL and less fatigue. These results support ongoing efforts to reduce glucocorticoids in patients with AAV.

Background

Anti-neutrophil cytoplasm antibody (ANCA)- associated vasculitis (AAV) is a multi-system disorder with organ- and life- threatening manifestations. Several randomised controlled trials have demonstrated the success of contemporary treatment strategies to induce remission in patients with AAV (1-4). Ongoing efforts to improve outcomes in the longer-term emphasise the importance of preventing relapse, minimising treatment-related toxicity and improving health-related quality of life (HRQoL) associated with AAV.

The impaired HRQoL in patients with AAV with new or relapsing disease has been confirmed in multiple studies using the short form-36 (SF-36) and Euroqol-5 Dimension (Eq-5D) questionnaires (5-10). HRQoL outcome measures demonstrated improvement among patients treated in clinical trials (5, 6, 8). Disease activity, however, is just one of several factors associated with HRQoL in patients with AAV. Fatigue and pain, two domains of illness not consistently considered part of physician-assessed disease activity, play an important role in determining the HRQoL of patients with AAV (7, 11-14).

Glucocorticoids have benefit in both in the induction and maintenance of remission in AAV (4, 15-17). These benefits are contrasted against the predictable adverse effects of glucocorticoids, recognized by both clinicians and patients (18, 19). The effect of glucocorticoids can be bidirectional; although some patients experience increased energy levels with glucocorticoids, it has also been attributed to increased fatigue and worse HRQoL outcomes (19, 20). With the recent demonstration of the successful use of low-dose glucocorticoid regimens (21-23), it remains important to evaluate effects of lower-dose glucocorticoidon HRQoL in AAV.

RITAZAREM was an international multi-centre, multi-phase trial enrolling patients with a relapse of AAV to receive rituximab for induction of remission and comparing rituximab or azathioprine for the maintenance of remission (24). During the 4-month induction phase, patients received a high- or low-dose glucocorticoid regimen, chosen as the discretion of the treating investigator, in addition to rituximab for induction of remission.

This study aimed to i) describe and quantify the HRQoL in patients with a relapse of AAV; ii) examine and compare HRQoL after treatment with 2 different glucocorticoid regimens for AAV

Methods

This analysis focused on the HRQoL outcomes of patients during the 4-month induction phase of the multi-centre international RITAZAREM trial. Full details on the trial participants and protocol have been published (24). The trial enrolled patients with a relapse of AAV into a 3-phase study (24). During the induction phase (months 0 – 4), patients with AAV were enrolled into the study at the time of relapse and received rituximab (4 doses of 375 mg/m^2 at weekly intervals) and glucocorticoids (non-randomised allocation of higher and lower dose). This was followed by a maintenance phase (months 4 – 24) when enrolled patients who had achieved remission were randomized to receive rituximab or azathioprine maintenance therapy. Finally, the follow-up phase (months 24 - ≥ 36) continued for a minimum of 12 months.

In the induction phase, patients could receive up to a maximum of 3000 mg of methylprednisolone intravenously at the time of relapse, and investigators selected either a higher- or lower-dose glucocorticoid regimen. The starting dose of prednis(ol)one was 1 mg/kg/day up to 60 mg daily in the higher-dose group, and 0.5 mg/kg/day in the lower dose group up to 30 mg daily. Both groups were tapered to 10 mg daily by Month 4.

Disease activity and damage

Assessments of disease activity and damage were collected at all timepoints (baseline, month 1.5, month 3 and month 4). Disease activity was measured using the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) (25), which includes a score (0-63) and physician global assessment (0-10) where higher scores indicate greater disease activity. At baseline and month-4, damage was assessed using the Combined Damage Assessment (CDA) (26).

Health-related quality of life measures

Enrolled patients completed questionnaires evaluating HRQoL as follows with scores standardized to the United States population where applicable:

- The short form-36 (SF-36) version 1 was assessed at baseline and 4 months. Scores were summarised into physical and mental component scores (PCS & MCS), and eight domains (physical function, role physical, general health, vitality, mental health, emotional role, social function and bodily pain). The SF-36 Stata module was used to derive SF-36 PCS, MCS and the eight domain scores (27).
- The EuroQoL Group 5-Dimensions 5-Level Questionnaire (EQ-5D) was assessed at baseline and 4 months. With the EQ-5D patients record overall current health on a visual analogue scale (0 – 100) and responses to questions on dimensions are summarised as an index value for health status. The Eq-5D Stata command was used for Eq-5D index scores (28).
- The Patient-Reported Outcome Measurement Information System (PROMIS) short form questionnaire sets for fatigue, physical function, and pain interference were completed at all visits (month 0, 1.5, 3 and 4). The HeathMeasures scoring service was used to derive PROMIS scores.
- A patient global assessment (PtGA) asking patients to rate their vasculitis disease activity over the previous 28 days was assessed at all visits (month 0, 1.5, 3 and 4).

The PROMIS questionnaire sets were introduced following a protocol amendment after study commencement, available only to patients enrolling after November 2013. The SF-36 and EQ-5D were available to patients in English and Japanese, as applicable. Japanese patients did not complete the PROMIS questionnaire sets and patient global assessments as translations were not available during the trial.

Statistical analysis

Demographic data are presented as median [interquartile range], and proportion (percentage). Each of the SF-36 component and domain scores, and PROMIS questionnaire scores were transformed to make the results comparable to Untied States (US) population norm values. Both SF-36 and PROMIS US population norm values were used for scoring; both are standardized as T-scores to a mean of 50 and standard deviation of 10. All HRQoL scores are presented as mean ± standard deviation. Data for HRQoL outcome measures were compared between baseline and 4 months using paired t-tests, and between 4-month data and population norms with t-tests.

Unadjusted ANCOVA and adjusted with propensity score weighting were used to compare HRQoL outcome measures at 4 months between patients who received the higher-dose glucocorticoid vs. the lower-dose glucocorticoid regimen. Adjustment using propensity score weighting was chosen to account for potential bias in the selection of the glucocorticoid treatment dose regimen as this was not randomized, and after confirming the absence of endogeneity (correlation between the residuals of treatment selection and outcome models).

A propensity score represents the predicted probability of treatment assignment, derived from a logistic regression model. The aim in deriving a propensity score is to balance baseline characteristics considered influential to the outcome of interest, and the addition of variables to increase the accuracy of treatment selection does not provide additional advantage to the model (29, 30). Of the four main methods to use propensity scores in analyses, matching and stratification can result in smaller sample sizes for comparisons. The use of adjustment or inverse probability weighting allows for the inclusion of all participants. Inverse probability weighting performs better than matching in the sample size of this study (31).

Firstly, a treatment selection (propensity score) model was constructed. Covariates were considered due to either baseline imbalances or background factors considered influential to glucocorticoid treatment decisions. Baseline imbalances included age, sex, relapse severity, BVAS/WG, previous use of rituximab, previous co-trimoxazole, and region (North America, United Kingdom/Europe, Japan and Australia). Background factors considered were CDA score, disease duration, comorbidities and AAV manifestations (neurological, otorhinolaryngologic and renal). In previous studies otolaryngological (ENT) manifestations and neurological manifestations are impactful to patients' HRQoL (6, 7, 20, 32). Patients with chronic kidney disease, including those in the earlier stages, have impaired HRQoL (33, 34); this has not been demonstrated in patients with AAV but was considered an important consideration for the model. Each covariate was sequentially added to assess the impact on overlap plots and balance of covariates. After this process, the factors included were age, sex, relapse severity, baseline BVAS/WG physician global assessment, baseline CDA and neurological manifestations.

The next step was to incorporate the treatment selection (propensity score) model into the outcome model. Baseline values of each score were incorporated into the outcome models for the relevant 4-month comparisons.

Finally, a sensitivity analysis was performed incorporating adjustment for region into the outcome model. Although baseline imbalances in region were evident between the higher- and lower-dose glucocorticoid groups, reflecting variations in local practice patterns, adjusting for this factor did not improve balance or overlap plots, resulting in violations for some outcomes, and was therefore not included in the treatment selection model. Geographic region of study sites (North America, United Kingdom/Europe, Japan and Australia) was included in a sensitivity analysis due to the noted baseline imbalance and the standardization of all HRQoL outcomes to US population data.

Analyses were conducted in Stata v14; the Stata teffects augmented inverse propensity weight estimators were used for the adjusted models using propensity score weighting.

Results

Baseline demographics

The baseline demographics and disease response of patients enrolled in the induction phase of the RITAZAREM trial have been published (24). Most patients (171, 90%) achieved remission during the induction phase of the study.

Of the 188 patients included in the induction phase, 134 (71%) were assigned to the lower-dose glucocorticoid regimen and 54 (29%) to the higher-dose regimen. As previously reported, total cumulative oral glucocorticoid exposure in the induction phase was 1960 mg (1715 – 3535) in the lower-dose group and 3010 mg (2485 – 7875) in the higher-dose group. Imbalances of baseline characteristics are noted between participants where lower dose glucocorticoid was selected compared with patients with higher dose glucocorticoid selected (Table 1). Although most participants received lower-dose glucocorticoids, greater use was observed among female participants and participants with a non-severe relapse entering the trial (**Table 1**). Consequently, baseline BVAS/WG were lower in participants on lower-dose glucocorticoids, but no difference in baseline disease damage (CDA score) was identified (**Table 1**). Participants receiving lower-dose glucocorticoids were more likely to have previously received rituximab for treatment of AAV. Patients in both glucocorticoid groups had similar prior exposure to other immunosuppressive treatments for AAV, including cyclophosphamide. There were no overall differences in the frequency of pre-defined baseline comorbidities between patients receiving lower- or higher-dose glucocorticoids (**Table 1**).

Regional variation was noted between the two glucocorticoid groups. Higher-dose glucocorticoid use was more common in North America than in the UK/Europe (**Table 1**).

Questionnaire completion rates

Individual questionnaire completion rates for each questionnaire were between 89% and 97% (**Table 2**). The PROMIS questionnaires and patient global assessment were introduced later after study recruitment had commenced and was restricted by available language translations. Consequently, this was only offered to 165 patients.

Change in health-related quality of life during the induction phase

All HRQoL scores improved from Month 0 to Month 4 in all patients and in each glucocorticoid subgroup ($p < 0.001$ for all). Physical component scores (PCS), mental component scores (MCS), and eight domain scores were derived from participants' responses to the SF-36 at baseline and 4 months. Average SF-36 PCS and MCS were impaired at baseline (PCS: mean 35.1 ± SD 10.0, MCS: mean 46.0 ± 11.6), and improved at the end of the 4-month induction phase (**Supplementary Table 1**). At month-4, completion of the induction phase, average SF-36 PCS remained impaired and average SF-36 MCS were similar to population norms (PCS mean 40.5 ± 11.6, MCS mean 50.5 ± SD 10.2, **Supplementary Table 1**). Changes in the mean transformed SF-36 domain scores from Month 0 to Month 4 is represented in **Supplementary Figure 1** for all patients and the two glucocorticoid regimens. PROMIS scores for fatigue, pain interference, and physical activity were, on average, impaired compared to population norms at baseline and improved after 4 months (**Supplementary Table 1**). EQ-5D index score and scales also both improved during the induction phase of the study.

Glucocorticoid dose and health-related quality of life

In an unadjusted ANCOVA model, there were no differences in the HRQoL measures between the lower- and higher-dose glucocorticoid groups (**Figure 2**). Due to baseline imbalances between the two groups, propensity score weighting was used to adjust for glucocorticoid group allocation.

In the AIPW model, patients receiving lower dose glucocorticoid had greater average SF-36 PCS at Month 4 than patients receiving higher-dose glucocorticoid (mean difference (MD) 5.29 (95% CI 1.10, 9.48), **Figure 2, Supplementary Table 2**). In a sensitivity analysis, adjusting for region, both SF-36 PCS and PROMIS physical function scores were on average greater in patients receiving lower-dose glucocorticoid compared with those receiving higher-dose glucocorticoid **(Figure 2)**.

Reduced fatigue was also observed at Month 4 in the lower-dose glucocorticoid group compared with the higher-dose glucocorticoid group (MD -3.50 points (95% CI -6.93, -0.06), **Figure 2, Supplementary Table 2**). In a sensitivity analysis, adjusting for region, the direction of this result remained unchanged (MD -5.76 (95% CI -9.34, -2.18), **Figure 2 Supplementary Table 2**).

Month 4 SF-36 MCS, Eq5D measures and PROMIS pain interference and physical function scores did not differ between the two glucocorticoid groups. Patient global assessments of vasculitis disease activity were similar between the two glucocorticoid groups at Month 4.

Discussion

The induction phase of the RITAZAREM trial represents the initial 4-month phase during which patients with AAV with a relapse of disease were treated with rituximab and glucocorticoids. This study of the HRQoL outcomes in the induction phase confirms that patients with a relapse of AAV have impaired HRQoL, and improvement in HRQoL occurs after induction of remission. Ongoing impairment in physical function remained, however, even after patients achieved remission. Although no difference in rates of remission were observed in patients receiving the lower-dose glucococorticoid regimen, compared with higher-dose glucocorticoid regimen (24), at 4 months patients receiving lower-dose glucocorticoid had less fatigue and better SF-36 physical function scores compared with those who received higher-dose glucocorticoid.

Improvement in HRQoL with induction treatment occurred in parallel with successful induction of remission in the majority (90%) of RITAZAREM participants. These results are consistent with observations in patients with newly-diagnosed AAV (6, 8) and mixed groups of new and prevalent cases of AAV (4, 5). Moreover, a similar relatively rapid improvement in HRQoL after high disease activity was observed in a study of patients with GPA (5). Given the longer maintenance phase of the RITAZAREM trial, the HRQoL of patients and the influence of other factors remains of interest. In the MAINRITSAN trial, in which new and relapsing patients with AAV were randomized to receive rituximab or azathioprine for maintenance of remission after induction of remission with cyclophosphamide, HRQoL measures were collected over 24 months after completion of induction therapy (35). Patients receiving rituximab had fewer relapses and an overall improvement in SF-36 PCS was observed in the rituximab group in contrast to a decline in the azathioprine group. No overall difference in SF-36 PCS change between groups was observed, however. Whilst SF-36 MCS improved for both groups, this improvement was greater in the azathioprine arm (8).

Fatigue in AAV is complex, with multiple contributing factors, and remains a prominent symptom for patients (13, 20, 36). Fatigue is commonly attributed to disease activity but is also considered an adverse effect of glucocorticoids. Systemic inflammation and pain contribute to fatigue in patients with AAV (14). Despite glucocorticoids role in reducing disease activity, glucocorticoids have also been implicated in contributing to fatigue in patients with AAV (12, 19). In qualitative studies, in addition to recognizing its role in treating AAV, and the euphoric and hyperactive effects of glucocorticoids, patients also describe sleep disturbance, mood disturbance, muscle weakness, and the emotional burden of use of glucocorticoid (19).

The results of this study suggest that among patients with AAV, use of a lower-dose glucocorticoid regimen may be associated with improved SF-36 PCS and fatigue scores at Month 4 compared with a higher-dose glucocorticoid regimen, suggesting the balance favours less glucocorticoid in induction regimens and is in line with the clinical outcomes observed in RITAZAREM and recent studies (21, 23, 24). These results are in keeping with the results from the recently-reported ADVOCATE randomized controlled trial, in which patients with AAV randomized to receive avacopan without glucocorticoids experienced greater improvement in SF-36 PCS than those receiving a standard glucocorticoid regimen (22). In the LOVAS trial comparing reduced-dose and high-dose prednisolone in addition to rituximab for induction in patients with a new diagnosis of AAV, however, SF-36 PCS and MCS six months after randomisation were not significantly different between the two groups (23). Differences among these trials and their patient populations make the results of each difficult to directly compare. For example, patients in LOVAS differ from those included in RITAZAREM, with LOVAS including patients with newly diagnosed AAV and RITAZAREM including only patients who have relapsed.

Notably, the glucocorticoid regimens differed; in RITAZAREM the protocol for both groups was to reach 10 mg daily by 12 weeks (the differences between lower- and higher-dose groups occurring prior to this point) and in LOVAS the reduced-dose protocol was for 3 mg daily and high-dose group 0.35 mg/kg daily at 12 weeks. Less than half (39.1%) of the patients in LOVAS in the reduced-dose group reached the target of prednisolone cessation at 6 months due to disease activity or biomarker elevations (23).

During the induction period of RITAZAREM, average SF-36 MCS returned to population norms, and no difference was identified at the end of the induction period despite differences in fatigue and physical function. This is in contrast to observational studies indicating that SF-36 MCS is associated with greater fatigue, anxiety, and depression (7). This may be confounded by clinical improvements given most patients in this study were in remission at the end of the induction period. The differences in fatigue scores despite similar SF-36 MCS, however, pose further questions on the utility of the measurement tools over different time periods, but more importantly whether the differences in fatigue suggest differences in patients' experience of disease, damage or treatment effects.

A key strength of this study is the range of HRQoL outcomes examined in patients with a relapse of AAV. Levels of completion HRQoL questionnaire at each timepoint were high. Multiple questionnaires enabled analysis of each in parallel, and future work to compare these measures will be useful to clarify the utility of these outcome measures in clinical trials.

Until recently, limited evidence existed for the efficacy of lower-dose glucocorticoid treatment regimens for AAV, with clinicians and patients recognizing both the positive and negative effects. The non-randomised use of lower- and higher-dose regimens was a key source of bias. Accounting for the influence of selection bias was therefore a key consideration in the choice of analysis. Although the use of propensity scores does not replace the value of randomized allocation, it accounted for the influence of these confounders.

The results of this study provide a closer examination of the HRQoL outcomes in patients with a relapse of AAV. Increasing evidence supports the use of less glucocorticoid with respect to disease control outcomes (21, 22, 24), and the findings of this study provides further support the use of lower-dose glucocorticoids in routine settings. Although significant improvement was seen in most HRQoL measures over the 4-month induction period, ongoing impairment of HRQoL remains. Future work to examine other modifiable factors that influence patients' HRQoL, including fatigue and physical function, is required. These data may also provide insight into the impact of differing doses of glucocorticoids for patients with other systemic inflammatory conditions.

Table 1 Patient characteristics in the study cohort

	Overall N = 188	Higher-dose GC N = 54	Lower-dose GC N = 134	p-value
Age	59 [47.5 – 68]	57 [49 – 66]	59 [47 – 70]	0.370
Female	93/188 (49)	20/54 (37)	73/134 (54)	0.030
Ethnicity				0.534
White	168/188 (89)	46/54 (85)	122/134 (91)	
Asian	13/188 (9)	5/54 (9)	8/134 (6)	
Hispanic	3/188 (2)	1/54 (2)	2/134 (1)	
Black	1/188 (1)	0/54 (0)	1/134 (1)	
Other	3/188 (2)	2/54 (4)	1/134 (1)	
Relapse type				0.001
Non-severe	69/188 (37)	10/54 (19)	59/134 (44)	
Severe	119/188 (63)	44/54 (81)	75/134 (56)	
ANCA type				0.899
PR3 positive	137/188 (73)	39/54 (72)	98/134 (73)	
MPO positive	51/188 (27)	15/54 (28)	36/134 (27)	
Disease duration	5.1 [1.9 – 9.5]	5.3 [1.4 – 9.8]	5.1 [2.2 – 9.3]	0.695
Baseline BVAS/WG	5 [4 – 7]	6 [4 – 8]	5 [4 – 6]	0.002
Basline CDA	3 [1 – 5]	3 [1 – 5]	3 [1 – 4]	0.313
Manifestations of AAV				
ENT	138/188 (73)	38/54 (70)	100/134 (75)	0.550
Renal	127/188 (68)	41/54 (76)	86/134 (64)	0.120
Cutaneous	58/188 (31)	17/54 (31)	41/134 (31)	0.905
Pulmonary	115/188 (61)	35/54 (65)	80/134 (60)	0.515
Neurological	49/188 (26)	13/54 (24)	36/134 (27)	0.693
Previous treatment				
Cyclophosphamide	149/188 (79)	43/54 (80)	106/134 (79)	0.936
Rituximab	67/188 (36)	13/54 (24)	54/134 (40)	0.036
Azathioprine	135/188 (72)	39/54 (72)	96/134 (72)	0.936
Methotrexate	60/188 (32)	19/54 (35)	41/134 (31)	0.541
Mycophenolate	48/188 (26)	10/54 (19)	38/134 (28)	0.162
Co-trimoxazole	67/188 (36)	25/54 (46)	42/134 (31)	0.053
Hypertension	93/188 (49)	23/54 (43)	70/134 (52)	0.376
Diabetes mellitus	23/188 (12)	8/54 (15)	15/134 (11)	0.653
IHD	9/188 (5)	1/54 (2)	8/134 (6)	0.394
Cerebrovascular	6/188 (3)	2/54 (4)	4/134 (3)	0.792
Lung disease	29/188 (15)	8/54 (15)	21/134 (16)	0.883
Cancer	20/188 (11)	8/54 (15)	12/134 (9)	0.238
VTE	20/188 (11)	7/54 (13)	13/134 (10)	0.512

	Overall N = 188	Higher-dose GC N = 54	Lower-dose GC N = 134	p-value
Number of comorbidities				0.406
0	58/188 (31)	19/54 (35)	39/134 (29)	
1	77/188 (41)	21/54 (39)	56/134 (42)	
2	40/188 (21)	8/54 (15)	32/134 (24)	
3	9/188 (5)	4/54 (7)	5/134 (4)	
4	4/188 (2)	2/54 (4)	2/134 (2)	
Region				<0.001
North America	80/188 (43)	42/54 (78)	38/134 (28)	
UK Europe	85/188 (45)	9/54 (17)	76/134 (57)	
Japan	5/188 (3)	1/54 (2)	4/134 (3)	
Australia	18/188 (10)	2/54 (4)	16/134 (12)	

GC Glucocorticoid ANCA *anti-neutrophil cytoplasm antibody,* PR3 *proteinase 3,* MPO *myeloperoxidase,* BVAS/WG *Birmingham Vasculitis Activity Score for Wegener's Granulomatosis,* CDA *combined damage assessment,* ENT *ear, nose, throat,* IHD *ischaemic heart disease,* VTE *venous thromboembolism,* UK *United Kingdom*

Data presented as median [interquartile range] or proportion (percentage)

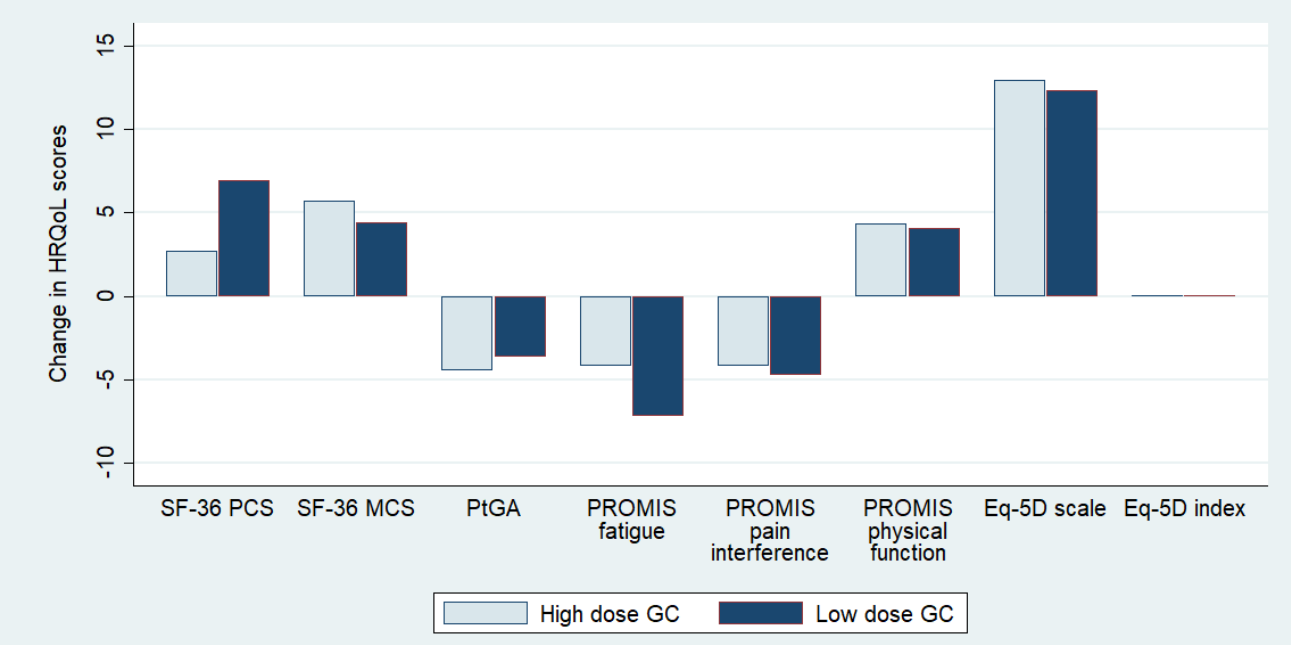
Table 2 Questionnaire completion rates in the induction phase of the RITAZAREM trial

	Month 0	Month 1.5	Month 3	Month 4
SF-36 PCS & MCS	167/188 (89%)	-	-	169/188 (90%)
Eq-5D scale	182/188 (97%)	-	-	175/188 (93%)
Eq-5D index	178/188 (95%)	-	-	175/188 (93%)
PROMIS fatigue	152/159 (96%)	157/159 (99%)	150/159 (94%)	152/159 (96%)
PROMIS pain interference	152/159 (96%)	157/159 (99%)	150/159 (94%)	153/159 (96%)
PROMIS physical function	152/159 (96%)	157/159 (99%)	150/159 (94%)	153/159 (96%)
PROMIS patient global assessment	150/159 (94%)	153/159 (96%)	149/159 (94%)	149/159 (94%)

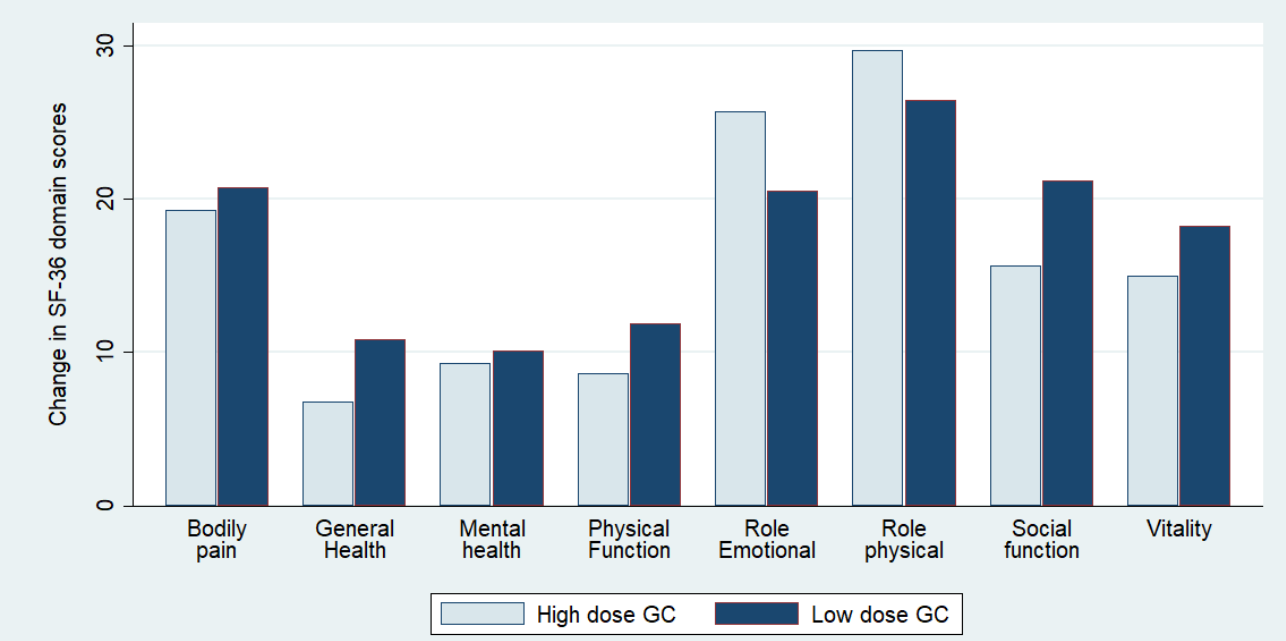
SF-36 *short form-36,* PCS *physical component score,* MCS *mental component score*, Eq-5D *EuroQoL Group 5-Dimensions 5-Level,* PROMIS *Patient-Reported Outcome Measurement Information System*

Figure 1. Mean change in health-related quality of life scores from Month 0 to Month 4 in the RITAZAREM trial

a



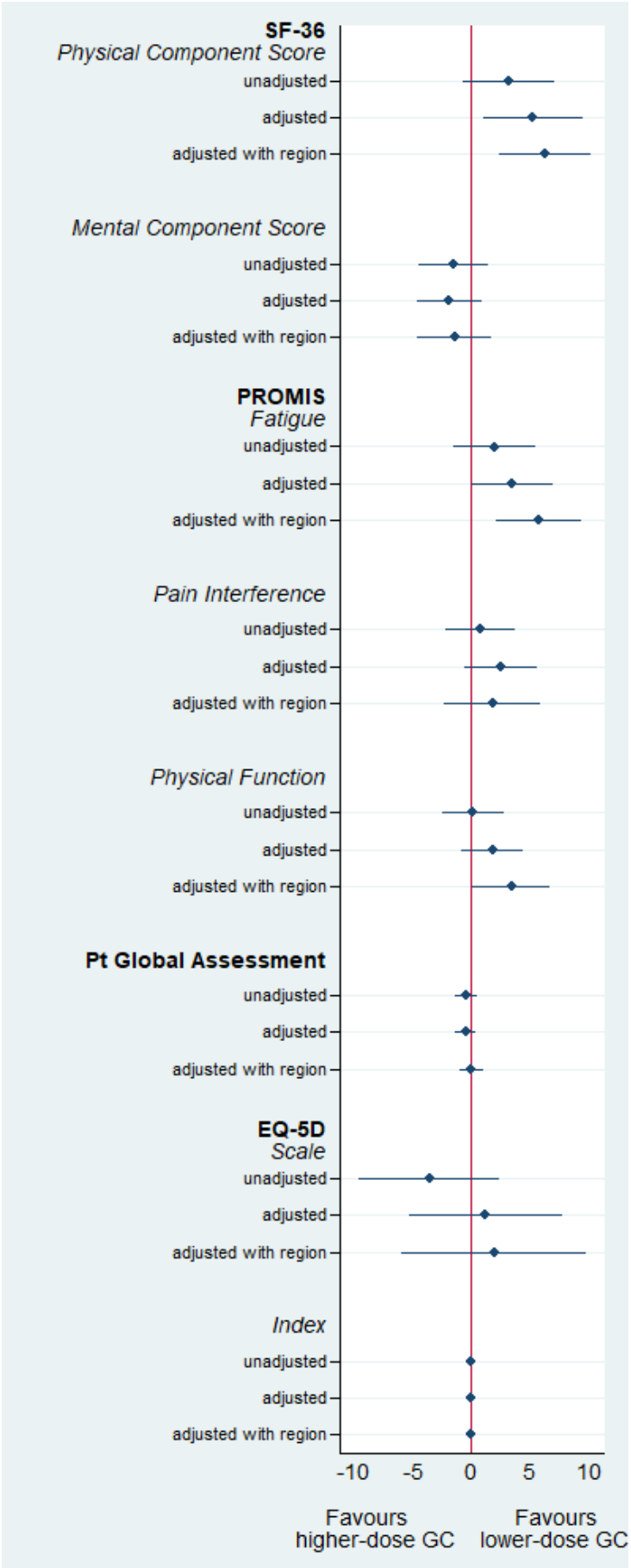
b



HRQoL *health related quality of life,* SF-36 *short form-36,* PCS *physical component score,* MCS *mental component score*, PROMIS *Patient-Reported Outcome Measurement Information System*, PtGA *patient global assessment*, PROMIS pain *PROMIS pain interference*, PROMIS physical *PROMIS physical function*, Eq-5D *EuroQoL Group 5-Dimensions 5-Level*.

In contrast to other scores, patient global assessment of vasculitis disease activity, PROMIS fatigue and pain interference are negatively worded such that lower scores are better and higher scores are worse. A negative value for the change in these scores from Month 0 to Month 4 indicates improvement.

Figure 2. Differences in health-related quality of life measures at Month-4 among patients with ANCA-associated vasculitis receiving lower dose or higher dose glucocorticoid in the RITAZAREM trial



HRQoL *health-related quality of life,* SF-36 *short form-36,* PCS *physical component score,* MCS *mental component score*, PROMIS *Patient-Reported Outcome Measurement Information System*, PROMIS pain *PROMIS pain interference*, PROMIS physical *PROMIS physical function*, PtGA *patient global assessment*, Eq-5D *EuroQoL Group 5-Dimensions 5-Level*.

Mean difference and 95% confidence interval presented. Unadjusted model (ANCOVA), adjusted (AIPW model), adjusted with region (AIPW model with region included in outcome model).

Supplementary Table 1. Baseline and Month 4 Measures of Health-Related Quality of Life Among Patients with ANCA-Associated Vasculitis in the RITAZAREM Trial

	All N = 188	Higher-dose GC N = 54	Lower-dose GC N = 134
PROMIS*			
Fatigue			
Baseline	56.4 ± 10.9	54.3 ± 10.7	57.3 ± 10.9
Month 4	50.6 ± 10.2	51.5 ± 11.2	50.3 ± 9.9
Pain Interference			
Baseline	54.2 ± 10.5	54.3 ± 11.3	54.1 ± 10.2
Month 4	49.8 ± 9.0*	50.3 ± 9.4	49.6 ± 8.9
Physical Function			
Baseline	42.7 ± 9.9	42.2 ± 11.2	42.9 ± 9.3
Month 4	46.6 ± 9.6	46.0 ± 10.1	46.8 ± 9.5
PROMIS PtGA			
Baseline	6.3 ± 2.5	6.6 ± 2.6	6.2 ± 2.4
Month 4	2.4 ± 2.5	2.2 ± 2.5	2.6 ± 2.5
EQ5D*			
EQ5D-index			
Baseline	0.78 ± 0.18	0.79 ± 0.21	0.78 ± 0.16
Month 4	0.84 ± 0.14	0.84 ± 0.14	0.84 ± 0.14
EQ5D-scale			
Baseline	59.8 ± 20.9	60.6 ± 22.2	59.5 ± 20.5
Month 4	72.8 ± 17.4	72.8 ± 18.5	72.4 ± 17.0
SF-36*			
SF-36 PCS			
Baseline	35.1 ± 10.0	37.3 ± 10.6	34.3 ± 9.7
Month 4	40.5 ± 11.6	39.9 ± 11.7	40.8 ± 11.6
SF-36 MCS			
Baseline	46.0 ± 11.6	46.8 ± 12.3	45.6 ± 11.3
Month 4	50.5 ± 10.2	50.5 ± 10.1	50.5 ± 10.3

	All N = 188	Higher-dose GC N = 54	Lower-dose GC N = 134
SF-36 domains*			
Physical function			
Baseline	58.8 ± 27.9	62.4 ± 28.3	57.3 ± 27.7
Month 4	65.2 ± 29.1	61.1 ± 30.6	66.8 ± 28.6
General Health			
Baseline	45.1 ± 21.7	51.2 ± 20.5	42.5 ± 21.8
Month 4	52.0 ± 21.6	52.9 ± 21.3	51.6 ± 21.8
Vitality			
Baseline	40.6 ± 24.0	47.0 ± 24.4	38.0 ± 23.5
Month 4	54.0 ± 23.1	55.0 ± 22.5	53.7 ± 23.3
Mental Health			
Baseline	68.6 ± 19.7	69.8 ± 20.4	69.1 ± 19.4
Month 4	75.5 ± 19.0	74.5 ± 19.9	75.8 ± 18.7
Role Physical			
Baseline	26.9 ± 37.2	31.0 ± 38.7	25.2 ± 36.6
Month 4	50.4 ± 43.2	49.5 ± 43.3	50.8 ± 43.3
Emotional Role			
Baseline	58.9 ± 43.7	57.3 ± 45.2	59.5 ± 43.3
Month 4	73.0 ± 38.3	73.6 ± 38.3	72.8 ± 38.4
Social Function			
Baseline	58.4 ± 28.3	64.0 ± 26.7	56.1 ± 28.7
Month 4	74.3 ± 25.6	72.1 ± 25.0	75.1 ± 25.9
Bodily Pain			
Baseline	53.7 ± 26.8	53.9 ± 26.7	53.7 ± 27.0
Month 4	72.1 ± 25.3	71.1 ± 25.5	72.4 ± 25.3

GC: glucocorticoid, PROMIS: Patient Reported Outcome Measurement Information System, PtGA: Patient global assessment, Eq-5D: EuroQoL Group 5-Dimensions 5-Level questionnaire, SF-36: Short form-36,
PCS: physical component score, MCS: mental component score.

* $p < 0.001$, paired t-test Month 4 vs Month 0 for All, Higher-dose GCs and Lower-dose GC groups

Supplementary Table 2: Differences in health-related quality of life measures at Month-4 among patients with ANCA-associated vasculitis in the RITAZAREM trial receiving lower dose and higher dose glucocorticoid

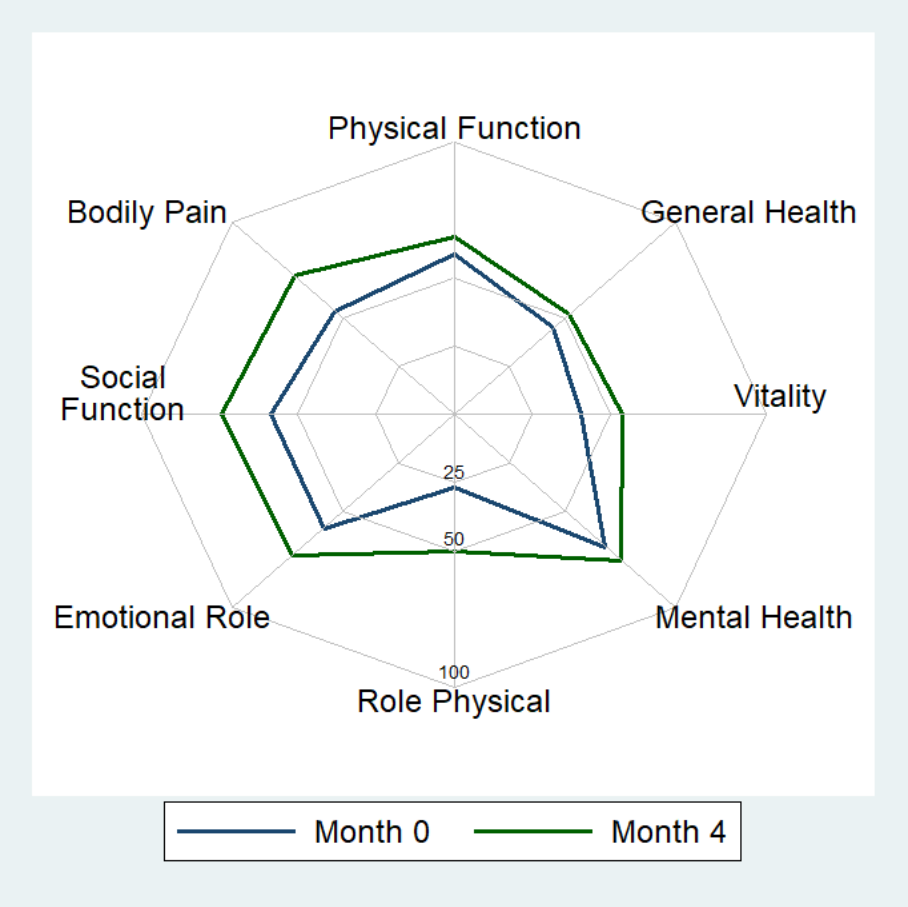
	ANCOVA mean difference (95% confidence interval)	p-value	**Propensity- Score Weighted** mean difference (95% confidence interval)	p-value	***Sensitivity Analysis with Region*** mean difference (95% confidence interval)	p-value
SF-36 physical	3.19 (-0.67, 7.04)	0.105	5.29 (1.10, 9.48)	0.013	6.32 (2.40, 10.23)	0.002
SF-36 mental	-1.46 (-4.45, 1.53)	0.337	-1.82 (-4.54, 0.90)	0.189	-1.34 (-4.49, 1.81)	0.403
Patient Global Assessment	0.37 (-0.57, 1.30)	0.439	0.40 (-0.46, 1.27)	0.362	-0.07 (-1.05, 0.92)	0.892
PROMIS fatigue	-2.01 (-5.53, 1.51)	0.261	-3.50 (-6.93, -0.06)	0.046	-5.76 (-9.34, -2.18)	0.002
PROMIS pain interference	-0.86 (-3.81, 2.09)	0.567	-2.55 (-5.65, 0.56)	0.108	-1.82 (-5.95, 2.30)	0.387
PROMIS physical function	-0.17 (-2.47, 2.81)	0.897	1.84 (-0.73, 4.41)	0.161	3.46 (0.16, 6.76)	0.040
EQ-5D scale	-3.52 (-9.46, 2.42)	0.243	1.25 (-5.20, 7.71)	0.703	1.95 (-5.86, 9.77)	0.624
EQ-5D index	-0.01 (-0.06, 0.04)	0.666	0.02 (-0.02, 0.06)	0.419	0.04 (-0.01, 0.09)	0.126

ANCOVA: analysis of covariance

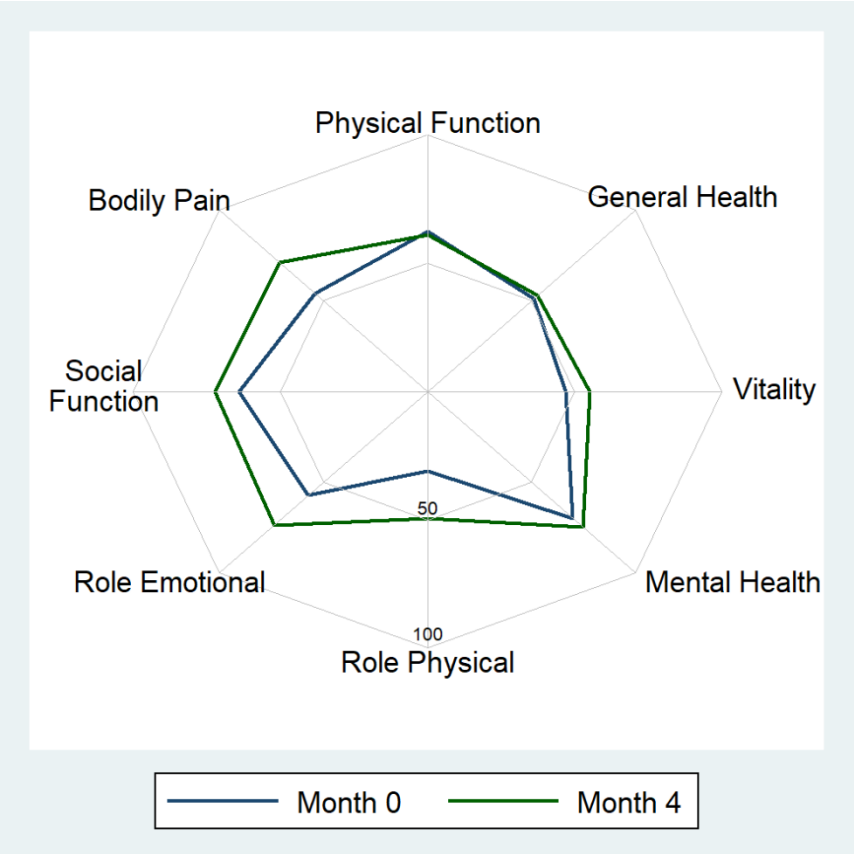
SF-36 *short form-36,* PCS *physical component score,* MCS *mental component score*, PROMIS *Patient-Reported Outcome Measurement Information System*, Eq-5D *EuroQoL Group 5-Dimensions 5-Level*

Supplementary Figure 1: Short Form-36 domain scores at baseline and at Month 4 of the RITAZAREM trial

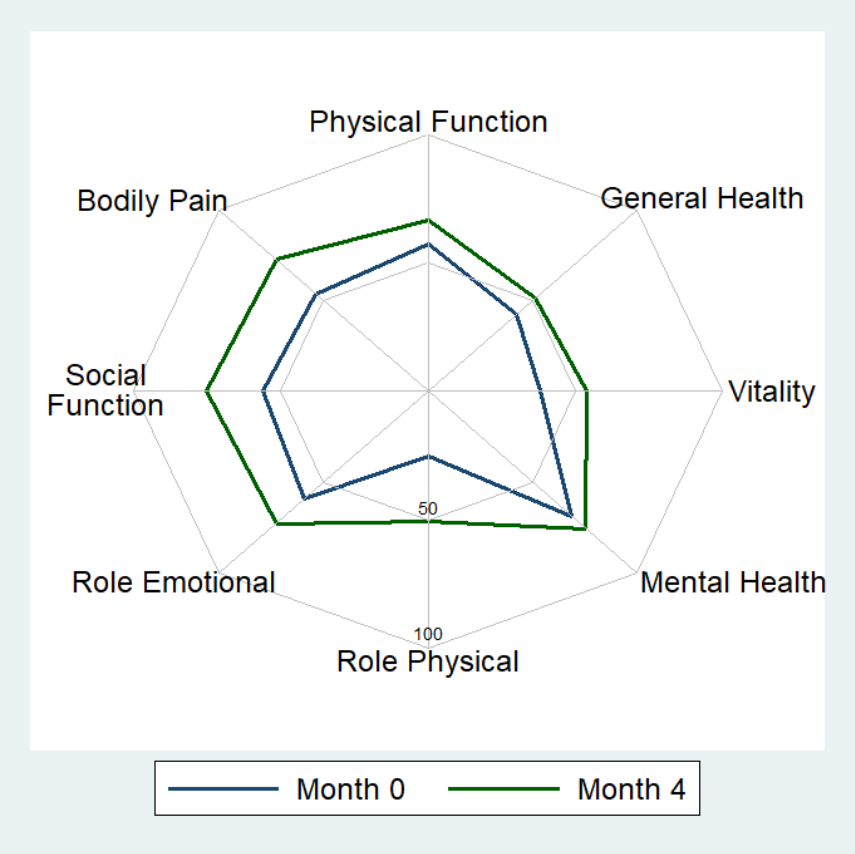
A) Mean SF-36 domain scores at Month 0 and Month 4 for all patients



B) Mean SF-36 domain scores in patients receiving higher-dose glucocorticoid



C) Mean SF-36 domain scores in patients receiving lower-dose glucocorticoid



These radar plots depict the mean of each Short Form 36 (SF-36) domain score is presented at Month 0 and Month 4 for A) all participants in the induction phase of RITAZAREM, B) patients who received higher-dose glucocorticoid, and C) patients who received lower-dose glucocorticoid. All SF-36 and PROMIS scores were transformed to make the results comparable to United States population norm values, standardized as T-scores to a mean of 50 and standard deviation of 10

References

1. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2009;150(10):670-80.
2. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. Ann Rheum Dis. 2012;71(6):955-60.
3. Jones RB, Cohen Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. New England Journal of Medicine. 2010;363(3):211-20.
4. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis. New England Journal of Medicine. 2010;363(3):221-32.
5. Tomasson G, Boers M, Walsh M, LaValley M, Cuthbertson D, Carette S, et al. Assessment of health-related quality of life as an outcome measure in granulomatosis with polyangiitis (Wegener's). Arthritis Care Res (Hoboken). 2012;64(2):273-9.
6. Walsh M, Mukhtyar C, Mahr A, Herlyn K, Luqmani R, Merkel PA, et al. Health-related quality of life in patients with newly diagnosed antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Care Res (Hoboken). 2011;63(7):1055-61.
7. Basu N, McClean A, Harper L, Amft EN, Dhaun N, Luqmani RA, et al. The characterisation and determinants of quality of life in ANCA associated vasculitis. Ann Rheum Dis. 2014;73(1):207-11.
8. Pugnet G, Pagnoux C, Terrier B, Perrodeau E, Puéchal X, Karras A, et al. Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life. Clin Exp Rheumatol. 2016;34(3 Suppl 97):S54-9.
9. Carpenter DM, Thorpe CT, Lewis M, Devellis RF, Hogan SL. Health-related quality of life for patients with vasculitis and their spouses. Arthritis Care & Research. 2009;61(2):259-65.
10. Suka M, Hayashi T, Kobayashi S, Ito S, Yumura W, Ozaki S. Improvement in health-related quality of life in MPO-ANCA-associated vasculitis patients treated with cyclophosphamide plus prednisolone: an analysis of 18 months of follow-up data from the JMAAV study. Mod Rheumatol. 2012;22(6):877-84.
11. Hajj-Ali RA, Wilke WS, Calabrese LH, Hoffman GS, Liu X, Bena J, et al. Pilot study to assess the frequency of fibromyalgia, depression, and sleep disorders in patients with granulomatosis with polyangiitis (Wegener's). Arthritis Care Res (Hoboken). 2011;63(6):827-33.
12. Koutantji M, Harrold E, Lane SE, Pearce S, Watts RA, Scott DG. Investigation of quality of life, mood, pain, disability, and disease status in primary systemic vasculitis. Arthritis Rheum. 2003;49(6):826-37.
13. Basu N, Jones GT, Fluck N, MacDonald AG, Pang D, Dospinescu P, et al. Fatigue: a principal contributor to impaired quality of life in ANCA-associated vasculitis. Rheumatology (Oxford). 2010;49(7):1383-90.
14. Basu N, McClean A, Harper L, Amft EN, Dhaun N, Luqmani RA, et al. Explaining fatigue in ANCA-associated vasculitis. Rheumatology (Oxford). 2013;52(9):1680-5.
15. Karras A, Pagnoux C, Haubitz M, Groot K, Puechal X, Tervaert JWC, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. Ann Rheum Dis. 2017;76(10):1662-8.
16. Walsh M, Merkel PA, Mahr A, Jayne D. Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: A meta-analysis. Arthritis Care Res (Hoboken). 2010;62(8):1166-73.
17. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992;116(6):488-98.

18. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Hoglund P, et al. Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. Ann Rheum Dis. 2015;74(1):177-84.
19. Robson JC, Dawson J, Cronholm PF, Ashdown S, Easley E, Kellom KS, et al. Patient perceptions of glucocorticoids in anti-neutrophil cytoplasmic antibody-associated vasculitis. Rheumatol Int. 2018;38(4):675-82.
20. Robson JC, Dawson J, Cronholm PF, Milman N, Kellom KS, Ashdown S, et al. Health-related quality of life in ANCA-associated vasculitis and item generation for a disease-specific patient-reported outcome measure. Patient Relat Outcome Meas. 2018;9:17-34.
21. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puechal X, Fujimoto S, et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. N Engl J Med. 2020;382(7):622-31.
22. Jayne DRW, Merkel PA, Schall TJ, Bekker P, Group AS. Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med. 2021;384(7):599-609.
23. Furuta S, Nakagomi D, Kobayashi Y, Hiraguri M, Sugiyama T, Amano K, et al. Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis: A Randomized Clinical Trial. JAMA. 2021;325(21):2178-87.
24. Smith RM, Jones RB, Specks U, Bond S, Nodale M, Aljayyousi R, et al. Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. Ann Rheum Dis. 2020;79(9):1243-9.
25. Stone JH, Hoffman GS, Merkel PA, Min YI, Uhlfelder ML, Hellmann DB, et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). Arthritis Rheum. 2001;44(4):912-20.
26. Seo P, Luqmani RA, Flossmann O, Hellmich B, Herlyn K, Hoffman GS, et al. The future of damage assessment in vasculitis. J Rheumatol. 2007;34(6):1357-71.
27. Ryan P. SF36: Stata module to calculate summary statistics for the SF-36 Health Survey Instrument. Statistical Software Components. https://ideas.repec.org/c/boc/bocode/s377601.html: Boston College Department of Economics; 1999.
28. Ramos-Goñi JM, Rivero-Arias O. eq5d: A command to calculate index values for the EQ-5D quality-of-life instrument. Stata Journal. 2011;11(1):120-5.
29. Westreich D, Cole SR, Funk MJ, Brookhart MA, Stürmer T. The role of the c-statistic in variable selection for propensity score models. Pharmacoepidemiology and Drug Safety. 2011;20(3):317-20.
30. Almaghlouth I, Pullenayegum E, Gladman DD, Urowitz MB, Johnson SR. Propensity Score Methods in Rare Disease: A Demonstration Using Observational Data in Systemic Lupus Erythematosus. J Rheumatol. 2021;48(3):321-5.
31. Pirracchio R, Resche-Rigon M, Chevret S. Evaluation of the Propensity score methods for estimating marginal odds ratios in case of small sample size. BMC Medical Research Methodology. 2012;12(1):70.
32. Cazzador D, Padoan R, Colangeli R, Pendolino AL, Felicetti M, Zanoletti E, et al. Health-Related Quality of Life in Patients With ANCA-Associated Vasculitis and Sinonasal Involvement: A Single-Center Cross-Sectional Study. J Clin Rheumatol. 2020.
33. Pagels AA, Söderkvist BK, Medin C, Hylander B, Heiwe S. Health-related quality of life in different stages of chronic kidney disease and at initiation of dialysis treatment. Health Qual Life Outcomes. 2012;10:71.
34. Legrand K, Speyer E, Stengel B, Frimat L, Ngueyon Sime W, Massy ZA, et al. Perceived Health and Quality of Life in Patients With CKD, Including Those With Kidney Failure: Findings From National Surveys in France. Am J Kidney Dis. 2020;75(6):868-78.
35. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaître O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371(19):1771-80.

36. Herlyn K, Hellmich B, Seo P, Merkel PA. Patient-reported outcome assessment in vasculitis may provide important data and a unique perspective. Arthritis Care Res (Hoboken). 2010;62(11):1639-45.

Chapter 6 – Discussion & Future directions

6.1 Summary of findings

Although an uncommon condition, the impact of AAV on patients and the broader implications for health services is substantial. This thesis has addressed the overarching theme of optimising the management of patients with AAV by exploring the impact on mortality and malignancy risk in Australia, evaluating rituximab strategies for maintenance of remission in AAV, assessing hypogammaglobulinaemia as a potential adverse effect of rituximab, and finally, reviewing the HRQoL of patients with AAV.

Observational cohorts and RCTs have addressed important questions related to patient outcomes in AAV but have known limitations when examining rarer and longer-term outcomes such as malignancy and mortality. Population-based studies provide a unique perspective in addressing these questions. Population-based studies examining malignancy and mortality over longer term follow-up, however, have not previously accounted for the time-varying changes to underlying risk of both outcomes over time [102, 109, 110, 113, 139-141, 143]. Furthermore, there is little epidemiological information on patients with AAV in Australia. Although Australian patients have been included in contemporary multi-centre RCTs [57, 63, 70, 75], there has been limited information on what role, if any, the Australian context plays in outcomes, noting differences in population size, limitations to care in rural and regional areas, environmental factors, and ethnic composition.

Work presented in Chapter 2 of this thesis seeks to address these gaps in the literature, using data linkage of WA hospitalisation, cancer registry and death registry data. Notably, these studies have included patients with both AAV and PAN, owing to the reliance of hospitalisation data on ICD coding changes. As outlined in Chapter 2, there was previously one ICD code for GPA and EGPA, and one ICD code for MPA and PAN. In the latest iteration (ICD-10), each condition has its own ICD code. Following updates to the nomenclature of vasculitides, first ICD code structures must be changed before hospitals then implement newer editions of ICD codes into existing systems. This time-lag occurs in addition to time taken for the uptake of new nomenclature and understandings of disease into clinical practice. This may be improved by additional clinical data including biopsy results and ANCA testing, which were not available in this dataset. Data linkage does, however, provide the advantages of including data from patients that would not be included in registries for observational studies or RCTs and providing data on rarer and longer- term outcomes. This arguably provides “real world” data on patient outcomes,

including those who die early in the disease course, have multiple diagnoses or comorbidities that limit their inclusion in trials, or where fulfilling inclusion criteria or classification criteria is not feasible.

Although European studies examining cancer risk in patients with AAV have identified an increased risk of skin SCC without an increase in other skin cancers [111, 113, 142], we demonstrated an increased risk of skin cancers, excluding SCC and BCC, in patients with AAV/PAN compared with Australian population rates. These findings emphasise the potential influence of environmental factors on cancer development in these patients. Time varying analyses of excess cancer rates in this paper provided additional information on the pattern of cancers, which are important to confirm in future work, and together with the differences in types of cancer in Australia compared with existing international data, highlight the potential to explore targeted cancer screening in patients.

Similar to cancer analyses, studies of mortality in AAV and PAN have not accounted for background time-varying changes in mortality rates. Data on mortality in patients with AAV/PAN presented in Chapter 2 demonstrated high early mortality, with a persistent increase in mortality over long-term follow-up, compared with matched controls and the general population. Previous population-based studies have examined UCOD alone when considering CODs, with vasculitis, infection, kidney disease and malignancy implicated [100-103]. The population-based studies examining COD have recognised that although some causes are predominant, the absolute contributions of each are small and incompletely explain the increased mortality observed [102, 103]. Nationally reported death data increasingly recognises the utility of multiple COD, in providing a better understanding of the joint role of diseases in mortality. Our data additionally supports the increasing awareness of multi-morbidity in patients with vasculitis [106, 188], and the contribution of these to death over time. Using time-varying analyses and including all COD (UCOD and contributing COD) in analyses provides greater appreciation of the true burden of diseases for AAV/PAN patients. Early and persistent contributors to mortality were infection, non-infective respiratory disease and renal impairment (acute and chronic). In our data, the contribution of ischaemic heart disease to mortality was greater than for controls, and this persisted over long-term follow-up. Consistent with the cancer paper, deaths related to malignancy accrued over time. Advances in treatment over time have led to improvements in survival, which are demonstrated in the data presented and other studies. The results of COD analyses highlight potential areas where mortality could be further reduced. In both papers included in Chapter 2, incorporating data on patient's medications would also better inform patients and clinicians on these influences on patient outcomes.

It is notable that significant advances have been made in the treatment of AAV, with increasing recognition of the need to maintain remission in patients to prevent accrual of disease related damage and improve HRQoL whilst also reducing treatment related adverse effects, and long-term sequelae including malignancy and mortality. Chapter 3 presents a review of the literature for the use of rituximab in the maintenance of remission in AAV and present guidelines for its use. The Delphi exercise highlighted expert vasculitis physicians' considerations of potential adverse effects of treatments and concomitant therapies. In a paper included in Appendix 3, prophylactic antibiotic therapy with trimethoprim-sulfamethoxazole was shown to reduce the risk of severe infections. Infection and hypogammaglobulinaemia are further explored in Chapter 4, which examined the longer-term outcomes of patients with rituximab associated hypogammaglobulinaemia. The data presented shows substantial change in gammaglobulin levels over time, but also highlights the impact of recurrent infections, with 53/142 (37%) patients commencing antibiotic prophylaxis and 29/142 (20%) commencing immunoglobulin replacement therapy. Although immunoglobulin replacement therapy reduced infections in patients, there is limited experience and evidence for weaning or cessation of this therapy. Moreover, the change in B-cell phenotype with high naïve and low memory B-cells in patients with rituximab associated hypogammaglobulinaemia with B-cell repopulation, suggests that B-cell function remains impaired even when repopulated. Recognising the benefits of rituximab in maintaining remission in patients with AAV, Chapter 4 underscores some of the adverse impacts of treatments to patients. This has become increasingly relevant with the recent Severe Acute Respiratory Syndrome associated Coronavirus 2 (SARS-CoV-2) "COVID-19" epidemic, as observational studies have reported more severe COVID-19 infections in patients who have received rituximab [189, 190]. Further, similar to what has been observed in rituximab treated patients receiving pneumococcal vaccinations, serological response to COVID-19 vaccination is reduced [191]. It remains unclear whether the serological response in these patients correlates to clinical outcomes with COVID-19 exposure.

The competing interests of improving HRQoL and patient outcomes by achieving and maintaining remission, and reducing treatment related adverse effects is also apparent in qualitative data from patients with AAV [121]. Although glucocorticoids have long had clear benefit in patients with AAV, the known and predictable toxicities common to most patients are well recognised [121]. Notably in the work on glucocorticoids included in Appendix 7, the difficult balance between benefits and adverse effects of glucocorticoids is highlighted by patients with AAV, but also by patients with a range of rheumatological conditions [172, 175].

In Chapter 5, data over the 4-month induction phase of the RITAZAREM trial are presented, exploring HRQoL in patients with a relapse of AAV who are treated with rituximab and one of two glucocorticoid regimens (higher- and lower-dose regimens). This paper explores HRQoL in these patients using traditional HRQoL measures, and newer tools including patient global assessment, and specific measures of fatigue, pain interference and physical function, recognising the interplay between many factors including fatigue, pain and disease activity on HRQoL in patients with AAV highlighted in the literature [123, 125, 171].

The data presented in Chapter 5 suggests patients receiving lower-dose glucocorticoids reported better physical function and less fatigue compared with those taking traditionally standard "higher-dose" glucocorticoids four months after trial enrolment, at the end of the induction phase. During the induction phase of the RITAZAREM trial, clinical remission rates in patients in both glucocorticoid groups were similar [75]. These findings contrast with recent RCTs that reported similar physical and mental health in patients receiving higher and lower dose glucocorticoid regimens [63, 107]. In the LOVAS trial, comparing reduced-dose and high-dose prednisolone in addition to rituximab for induction in patients with a new diagnosis of AAV, SF-36 PCS and MCS six months after randomisation were not significantly different between the two groups [107]. The patients in this study differ from those included in RITAZAREM, with LOVAS including patients with newly diagnosed AAV and RITAZAREM including patients who have relapsed, and therefore prior experience with glucocorticoids. The glucocorticoid regimens for the higher and lower dose arms between the studies differed. Moreover, the comparison for RITAZAREM is derived using propensity score weighting whereas patients in LOVAS were randomised to glucocorticoid regimens. In the ADVOCATE trial, however, patients receiving avacopan with very low dose glucocorticoid and cyclophosphamide or rituximab reported better physical function (SF-36 PCS) compared with those receiving standard dose glucocorticoid with cyclophosphamide or rituximab [57]. Importantly in this trial, avacopan was superior to assigned standard dose glucocorticoid at 52 weeks with regard to sustained remission. Whether the HRQoL effects relate to differences in disease control, the magnitude of difference in glucocorticoid dose, the addition of avacopan or other factors remains unclear. The results of the RITAZAREM HRQoL data in Chapter 5 raise additional questions on the impact of the induction phase differences, subsequent relapse and different medications on patients' HRQoL in the maintenance phase and long-term. Moreover, how the tools used to assess HRQoL fare in discriminating disease states requires further study.

6.2 Skills acquired

As summarised in Chapter 6.1, the body of work contributing to this thesis has provided a unique learning experience in various research methodologies, both their strengths and limitations, in answering questions pertinent to the overarching themes of this thesis.

This has included the principles of data collection and management in observational studies, clinical trials and linked administrative and population-based datasets. I have gained experience and knowledge in the use of ICD codes and summary population data, and the use of advanced statistical methods for data cleaning, processing, and analysis using a large longitudinal dataset. These skills further evolved in the data cleaning and analysis of the RITAZAREM dataset. Further understanding of statistical modelling was developed in exploring a propensity score weighted model in the RITAZAREM HRQoL analyses.

In addition to gaining skills in preparing the work as manuscripts for publication, I have developed a greater understanding of how research can be translated into clinical guidelines and practice. Better understanding of the value of appropriate outcome measurement evolved with the ongoing work of the OMERACT glucocorticoid group, but also the in the RITAZAREM HRQoL analyses, examining patient reported outcome measures not traditionally used in patients with AAV.

Beyond these invaluable practical research skills, the work has shaped my approach to considering research questions arising from current research and clinical practice, appraisal of different methods of statistical analysis and communication of results.

More broadly, the work from this thesis has demonstrated to me the value of research collaboration and provided a foundation from which to continue to work as a clinician researcher.

6.3 Future directions

Clinical trials in AAV have focused predominantly on the response of clinician assessed disease activity to treatment. This thesis has highlighted the impacts of AAV that extend beyond achieving disease remission, which have become increasingly important with the successful induction of remission in most patients.

Data linkage of hospitalisation, death and cancer registries have provided useful data to comment on outcomes of patients with AAV and PAN in Chapter 2. This data did not, however, include patients who never required hospitalisation for investigation, management or complications of their AAV. As clinical practice has changed, with the greater awareness of AAV and increasing availability of ANCA ELISA testing from the late 1990s, the proportion of such patients is likely to have increased. The studies in Chapter 2 also did not include data on laboratory investigations or treatment and were not able to separate patients with AAV and PAN diagnoses. Incorporating these data in improving evaluation of outcomes including cancer and mortality in these patients remains important, but also addressing the wider impact of AAV, including both inpatient and outpatient health care utilisation required for the direct care of their vasculitis and comorbidities provides a better picture of its impact. Beyond healthcare use, economic implications of reduced work participation and use of welfare require consideration in this chronic illness.

To address these questions on the impact of AAV, a capture-recapture study to identify all patients with AAV in South Australia is proposed, using state-wide ANCA testing results, histopathology results and hospitalisation data to identify patients with AAV, and linking their data to state-based cancer registry, death registry and renal replacement registry data, and national health care reimbursement, drug utilisation and social service benefits data. This proposal is included as Appendix 8.

An update on the rituximab guidelines for maintenance of remission in AAV may be required considering the COVID-19 pandemic. These guidelines were developed prior to COVID-19, and recommendations were made recognising potential adverse effects relevant to these patients at the time.

Although strategies to limit glucocorticoid use have been successful in AAV, none of these treatment regimens have avoided glucocorticoids altogether. There remains overlap in the impact of glucocorticoids and AAV on patients. In view of the preliminary findings from the induction phase of RITAZAREM, further work to explore the impact of glucocorticoids to HRQoL over the maintenance phase is required. Questions also remain on the utility of these HRQoL tools in discriminating disease states in patients over long-term follow-up, and the impact of treatments including glucocorticoids, and disease relapse over a longer period. Such questions will be explored in analysis of the full RITAZAREM trial data.

A newer tool developed using OMERACT principles and methodology, the AAV-PRO, has demonstrated construct validity against the Eq-5D and patient reported disease states [122] .

However, whether the AAV-PRO discriminates between clinician assessed active disease and remission, and how domain scores correlate with clinician assessed measures of disease activity remain unclear. The formation of the Australia and New Zealand Vasculitis (ANZVASC) collaboration has led to development of a national vasculitis registry with routine collection of HRQoL outcomes in Australian and New Zealand patients with AAV and may be used to address these questions [192].

Ongoing work with the OMERACT glucocorticoid group also seeks to further the development of the core domain set already developed, as outlined in Chapter 5. This work has sought to expand on the definitions of these domains, with additional work underway to evaluate and develop instruments that can be utilised in clinical trials to assess the impact of glucocorticoids.

6.4 Conclusion

The work presented in this thesis has extended current knowledge on a range of clinical aspects that could be optimised in the care of patients with AAV. Cancer and mortality in patients with AAV and PAN have been explored in an Australian context and improved understanding of time-varying risks. The effects, both positive and negative, of rituximab in AAV highlight the importance of ongoing development of new therapeutic strategies to limit adverse effects whilst achieving success in maintaining remission. Finally, patients' perspectives of disease and treatment have been explored, comparing tools used for the evaluating HRQoL in AAV and assessing the effects of changing clinical practices for glucocorticoids on patients' HRQoL. Planned future work will continue the aim of optimising management for patients with AAV.

References

1. Jennette, J.C., et al., *2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides.* Arthritis Rheum, 2013. **65**(1): p. 1-11.
2. Matteson, E.L., *A history of early investigation in polyarteritis nodosa.* Arthritis Care Res, 1999. **12**(4): p. 294-302.
3. Wegener, F., *Über eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arterien systems und der Nieren.* Beiträge zur Pathologie, 1976. **158**(1): p. 127-143.
4. Dickson, W.E.C., *Polyarteritis acuta nodosa and periarteritis nodosa.* The Journal of Pathology and Bacteriology, 1908. **12**(1): p. 31-57.
5. Ferrari, E., *Ueber Polyarteritis acuta nodosa (sogenannte Periarteritis nodosa), und ihre Beziehungen zur Polymyositis und Polyneuritis acuta.* Beitr Pathol Anat, 1903. **34**: p. 350-386.
6. Davson, J., J. Ball, and R. Platt, *THE KIDNEY IN PERIARTERITIS NODOSA.* QJM: An International Journal of Medicine, 1948. **17**(3): p. 175-202.
7. Savage, C.O.S., et al., *Microscopic Polyarteritis: Presentation, Pathology and Prognosis.* QJM: An International Journal of Medicine, 1985. **56**(2): p. 467-483.
8. Guillevin, L. and F. Lhote, *Polyarteritis nodosa and microscopic polyangiitis.* Clin Exp Immunol, 1995. **101 Suppl 1**(Suppl 1): p. 22-3.
9. Jennette, J.C., et al., *Nomenclature of systemic vasculitides. Proposal of an international consensus conference.* Arthritis Rheum, 1994. **37**(2): p. 187-92.
10. Wegener, F.W., *Über eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arterien systems und der Nieren.* Beitrd ge zur Pathologie, 1939. **158**: p. 127-143.
11. Wegener, F., *Uber generalisierte septische Gefgsserkrankungen.* Verhandlungen der Deutschen Pathologischen Gesellschaft, 1936. **29**.
12. McBride, P., *Photographs of a Case of Rapid Destruction of the Nose and Face.* The Journal of Laryngology & Otology, 2007. **105**(12): p. 1120-1120.
13. Klinger, H., *Grenzformen der Periarteritis nodosa.* Frankf Z Pathol, 1931. **42**: p. 455-480.
14. Godman, G.C. and J. Churg, *Wegener's granulomatosis: pathology and review of the literature.* AMA Arch Pathol, 1954. **58**(6): p. 533-53.
15. Falk, R.J. and J.C. Jennette, *ANCA disease: where is this field heading?* J Am Soc Nephrol, 2010. **21**(5): p. 745-52.
16. Falk, R.J., et al., *Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis.* Ann Rheum Dis, 2011. **70**(4): p. 704.
17. Churg, J. and L. Strauss, *Allergic granulomatosis, allergic angiitis, and periarteritis nodosa.* The American journal of pathology, 1951. **27**(2): p. 277-301.
18. Davies, D.J., et al., *Segmental necrotising glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology?* British medical journal (Clinical research ed.), 1982. **285**(6342): p. 606-606.
19. van der Woude, F.J., et al., *Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis.* Lancet, 1985. **1**(8426): p. 425-9.
20. Bossuyt, X., et al., *Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis.* Nat Rev Rheumatol, 2017. **13**(11): p. 683-692.
21. Xiao, H., et al., *Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice.* J Clin Invest, 2002. **110**(7): p. 955-63.

22. Little, M.A., et al., *Anti-proteinase 3 anti-neutrophil cytoplasm autoantibodies recapitulate systemic vasculitis in mice with a humanized immune system.* PLoS One, 2012. **7**(1): p. e28626.
23. Tomasson, G., et al., *Value of ANCA measurements during remission to predict a relapse of ANCA-associated vasculitis--a meta-analysis.* Rheumatology (Oxford), 2012. **51**(1): p. 100-9.
24. Unizony, S., et al., *Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type.* Ann Rheum Dis, 2016. **75**(6): p. 1166-9.
25. Mahr, A., et al., *Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis.* Ann Rheum Dis, 2013. **72**(6): p. 1003-10.
26. Sinico, R.A., et al., *Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome.* Arthritis Rheum, 2005. **52**(9): p. 2926-35.
27. Sablé-Fourtassou, R., et al., *Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome.* Ann Intern Med, 2005. **143**(9): p. 632-8.
28. Watts, R., et al., *Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies.* Ann Rheum Dis, 2007. **66**(2): p. 222-7.
29. Robson, J.C., et al., *OP0021 Draft classification criteria for the anca associated vasculitides.* Annals of the Rheumatic Diseases, 2018. **77**(Suppl 2): p. 60-61.
30. Leavitt, R.Y., et al., *The American College of Rheumatology 1990 criteria for the classification of wegener's granulomatosis.* Arthritis & Rheumatism, 1990. **33**(8): p. 1101-1107.
31. Masi, A.T., et al., *The American College of Rheumatology 1990 criteria for the classification of churg-strauss syndrome (allergic granulomatosis and angiitis).* Arthritis & Rheumatism, 1990. **33**(8): p. 1094-1100.
32. Lane, S.E., et al., *Primary systemic vasculitis: clinical features and mortality.* QJM, 2005. **98**(2): p. 97-111.
33. Lyons, P.A., et al., *Genetically distinct subsets within ANCA-associated vasculitis.* N Engl J Med, 2012. **367**(3): p. 214-23.
34. Lyons, P.A., et al., *Genome-wide association study of eosinophilic granulomatosis with polyangiitis reveals genomic loci stratified by ANCA status.* Nat Commun, 2019. **10**(1): p. 5120.
35. Lionaki, S., et al., *Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis.* Arthritis Rheum, 2012. **64**(10): p. 3452-62.
36. Robson, J., et al., *Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials.* Ann Rheum Dis, 2015. **74**(1): p. 177-84.
37. Mohammad, A.J., et al., *Pulmonary Involvement in Antineutrophil Cytoplasmic Antibodies (ANCA)-associated Vasculitis: The Influence of ANCA Subtype.* J Rheumatol, 2017. **44**(10): p. 1458-1467.
38. Comarmond, C., et al., *Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort.* Arthritis Rheum, 2013. **65**(1): p. 270-81.
39. Healy, B., et al., *Antineutrophil cytoplasmic autoantibodies and myeloperoxidase autoantibodies in clinical expression of Churg-Strauss syndrome.* J Allergy Clin Immunol, 2013. **131**(2): p. 571-6 e1-6.

40. Jennette, J.C. and P.H. Nachman, *ANCA Glomerulonephritis and Vasculitis.* Clinical Journal of the American Society of Nephrology, 2017. **12**(10): p. 1680-1691.
41. Watts, R.A., et al., *Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.* Nephrol Dial Transplant, 2015. **30 Suppl 1**: p. i14-22.
42. Jardel, S., et al., *Mortality in systemic necrotizing vasculitides: A retrospective analysis of the French Vasculitis Study Group registry.* Autoimmun Rev, 2018. **17**(7): p. 653-659.
43. Hissaria, P., et al., *Wegener's granulomatosis: epidemiological and clinical features in a South Australian study.* Intern Med J, 2008. **38**(10): p. 776-80.
44. Ormerod, A.S. and M.C. Cook, *Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales.* Intern Med J, 2008. **38**(11): p. 816-23.
45. Mohammad, A.J., *An update on the epidemiology of ANCA-associated vasculitis.* Rheumatology (Oxford), 2020. **59**(Suppl 3): p. iii42-iii50.
46. Furuta, S., et al., *Comparison of the Phenotype and Outcome of Granulomatosis with Polyangiitis Between UK and Japanese Cohorts.* J Rheumatol, 2017. **44**(2): p. 216-222.
47. Furuta, S., et al., *Comparison of phenotype and outcome in microscopic polyangiitis between Europe and Japan.* J Rheumatol, 2014. **41**(2): p. 325-33.
48. O'Donnell, J.L., et al., *Wegener's granulomatosis in New Zealand: evidence for a latitude-dependent incidence gradient.* Intern Med J, 2007. **37**(4): p. 242-6.
49. Terrier, B., et al., *Granulomatosis with polyangiitis according to geographic origin and ethnicity: clinical-biological presentation and outcome in a French population.* Rheumatology (Oxford), 2017. **56**(3): p. 445-450.
50. Mahr, A., et al., *Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: a capture-recapture estimate.* Arthritis Rheum, 2004. **51**(1): p. 92-9.
51. Cao, Y., et al., *DRB1*15 Allele Is a Risk Factor for PR3-ANCA Disease in African Americans.* Journal of the American Society of Nephrology, 2011. **22**(6): p. 1161-1167.
52. Jayne, D., et al., *A Randomized Trial of Maintenance Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Autoantibodies.* New England Journal of Medicine, 2003. **349**(1): p. 36-44.
53. De Groot, K., et al., *Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis.* Arthritis Rheum, 2005. **52**(8): p. 2461-9.
54. de Groot, K., et al., *Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial.* Ann Intern Med, 2009. **150**(10): p. 670-80.
55. Jones, R.B., et al., *Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis.* New England Journal of Medicine, 2010. **363**(3): p. 211-220.
56. Hiemstra, T.F., et al., *Mycophenolate Mofetil vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: A Randomized Controlled Trial.* JAMA, 2010. **304**(21): p. 2381-2388.
57. Jayne, D.R.W., et al., *Avacopan for the Treatment of ANCA-Associated Vasculitis.* N Engl J Med, 2021. **384**(7): p. 599-609.
58. Stone, J.H., et al., *Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis.* New England Journal of Medicine, 2010. **363**(3): p. 221-232.
59. Guillevin, L., et al., *Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis.* N Engl J Med, 2014. **371**(19): p. 1771-80.
60. Charles, P., et al., *Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre,*

randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis, 2018. **77**(8): p. 1143-1149.
61. Terrier, B., et al., *Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides.* Ann Rheum Dis, 2018. **77**(8): p. 1150-1156.
62. Charles, P., et al., *Long-Term Rituximab Use to Maintain Remission of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: A Randomized Trial.* Ann Intern Med, 2020. **173**(3): p. 179-187.
63. Walsh, M., et al., *Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis.* N Engl J Med, 2020. **382**(7): p. 622-631.
64. Yates, M., et al., *EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis.* Ann Rheum Dis, 2016. **75**(9): p. 1583-94.
65. Chung, S.A., et al., *2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis.* Arthritis Rheumatol, 2021.
66. Fauci, A.S., S.M. Wolff, and J.S. Johnson, *Effect of cyclophosphamide upon the immune response in Wegener's granulomatosis.* N Engl J Med, 1971. **285**(27): p. 1493-6.
67. Fahey, J.L., et al., *Wegener's granulomatosis.* Am J Med, 1954. **17**(2): p. 168-79.
68. Hoffman, G.S., et al., *Wegener granulomatosis: an analysis of 158 patients.* Ann Intern Med, 1992. **116**(6): p. 488-98.
69. Harper, L., et al., *Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up.* Ann Rheum Dis, 2012. **71**(6): p. 955-60.
70. Jones, R.B., et al., *Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial.* Ann Rheum Dis, 2019. **78**(3): p. 399-405.
71. Specks, U., et al., *Efficacy of remission-induction regimens for ANCA-associated vasculitis.* N Engl J Med, 2013. **369**(5): p. 417-27.
72. Walsh, M., et al., *Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: A meta-analysis.* Arthritis Care Res (Hoboken), 2010. **62**(8): p. 1166-73.
73. Pagnoux, C., et al., *Azathioprine or Methotrexate Maintenance for ANCA-Associated Vasculitis.* New England Journal of Medicine, 2008. **359**(26): p. 2790-2803.
74. Karras, A., et al., *Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis.* Ann Rheum Dis, 2017. **76**(10): p. 1662-1668.
75. Smith, R.M., et al., *Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis.* Ann Rheum Dis, 2020. **79**(9): p. 1243-1249.
76. Pendergraft, W.F., 3rd, et al., *Long-term maintenance therapy using rituximab-induced continuous B-cell depletion in patients with ANCA vasculitis.* Clin J Am Soc Nephrol, 2014. **9**(4): p. 736-44.
77. Cortazar, F.B., et al., *Effect of Continuous B Cell Depletion With Rituximab on Pathogenic Autoantibodies and Total IgG Levels in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis.* Arthritis Rheumatol, 2017. **69**(5): p. 1045-1053.
78. Cartin-Ceba, R., F.C. Fervenza, and U. Specks, *Treatment of antineutrophil cytoplasmic antibody-associated vasculitis with rituximab.* Curr Opin Rheumatol, 2012. **24**(1): p. 15-23.
79. Smith, R.M., et al., *Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis.* Arthritis Rheum, 2012. **64**(11): p. 3760-9.
80. Alberici, F., et al., *Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis.* Rheumatology (Oxford), 2015. **54**(7): p. 1153-60.

81. Calich, A.L., et al., *Rituximab for induction and maintenance therapy in granulomatosis with polyangiitis (Wegener's). Results of a single-center cohort study on 66 patients.* J Autoimmun, 2014. **50**: p. 135-41.
82. Charles, P., et al., *Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients.* Rheumatology (Oxford), 2014. **53**(3): p. 532-9.
83. Md Yusof, M.Y., et al., *Repeat cycles of rituximab on clinical relapse in ANCA-associated vasculitis: identifying B cell biomarkers for relapse to guide retreatment decisions.* Ann Rheum Dis, 2015. **74**(9): p. 1734-8.
84. Miloslavsky, E.M., et al., *Rituximab for the treatment of relapses in antineutrophil cytoplasmic antibody-associated vasculitis.* Arthritis Rheumatol, 2014. **66**(11): p. 3151-9.
85. Besada, E., W. Koldingsnes, and J.C. Nossent, *Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre.* Rheumatology (Oxford), 2013. **52**(11): p. 2041-7.
86. Fussner, L.A., et al., *Factors Determining the Clinical Utility of Serial Measurements of Antineutrophil Cytoplasmic Antibodies Targeting Proteinase 3.* Arthritis Rheumatol, 2016. **68**(7): p. 1700-10.
87. Puechal, X., et al., *Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial.* Arthritis Rheumatol, 2017. **69**(11): p. 2175-2186.
88. Guillevin, L., et al., *Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients.* Medicine (Baltimore), 1996. **75**(1): p. 17-28.
89. Ribi, C., et al., *Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: A prospective randomized study of one hundred twenty-four patients.* Arthritis Rheum, 2010. **62**(4): p. 1186-97.
90. Guillevin, L., et al., *The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort.* Medicine (Baltimore), 2011. **90**(1): p. 19-27.
91. Moosig, F., et al., *A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients.* Ann Rheum Dis, 2013. **72**(6): p. 1011-7.
92. Teixeira, V., et al., *Efficacy and safety of rituximab in the treatment of eosinophilic granulomatosis with polyangiitis.* RMD Open, 2019. **5**(1): p. e000905.
93. Thiel, J., et al., *Rituximab in the treatment of refractory or relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).* Arthritis Res Ther, 2013. **15**(5): p. R133.
94. ClinicalTrials.gov, *Rituximab in Eosinophilic Granulomatosis With Polyangiitis (REOVAS) NCT02807103*, in *[Internet]*. 2016: National Library of Medicine (US).
95. Wechsler, M.E., et al., *Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis.* N Engl J Med, 2017. **376**(20): p. 1921-1932.
96. Walton, E.W., *Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis).* British medical journal, 1958. **2**(5091): p. 265-270.
97. Hollander D and M. RT., *The Use of Alkylating Agents in the Treatment of Wegener's Granulomatosis.* Annals of Internal Medicine, 1967. **67**(2): p. 393-398.
98. Wallace, Z.S., et al., *Improved survival in granulomatosis with polyangiitis: A general population-based study.* Semin Arthritis Rheum, 2016. **45**(4): p. 483-9.
99. Tan, J.A., et al., *Mortality in ANCA-associated vasculitis: ameta-analysis of observational studies.* Ann Rheum Dis, 2017. **76**(9): p. 1566-1574.

100. Flossmann, O., et al., *Long-term patient survival in ANCA-associated vasculitis.* Ann Rheum Dis, 2011. **70**(3): p. 488-94.
101. Luqmani, R., et al., *Mortality in Wegener's granulomatosis: a bimodal pattern.* Rheumatology (Oxford), 2011. **50**(4): p. 697-702.
102. Tan, J.A., et al., *All-Cause and Cause-Specific Mortality in Patients With Granulomatosis With Polyangiitis: A Population-Based Study.* Arthritis Care Res (Hoboken), 2019. **71**(1): p. 155-163.
103. Wallace, Z.S., et al., *All-cause and cause-specific mortality in ANCA-associated vasculitis: overall and according to ANCA type.* Rheumatology (Oxford), 2020. **59**(9): p. 2308-2315.
104. Redelings, M.D., F. Sorvillo, and P. Simon, *A comparison of underlying cause and multiple causes of death: US vital statistics, 2000-2001.* Epidemiology, 2006. **17**(1): p. 100-3.
105. Robson, J., et al., *Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials.* Rheumatology (Oxford), 2015. **54**(3): p. 471-81.
106. Sarica, S.H., et al., *Multimorbidity in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: Results From a Longitudinal, Multicenter Data Linkage Study.* Arthritis Rheumatol, 2021. **73**(4): p. 651-659.
107. Furuta, S., et al., *Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis: A Randomized Clinical Trial.* JAMA, 2021. **325**(21): p. 2178-2187.
108. van Daalen, E.E., et al., *Effect of rituximab on malignancy risk in patients with ANCA-associated vasculitis.* Ann Rheum Dis, 2017. **76**(6): p. 1064-1069.
109. Knight, A., J. Askling, and A. Ekbom, *Cancer incidence in a population-based cohort of patients with Wegener's granulomatosis.* Int J Cancer, 2002. **100**(1): p. 82-5.
110. Faurschou, M., et al., *Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients.* The Journal of Rheumatology, 2008. **35**(1): p. 100-105.
111. Rahmattulla, C., et al., *Incidence of Malignancies in Patients With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Diagnosed Between 1991 and 2013.* Arthritis Rheumatol, 2015. **67**(12): p. 3270-8.
112. Heijl, C., et al., *Incidence of malignancy in patients treated for antineutrophil cytoplasm antibody-associated vasculitis: follow-up data from European Vasculitis Study Group clinical trials.* Ann Rheum Dis, 2011. **70**(8): p. 1415-21.
113. Heijl, C., et al., *Malignancies in Patients with Antineutrophil Cytoplasmic Antibody-associated Vasculitis: A Population-based Cohort Study.* J Rheumatol, 2020. **47**(8): p. 1229-1237.
114. Titeca-Beauport, D., et al., *Early predictors of one-year mortality in patients over 65 presenting with ANCA-associated renal vasculitis: a retrospective, multicentre study.* BMC Nephrol, 2018. **19**(1): p. 317.
115. Little, M.A., et al., *Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis.* Ann Rheum Dis, 2010. **69**(6): p. 1036-43.
116. Rathmann, J., et al., *Incidence and predictors of severe infections in ANCA-associated vasculitis: a population-based cohort study.* Rheumatology (Oxford), 2021. **60**(6): p. 2745-2754.
117. Roberts, D.M., et al., *Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease.* J Autoimmun, 2015. **57**: p. 60-5.

118. Walsh, M., et al., *Health-related quality of life in patients with newly diagnosed antineutrophil cytoplasmic antibody-associated vasculitis.* Arthritis Care Res (Hoboken), 2011. **63**(7): p. 1055-61.
119. Tomasson, G., et al., *Assessment of health-related quality of life as an outcome measure in granulomatosis with polyangiitis (Wegener's).* Arthritis Care Res (Hoboken), 2012. **64**(2): p. 273-9.
120. Pugnet, G., et al., *Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life.* Clin Exp Rheumatol, 2016. **34**(3 Suppl 97): p. S54-9.
121. Robson, J.C., et al., *Health-related quality of life in ANCA-associated vasculitis and item generation for a disease-specific patient-reported outcome measure.* Patient Relat Outcome Meas, 2018. **9**: p. 17-34.
122. Robson, J.C., et al., *Validation of the ANCA-associated vasculitis patient-reported outcomes (AAV-PRO) questionnaire.* Ann Rheum Dis, 2018. **77**(8): p. 1157-1164.
123. Basu, N., et al., *The characterisation and determinants of quality of life in ANCA associated vasculitis.* Ann Rheum Dis, 2014. **73**(1): p. 207-11.
124. Grayson, P.C., et al., *Illness perceptions and fatigue in systemic vasculitis.* Arthritis Care Res (Hoboken), 2013. **65**(11): p. 1835-43.
125. Basu, N., et al., *Fatigue: a principal contributor to impaired quality of life in ANCA-associated vasculitis.* Rheumatology (Oxford), 2010. **49**(7): p. 1383-90.
126. Herlyn, K., et al., *Patient-reported outcome assessment in vasculitis may provide important data and a unique perspective.* Arthritis Care Res (Hoboken), 2010. **62**(11): p. 1639-45.
127. Koutantji, M., et al., *Investigation of quality of life, mood, pain, disability, and disease status in primary systemic vasculitis.* Arthritis Rheum, 2003. **49**(6): p. 826-37.
128. Robson, J.C., et al., *Patient perceptions of glucocorticoids in anti-neutrophil cytoplasmic antibody-associated vasculitis.* Rheumatol Int, 2018. **38**(4): p. 675-682.
129. Reinhold-Keller, E., et al., *Effect of Wegener's granulomatosis on work disability, need for medical care, and quality of life in patients younger than 40 years at diagnosis.* Arthritis Rheum, 2002. **47**(3): p. 320-5.
130. Heron, V., et al., *The impact of antineutrophil cytoplasmic antibody-associated vasculitis on employment and work disability in an Australian population.* Int J Rheum Dis, 2021. **24**(7): p. 904-911.
131. Basu, N., et al., *Markers for work disability in anti-neutrophil cytoplasmic antibody-associated vasculitis.* Rheumatology (Oxford), 2014. **53**(5): p. 953-6.
132. Carpenter, D.M., et al., *Health-related quality of life for patients with vasculitis and their spouses.* Arthritis Care & Research, 2009. **61**(2): p. 259-265.
133. Mooney, J., K. Graham, and R.A. Watts, *Impact of caring for someone with a rare rheumatic condition, views from patients and informal carers—the need for cat-like vigilance.* Rheumatology Advances in Practice, 2019. **3**(1).
134. Raimundo, K., et al., *Clinical and Economic Burden of Antineutrophil Cytoplasmic Antibody-associated Vasculitis in the United States.* J Rheumatol, 2015. **42**(12): p. 2383-91.
135. Spearpoint, P., et al., *THU0652 THE ECONOMIC BURDEN OF ANCA-ASSOCIATED VASCULITIS IN GERMANY – A CLAIMS DATA STUDY.* Annals of the Rheumatic Diseases, 2019. **78**(Suppl 2): p. 622-622.
136. Quartuccio, L., et al., *Healthcare and economic burden of ANCA-associated vasculitis in Italy: an integrated analysis from clinical and administrative databases.* Intern Emerg Med, 2021. **16**(3): p. 581-589.
137. Tieu J, et al., *Mortality and cause of death in patients with AAV/PAN in Australia- a population-based study.* Rheumatology (Oxford), 2021. ***in press***.

138. Tieu, J., et al., *Cancer in Anti-Neutrophil Cytoplasm Antibody-Associated Vasculitis and Polyarteritis Nodosa in Australia: A Population-Based Study.* ACR Open Rheumatol, 2021.
139. Choi, S.T., et al., *The cancer risk according to three subtypes of ANCA-associated vasculitis: a propensity score-matched analysis of a nationwide study.* Seminars in Arthritis and Rheumatism, 2021.
140. Ahn, S.S., et al., *Risk of Cancers in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: Results from the Korea National Health Insurance Claims Database 2010-2018.* J Clin Med, 2019. **8**(11).
141. Faurschou, M., et al., *Prolonged risk of specific malignancies following cyclophosphamide therapy among patients with granulomatosis with polyangiitis.* Rheumatology (Oxford), 2015. **54**(8): p. 1345-50.
142. van Daalen, E.E., et al., *Incidence of Malignancy Prior to Antineutrophil Cytoplasmic Antibody-associated Vasculitis Compared to the General Population.* J Rheumatol, 2017. **44**(3): p. 314-318.
143. Wallace, Z.S., et al., *All-cause and cause-specific mortality in ANCA-associated vasculitis: overall and according to ANCA type.* Rheumatology, 2019. **59**(9): p. 2308-2315.
144. Bourgarit, A., et al., *Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: a retrospective analysis of causes and factors predictive of mortality based on 595 patients.* Medicine (Baltimore), 2005. **84**(5): p. 323-330.
145. Nelveg-Kristensen, K.E., et al., *Increasing incidence and improved survival in ANCA-associated vasculitis-a Danish nationwide study.* Nephrol Dial Transplant, 2020.
146. Pagnoux, C., et al., *Comparability of patients with ANCA-associated vasculitis enrolled in clinical trials or in observational cohorts.* Clinical and experimental rheumatology, 2015. **33**(2 Suppl 89): p. S-83.
147. Sarica, S.H., et al., *Characterizing infection in anti-neutrophil cytoplasmic antibody-associated vasculitis: results from a longitudinal, matched-cohort data linkage study.* Rheumatology (Oxford), 2020. **59**(10): p. 3014-3022.
148. Ungprasert, P., et al., *Inpatient burden and association with comorbidities of polyarteritis nodosa: National Inpatient Sample 2014.* Semin Arthritis Rheum, 2020. **50**(1): p. 66-70.
149. Sreih, A.G., et al., *Development and validation of case-finding algorithms for the identification of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis in large healthcare administrative databases.* Pharmacoepidemiol Drug Saf, 2016. **25**(12): p. 1368-1374.
150. Paramalingam S, R.W., Sharma C, Dogra G, McLean-Tooke A, Nossent J., *Disease flares, damage accrual and survival in ANCA-associated vasculitis in Western Australia.* International Journal of Clinical Rheumatology, 2019. **14**(1): p. 31-36.
151. Peach, E., et al., *Risk of death among people with rare autoimmune diseases compared with the general population in England during the 2020 COVID-19 pandemic.* Rheumatology (Oxford), 2021. **60**(4): p. 1902-1909.
152. Takala, J.H., et al., *Wegener's granulomatosis in Finland in 1981–2000: clinical presentation and diagnostic delay.* Scandinavian Journal of Rheumatology, 2008. **37**(6): p. 435-438.
153. Poulton, C.J., et al., *Pathways to renal biopsy and diagnosis among patients with ANCA small-vessel vasculitis.* Clinical and experimental rheumatology, 2013. **31**(1 Suppl 75): p. S32-S37.

154. (WHO), W.H.O. *International statistical classification of diseases and related health problems- 10th revision. Volume 2 Instruction Manual.* World Health Organization, 2010.
155. Tieu, J., et al., *Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines-Executive summary.* Rheumatology (Oxford), 2020. **59**(4): p. 727-731.
156. Karras, A., et al., *Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis.* Ann Rheum Dis, 2017. **76**(10): p. 1662-1668.
157. Maritati, F., et al., *Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: A randomised trial.* PLoS One, 2017. **12**(10): p. e0185880.
158. Stone, J.H., et al., *Rituximab versus cyclophosphamide for ANCA-associated vasculitis.* N Engl J Med, 2010. **363**(3): p. 221-32.
159. Gopaluni, S., et al., *Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis (RITAZAREM): study protocol for a randomized controlled trial.* Trials, 2017. **18**(1): p. 112.
160. Jones, J. and D. Hunter, *Consensus methods for medical and health services research.* Bmj, 1995. **311**(7001): p. 376-80.
161. Altmetric. *Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines. Overview of attention for article published in Rheumatology, March 2020.* [cited 2021 12 Dec 2021, last updated 02 Sep 2021]; Available from: https://oxfordjournals.altmetric.com/details/76712288#score.
162. Reddy, V., et al., *Pragmatic Treatment of Patients With Systemic Lupus Erythematosus With Rituximab: Long-Term Effects on Serum Immunoglobulins.* Arthritis Care Res (Hoboken), 2017. **69**(6): p. 857-866.
163. van Vollenhoven, R.F., et al., *Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials.* J Rheumatol, 2010. **37**(3): p. 558-67.
164. De La Torre, I., et al., *Total serum immunoglobulin levels in patients with RA after multiple B-cell depletion cycles based on rituximab: relationship with B-cell kinetics.* Rheumatology (Oxford), 2012. **51**(5): p. 833-40.
165. Barmettler, S. and C. Price, *Continuing IgG replacement therapy for hypogammaglobulinemia after rituximab--for how long?* J Allergy Clin Immunol, 2015. **136**(5): p. 1407-9.
166. Nakou, M., et al., *Rituximab therapy reduces activated B cells in both the peripheral blood and bone marrow of patients with rheumatoid arthritis: depletion of memory B cells correlates with clinical response.* Arthritis Res Ther, 2009. **11**(4): p. R131.
167. Thiel, J., et al., *B cell repopulation kinetics after rituximab treatment in ANCA-associated vasculitides compared to rheumatoid arthritis, and connective tissue diseases: a longitudinal observational study on 120 patients.* Arthritis Res Ther, 2017. **19**(1): p. 101.
168. Wijetilleka, S., et al., *Immunoglobulin replacement for secondary immunodeficiency after B-cell targeted therapies in autoimmune rheumatic disease: Systematic literature review.* Autoimmun Rev, 2019. **18**(5): p. 535-541.
169. Wijetilleka, S., et al., *Iatrogenic antibody deficiency from B-cell targeted therapies in autoimmune rheumatic diseases.* Lupus Sci Med, 2019. **6**(1): p. e000337.
170. Kronbichler, A., et al., *Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis.* Ann Rheum Dis, 2018. **77**(10): p. 1440-1447.
171. Basu, N., et al., *Explaining fatigue in ANCA-associated vasculitis.* Rheumatology (Oxford), 2013. **52**(9): p. 1680-5.

172. Venter, G., et al., *Perspectives of Glucocorticoid Use in Patients with Rheumatoid Arthritis.* ACR Open Rheumatol, 2021. **3**(4): p. 231-238.
173. Black, R.J., et al., *A Patient-reported Outcome Measure for Effect of Glucocorticoid Therapy in Adults with Inflammatory Diseases Is Needed: Report from the OMERACT 2016 Special Interest Group.* J Rheumatol, 2017. **44**(11): p. 1754-1758.
174. Cheah, J.T.L., et al., *Toward a Core Domain Set for Glucocorticoid Impact in Inflammatory Rheumatic Diseases: The OMERACT 2018 Glucocorticoid Impact Working Group.* J Rheumatol, 2019. **46**(9): p. 1179-1182.
175. Tieu, J., et al., *Improving benefit-harm assessment of glucocorticoid therapy incorporating the patient perspective: The OMERACT glucocorticoid core domain set.* Semin Arthritis Rheum, 2021.
176. Ware, J.E., Jr. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**(6): p. 473-83.
177. Ramos-Goñi, J.M. and O. Rivero-Arias, *eq5d: A command to calculate index values for the EQ-5D quality-of-life instrument.* Stata Journal, 2011. **11**(1): p. 120-125.
178. Westreich, D., et al., *The role of the c-statistic in variable selection for propensity score models.* Pharmacoepidemiology and Drug Safety, 2011. **20**(3): p. 317-320.
179. Almaghlouth, I., et al., *Propensity Score Methods in Rare Disease: A Demonstration Using Observational Data in Systemic Lupus Erythematosus.* J Rheumatol, 2021. **48**(3): p. 321-325.
180. Bergstra, S.A., et al., *Three handy tips and a practical guide to improve your propensity score models.* RMD Open, 2019. **5**(1): p. e000953.
181. Elze, M.C., et al., *Comparison of Propensity Score Methods and Covariate Adjustment: Evaluation in 4 Cardiovascular Studies.* J Am Coll Cardiol, 2017. **69**(3): p. 345-357.
182. Brookhart, M.A., et al., *Variable selection for propensity score models.* Am J Epidemiol, 2006. **163**(12): p. 1149-56.
183. Pirracchio, R., M. Resche-Rigon, and S. Chevret, *Evaluation of the Propensity score methods for estimating marginal odds ratios in case of small sample size.* BMC Medical Research Methodology, 2012. **12**(1): p. 70.
184. Seo, P., et al., *Damage caused by Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET).* Arthritis Rheum, 2005. **52**(7): p. 2168-78.
185. Cazzador, D., et al., *Health-Related Quality of Life in Patients With ANCA-Associated Vasculitis and Sinonasal Involvement: A Single-Center Cross-Sectional Study.* J Clin Rheumatol, 2020.
186. Pagels, A.A., et al., *Health-related quality of life in different stages of chronic kidney disease and at initiation of dialysis treatment.* Health Qual Life Outcomes, 2012. **10**: p. 71.
187. Legrand, K., et al., *Perceived Health and Quality of Life in Patients With CKD, Including Those With Kidney Failure: Findings From National Surveys in France.* Am J Kidney Dis, 2020. **75**(6): p. 868-878.
188. Mercuzot, C., et al., *Comorbidities and health-related quality of life in Patients with Antineutrophil Cytoplasmic Antibody (ANCA) - associated vasculitis.* Autoimmun Rev, 2021. **20**(1): p. 102708.
189. Avouac, J., et al., *COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study.* The Lancet Rheumatology, 2021. **3**(6): p. e419-e426.
190. Strangfeld, A., et al., *Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry.* Ann Rheum Dis, 2021. **80**(7): p. 930-942.

191. Spiera, R., S. Jinich, and D. Jannat-Khah, *Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS- CoV-2 vaccination in patients with rheumatic diseases.* Annals of the Rheumatic Diseases, 2021. **80**(10): p. 1357-1359.
192. Ryan, J., et al., *Formation of the Australia and New Zealand Vasculitis Society to improve the care of patients with Vasculitis in Australian and New Zealand.* Intern Med J, 2020. **50**(7): p. 781-783.

Appendices

Appendix 1 WARDER data preparation

STATA do-file: malignancy data preparation

```
egen ID = group(rootnum)

/* malignancy data

0 - Benign'

1 - Uncertain benign or malignant'

2 - Carcinoma in situ'

3 - Malignant invasive, primary site'

6 - Malignant invasive, metastatic site'

8 - Suggestive of malignancy'

9 - Malignant, uncertain whether primary/metastatic'

NOTE: The special behaviour codes for first-of-many and subsequent tumopurs of similar type, are no longer used.

Only codes 3,5,6,9 are included in routine “Cancers” statistics. Code 8 cases are never included in any statistical data if not confirmed.  Other codes are included in special-purpose tabulations only.

*/

use "xxx…\WA population data\1. analysis\data\20200106 Master File.dta", clear


// Breast Cancer //

/*

ICD-10-AM codes for topography: C50* and D05* for carcinoma in situ

*/

gen breast=0

replace breast = 1 if (substr(cansite,1,3)=="C50")

gen breast_date = 0

replace breast_date = candate if breast == 1

format breast_date %tdD_m_Y


// Lung Cancer //

/* topography- C33 to C348*/

gen lung = 0
```

```
replace lung = 1 if (substr(cansite,1,3)=="C33")
replace lung = 1 if (substr(cansite,1,3)=="C34")
gen lung_date = 0
replace lung_date = candate if lung == 1
format lung_date %tdD_m_Y

// genitourinary cancer //
/* topography- C65 to C68 */
gen GU=0
replace GU = 1 if (substr(cansite,1,3)=="C65")
replace GU = 1 if (substr(cansite,1,3)=="C66")
replace GU = 1 if (substr(cansite,1,3)=="C67")
replace GU = 1 if (substr(cansite,1,3)=="C68")
gen GU_date = 0
replace GU_date = candate if GU == 1

format GU_date %tdD_m_Y

// pancreatic cancer //
/* topography- C25*/
gen pancreatic=0
replace pancreatic = 1 if (substr(cansite,1,3)=="C25")
gen pancreatic_date = 0
replace pancreatic_date = candate if pancreatic == 1
format pancreatic_date %tdD_m_Y

// colorectal cancer //
/* topography- C18-C20, C21.8)
NB: this excludes anal cancers
*/
gen colorectal = 0
replace colorectal = 1 if (substr(cansite,1,3)=="C18")
replace colorectal = 1 if (substr(cansite,1,3)=="C19")
replace colorectal = 1 if (substr(cansite,1,3)=="C20")
```

```
replace colorectal = 1 if (substr(cansite,1,3)=="C218")

gen colorectal_date = 0

replace colorectal_date = candate if colorectal == 1

format colorectal_date %tdD_m_Y


// prostate cancer //

/* topography- C61*/

gen prostate = 0

replace prostate = 1 if (substr(cansite,1,3)=="C61")

gen prostate_date = 0

replace prostate_date = candate if prostate == 1

format prostate_date %tdD_m_Y


// skin cancers- not SCC/BCC //

/* topography- C44*/

gen skin = 0

replace skin = 1 if (substr(cansite,1,3)=="C44")

gen skin_date = 0

replace skin_date = candate if skin == 1

format skin_date %tdD_m_Y


/* morphology more reliable for haem malig e.g. lymphoma- morphology hodgkin and NHL: 959-972;

9654/9655/9661/9662/9678/9724/9725/9726/9740/9742/9756/9759/9760/9762/9806/9807/9809/98
14/9815/9816/9817/9818/9865/9869/9870/9911/9965/9966/9967/9971/99713/9992 not included but
not in dataset

9715/9993 included in WA registry but not in WHO ICD-O classification - code not modified

kaposi sarcoma 9140 added

immunoproliferative diseases- only waldenstrom macroglobulinaemia is included in WA cancer registry,
2 patients- MGUS and lymphomatoid granulomatosis in dataset- code modified for greater specificity
for waldenstroms

 */


// lymphoma //

gen lymphoma = 0

replace lymphoma = 1 if (substr(cantissue,1,3)=="959")

replace lymphoma = 1 if (substr(cantissue,1,3)=="965")
```

```
replace lymphoma = 1 if (substr(cantissue,1,3)=="966")
replace lymphoma = 1 if (substr(cantissue,1,3)=="967")
replace lymphoma = 1 if (substr(cantissue,1,3)=="968")
replace lymphoma = 1 if (substr(cantissue,1,3)=="969")
replace lymphoma = 1 if (substr(cantissue,1,3)=="970")
replace lymphoma = 1 if (substr(cantissue,1,3)=="971")
replace lymphoma = 1 if (substr(cantissue,1,3)=="972")
gen lymphoma_date = 0
replace lymphoma_date = candate if lymphoma == 1
format lymphoma_date %tdD_m_Y

// leukaemia //
gen leukaemia = 0
replace leukaemia = 1 if (substr(cantissue,1,3)=="980")
replace leukaemia = 1 if (substr(cantissue,1,3)=="981")
replace leukaemia = 1 if (substr(cantissue,1,3)=="982")
replace leukaemia = 1 if (substr(cantissue,1,3)=="983")
replace leukaemia = 1 if (substr(cantissue,1,3)=="984")
replace leukaemia = 1 if (substr(cantissue,1,3)=="985")
replace leukaemia = 1 if (substr(cantissue,1,3)=="986")
replace leukaemia = 1 if (substr(cantissue,1,3)=="987")
replace leukaemia = 1 if (substr(cantissue,1,3)=="988")
replace leukaemia = 1 if (substr(cantissue,1,3)=="989")
replace leukaemia = 1 if (substr(cantissue,1,3)=="991")
replace leukaemia = 1 if (substr(cantissue,1,3)=="992")
replace leukaemia = 1 if (substr(cantissue,1,3)=="993")
replace leukaemia = 1 if (substr(cantissue,1,3)=="994")
gen leukaemia_date = 0
replace leukaemia_date = candate if leukaemia == 1
format leukaemia_date %tdD_m_Y

// all haematologic malignancy //
gen allhaem = 0
replace allhaem = 1 if leukaemia==1
```

```
replace allhaem = 1 if lymphoma==1
replace allhaem = 1 if (substr(cantissue,1,4)=="9140")
replace allhaem = 1 if (substr(cantissue,1,3)=="973")
replace allhaem = 1 if (substr(cantissue,1,3)=="974")
replace allhaem = 1 if (substr(cantissue,1,3)=="975")
replace allhaem = 1 if (substr(cantissue,1,4)=="9761")
replace allhaem = 1 if (substr(cantissue,1,3)=="995")
replace allhaem = 1 if (substr(cantissue,1,3)=="996")
replace allhaem = 1 if (substr(cantissue,1,3)=="997")
replace allhaem = 1 if (substr(cantissue,1,3)=="998")
replace allhaem = 1 if (substr(cantissue,1,3)=="999")
gen allhaem_date = 0
replace allhaem_date = candate if allhaem == 1
format allhaem_date %tdD_m_Y

// other haematologic malignancy //
gen otherhaem = 0
replace otherhaem = 1 if (substr(cantissue,1,4)=="9140")
replace otherhaem = 1 if (substr(cantissue,1,3)=="973")
replace otherhaem = 1 if (substr(cantissue,1,3)=="974")
replace otherhaem = 1 if (substr(cantissue,1,3)=="975")
replace otherhaem = 1 if (substr(cantissue,1,4)=="9761")

replace otherhaem = 1 if (substr(cantissue,1,3)=="995")
replace otherhaem = 1 if (substr(cantissue,1,3)=="996")
replace otherhaem = 1 if (substr(cantissue,1,3)=="997")
replace otherhaem = 1 if (substr(cantissue,1,3)=="998")
replace otherhaem = 1 if (substr(cantissue,1,3)=="999")
gen otherhaem_date = 0
replace otherhaem_date = candate if otherhaem == 1
format otherhaem_date %tdD_m_Y

// all cancers //
gen cancer = 0
```

```
replace cancer = 1 if (substr(canc_eventseq,1,2)=="ca")

gen cancer_date = 0

replace cancer_date = candate if cancer == 1

format cancer_date %tdD_m_Y


// other cancers //

gen othercancer = 0

replace othercancer = 1 if cancer == 1 & allhaem == 0 & skin == 0 & prostate == 0 & colorectal == 0 &
pancreatic == 0 & breast == 0 & GU == 0 & lung == 0

gen othercancer_date = 0

replace othercancer_date = candate if othercancer == 1

format othercancer_date %tdD_m_Y


// date for each cancer => candate //

// identified in subsequent analysis that haematologic malignancy occasionally identified in solid organ
biopsy- these should be amended to reflect the haematologic malignancy //

// change classification prior to duplicate management //

    +---------------+

manually sorted- details removed to limit publication of combinations of de-identified data

    +---------------+

// remove duplicates for each cancer by individual i.e. likely recurrences //

// remove breast cancer duplicates, 12 duplicates //

sort rootnum breast date candate

quietly by rootnum breast: gen dup = cond(_N==1,0,_n) if breast == 1

tabulate dup

drop if dup == 2

drop if dup == 3

drop dup

//remove lung cancer duplicates, 3 duplicates //

sort rootnum lung date candate

quietly by rootnum lung: gen dup = cond(_N==1,0,_n) if lung == 1

tabulate dup

drop if dup == 2

drop dup

// remove duplicates of GU, 51 duplicates //
```

```
sort rootnum GU date candate
quietly by rootnum GU: gen dup = cond(_N==1,0,_n) if GU == 1
tabulate dup
drop if dup == 2
drop if dup == 3
drop if dup == 4
drop if dup == 5
drop dup
// remove duplicates of pancreatic, no duplicates //
sort rootnum pancreatic date candate
quietly by rootnum pancreatic: gen dup = cond(_N==1,0,_n) if pancreatic == 1
tabulate dup
drop dup
// remove duplicates of colorectal, 18 duplicates //
sort rootnum colorectal date candate
quietly by rootnum colorectal: gen dup = cond(_N==1,0,_n) if colorectal == 1
tabulate dup
drop if dup == 2
drop if dup == 3
drop if dup == 4
drop dup
// remove duplicates of prostate, no duplicates //
sort rootnum prostate date candate
quietly by rootnum prostate: gen dup = cond(_N==1,0,_n) if prostate == 1
tabulate dup
drop dup
/* no duplicates */
// remove duplicates of skin, total 118 duplicates //
sort rootnum skin date candate
quietly by rootnum skin: gen dup = cond(_N==1,0,_n) if skin == 1
tabulate dup
drop if dup == 2
drop if dup == 3
drop if dup == 4
```

```
drop if dup == 5
drop dup
//remove duplicates of lymphoma, 1 duplicate //
sort rootnum lymphoma date candate
quietly by rootnum lymphoma: gen dup = cond(_N==1,0,_n) if lymphoma == 1
tabulate dup
drop if dup == 2
drop dup
// remove duplicates of leukaemia, 1 duplicate//
sort rootnum leukaemia date candate
quietly by rootnum leukaemia: gen dup = cond(_N==1,0,_n) if leukaemia == 1
tabulate dup
drop if dup == 2
drop dup
// check +/- remove otherhaem, //
sort rootnum otherhaem date candate
quietly by rootnum otherhaem: gen dup = cond(_N==1,0,_n) if otherhaem == 1
tabulate dup
list rootnum if dup == 2
     +---------------+
manually sorted- details removed to limit publication of combinations of de-identified data
     +---------------+
drop if dup == 2
drop dup
// check allhaem //
sort rootnum allhaem date candate
quietly by rootnum allhaem: gen dup = cond(_N==1,0,_n) if allhaem == 1
tabulate dup
* 10 duplicates *
list rootnum cantissue date if dup== 1|dup == 2
     +---------------+
manually sorted- details removed to limit publication of combinations of de-identified data
     +---------------+
drop if dup == 2
```

drop dup

// check +/- remove otherca //

sort rootnum othercancer date candate

quietly by rootnum othercancer: gen dup = cond(_N==1,0,_n) if othercancer == 1

tabulate dup

list rootnum if dup == 2

// RULES //

* if same organ system within 12 months => delete subsequent records; check tissue morphology if unclear *

* remove recurrences *

+---------------+

manually sorted- details removed to limit publication of combinations of de-identified data

+---------------+

STATA do-file: mortality data preparation

WITHIN WARDER

- pre 1997, no ucod data is available

- stored as 5 digit ICD9

1997-1998:

> ICD9

> entity axis data stored in positions across 1 line

> record axis data stored as 5 digit codes

1999-2005:

> ICD10

> entity axis data stored as 4 digit codes; was previously received as 5 digit codes; tab between lines; large tab between part I and part II

> record axis data stored as 4 digit codes; was previously received with 5th digit (corrected)

2006-onwards:

> ICD10

> entity axis data stored as received for the codes; first 2 digit are position codes- first is position in that line, second is line number (line 6 onwards is part II)

> record axis data 3-4 ditis separated by 1 space

*/

```
import delimited "***\1. analysis\data\extra codcodes_for merge.csv", varnames(1) clear

rename codtext1 codtext_1

rename codtext2 codtext_2

rename codtext3 codtext_3

rename antecedent1 antecedent_1

rename antecedent2 antecedent_2

rename antecedent3 antecedent_3

rename contrib1 contrib_1

rename contrib2 contrib_2

rename contrib3 contrib_3

save "***\1. analysis\data\extra codcodes_for merge.dta"

use "***\1. analysis\data\AAV Master File - 16.06.20.dta", clear

mmerge rootnum using "***\1. analysis\data\extra codcodes_for merge.dta"
```

```
browse rootnum lpnum date codcode entity_axis_data record_axis_data multi_cod_format_type codtext antecedent contrib_factors codtext_1 codtext_2 codtext_3 antecedent_1 antecedent_2 antecedent_3 contrib_1 contrib_2 contrib_3 if rectype == 4

** manual inclusion of UCOD from Dec 2013-Feb 2016 deaths **

** additional areas of text identified where the contributory COD was not coded **

import delimited "***\CODCODES.csv", varnames(1) clear

drop codtext

drop codtext1 codtext2 codtext3 codtext4 codtext5 codtext6

drop antecedent

drop antecedent1 antecedent2 antecedent3 antecedent4 antecedent5 contrib_factors

rename v27 contrib_4

gen rectype = 4

rename codcode codcode_ucod

rename codtext_1 codtext_1a

rename codtext_2 codtext_2a

rename codtext_3 codtext_3a

rename antecedent_1 antecedent_1a

rename antecedent_2 antecedent_2a

rename antecedent_3 antecedent_3a

rename contrib_1 contrib_1a

rename contrib_2 contrib_2a

rename contrib_3 contrib_3a

rename contrib_4 contrib_4a

save "***\1. analysis\data\20200915_extraucod.dta"

use "***\1. analysis\data\20200826 Masterlist with extra CODcodes.dta", clear

mmerge rootnum rectype using "***\1. analysis\data\20200915_extraucod.dta"

replace antecedent_1 = antecedent_1a if rectype == 4 & antecedent_1 =""

replace antecedent_2 = antecedent_2a if rectype == 4 & antecedent_2 =""

replace antecedent_3 = antecedent_3a if rectype == 4 & antecedent_3 =""

replace contrib_1 = contrib_1a if rectype == 4 & contrib_1 == "" & cf1 == ""

replace contrib_2 = contrib_2a if rectype == 4 & contrib_2 == "" & cf2 == ""

replace contrib_3 = contrib_3a if rectype == 4 & contrib_3 == "" & cf3 == ""

rename contrib_4a contrib_4

browse rootnum date dateofdeath dod dod_a codcode codtext antecedent contrib_factors codtext_1 codtext_2 codtext_3 codtext_1a codtext_2a codtext_3a codtext1 codtext2 codtext3 codtext4 codtext5 codtext6 codtext7 codtext8 codtext9 codtext10 antecedent_1 antecedent_2 antecedent_3
```

antecedent_1a antecedent_2a antecedent_3a antecedent1 antecedent2 antecedent3 antecedent4 antecedent5 antecedent6 antecedent7 antecedent8 antecedent9 antecedent10 cf1 cf2 cf3 cf4 cf5 cf6 cf7 cf8 cf9 cf10 contrib_1 contrib_2 contrib_3 contrib_1a contrib_2a contrib_3a contrib_4 if rectype == 4

// format without dot //

icd10 clean codtext1, replace

icd10 clean codtext2, replace

icd10 clean codtext3, replace

icd10 clean codtext4, replace

icd10 clean codtext5, replace

icd10 clean codtext6, replace

icd10 clean codtext7, replace

icd10 clean codtext8, replace

icd10 clean codtext9, replace

icd10 clean codtext10, replace

icd10 clean antecedent1, replace

icd10 clean antecedent2, replace

icd10 clean antecedent3, replace

icd10 clean antecedent4, replace

icd10 clean antecedent5, replace

icd10 clean antecedent6, replace

icd10 clean antecedent7, replace

icd10 clean antecedent8, replace

icd10 clean antecedent9, replace

icd10 clean antecedent10, replace

icd10 clean cf1, replace

icd10 clean cf2, replace

icd10 clean cf3, replace

icd10 clean cf4, replace

icd10 clean cf5, replace

icd10 clean cf6, replace

icd10 clean cf7, replace

icd10 clean cf8, replace

icd10 clean cf9, replace

icd10 clean cf10, replace

```
icd10 clean codtext_1, replace
icd10 clean codtext_2, replace
icd10 clean codtext_3, replace
icd10 clean antecedent_1, replace
icd10 clean antecedent_2, replace
icd10 clean antecedent_3, replace
icd10 clean contrib_1, replace
icd10 clean contrib_2, replace
icd10 clean contrib_3, replace
icd10 clean contrib_4, replace
// checking ICD code for turbocoder COD (code too long ignored for all) //
icd10 check codtext1, list
/*
Listing of invalid and undefined codes

     +-----------------------------+
     | codtext1   __prob           |
     |-----------------------------|
109985. | J9699     Code too long    |
109999. | J9601     Code too long    |
110012. | X789      Code not defined |
112607. | F039      Code not defined |
113159. | J810      Code not defined |
     |-----------------------------|
113353. | F039      Code not defined |
114771. | J810      Code not defined |
115767. | J9609     Code too long    |
116108. | F015      Code not defined |
117190. | E860      Code not defined |
     |-----------------------------|
117192. | F039      Code not defined |
117200. | X749      Code not defined |
118024. | C45 9     Invalid 4th char |
118166. | J9609     Code too long    |
```

```
118305. | G943      Code not defined |
      |-----------------------------|
118506. | J9690     Code too long    |
118550. | J9619     Code too long    |
      +-----------------------------+
replace codtext1 = "C459" in 118024
*/
icd10 check codtext2, list
icd10 check codtext3, list
icd10 check codtext4, list
icd10 check codtext5, list
icd10 check codtext6, list
icd10 check codtext7, list
icd10 check codtext8, list
icd10 check codtext9, list
icd10 check codtext10, list
icd10 check antecedent1, list
icd10 check antecedent2, list
icd10 check antecedent3, list
icd10 check antecedent4, list
icd10 check antecedent5, list
icd10 check antecedent6, list
icd10 check antecedent7, list
icd10 check antecedent8, list
icd10 check antecedent9, list
icd10 check antecedent10, list
icd10 check cf1, list
icd10 check cf2, list
icd10 check cf3, list
icd10 check cf4, list
icd10 check cf5, list
icd10 check cf6, list
icd10 check cf7, list
icd10 check cf8, list
```

```
icd10 check cf9, list

icd10 check cf10, list

/*

     +----------------------+

     | cf1    __prob       |

     |----------------------|

113151. | E14/8   Code too long |

118168. | I7020   Code too long |

118171. | M1999   Code too long |

     +----------------------+

replace cf1 = "E148" in 113151

*/

// death from vasculitis

/*

ICD 9: arteritis 446.5, AAV codes (446.0 & 446.4)

ICD 10: arteritis I77.6, AAV codes (M31.3, M31.7, M30.0, M30.8, M30.1, M30.9)

*/gen vasc_death = 0

replace vasc_death = 1 if strmatch(codcode, "4465*")| strmatch(record_axis_data, "4465")|
strmatch(record_axis_data, "*4465*")

replace vasc_death = 1 if strmatch(codcode, "4460*")| strmatch(record_axis_data, "4460")|
strmatch(record_axis_data, "*4460*")

replace vasc_death = 1 if strmatch(codcode, "4464*")| strmatch(record_axis_data, "4464")|
strmatch(record_axis_data, "*4464*")

browse rootnum lpnum date codcode entity_axis_data record_axis_data multi_cod_format_type
codtext antecedent contrib_factors if vasc_death == 1 & !(strmatch(codcode, "446*"))

browse rootnum lpnum date codcode entity_axis_data record_axis_data multi_cod_format_type
codtext antecedent contrib_factors if vasc_death == 1


/* RULES *

within ICD9, 5 digit

1. if ICD10 => replace vasc_death == 0

2. if ICD9 & entity_axis_data and record_axis_data don't align as vasc_death by codes above, noting
that they are stored as 5 digit codes => replace vasc_death == 0

*/

* no issues => no changes

* within ICD10, needs to be an exact match for at least 4 digits
```

```
replace vasc_death = 1 if strmatch(codcode, "I776")| strmatch(record_axis_data, "I776")|
strmatch(codtext1, "I77.6")|strmatch(codtext2, "I77.6")|strmatch(codtext3,
"I77.6")|strmatch(codtext4, "I77.6")|strmatch(codtext5, "I77.6")|strmatch(codtext6,
"I77.6")|strmatch(codtext7, "I77.6")|strmatch(codtext8, "I77.6")|strmatch(codtext9,
"I77.6")|strmatch(codtext10, "I77.6")|strmatch(antecedent1, "I77.6")|strmatch(antecedent2,
"I77.6")|strmatch(antecedent3, "I77.6")|strmatch(antecedent4, "I77.6")|strmatch(antecedent5,
"I77.6")|strmatch(antecedent6, "I77.6")|strmatch(antecedent7, "I77.6")|strmatch(antecedent8,
"I77.6")|strmatch(antecedent9, "I77.6")|strmatch(antecedent10, "I77.6")| strmatch(cf1,
"I77.6")|strmatch(cf2, "I77.6")|strmatch(cf3, "I77.6")|strmatch(cf4, "I77.6")|strmatch(cf5,
"I77.6")|strmatch(cf6, "I77.6")|strmatch(cf7, "I77.6")|strmatch(cf8, "I77.6")|strmatch(cf9,
"I77.6")|strmatch(cf10, "I77.6")|strmatch(codtext_1, "I77.6")|strmatch(codtext_2,
"I77.6")|strmatch(codtext_3, "I77.6")|strmatch(antecedent_1, "I77.6")|strmatch(antecedent_2,
"I77.6")|strmatch(antecedent_3, "I77.6")|strmatch(contrib_1, "I77.6")|strmatch(contrib_2,
"I77.6")|strmatch(contrib_3, "I77.6")|strmatch(contrib_4, "I77.6")

replace vasc_death = 1 if strmatch(record_axis_data, "*I776*")| strmatch(codtext1,
"*I77.6*")|strmatch(codtext2, "*I77.6*")|strmatch(codtext3, "*I77.6*")|strmatch(codtext4,
"*I77.6*")|strmatch(codtext5, "*I77.6*")|strmatch(codtext6, "*I77.6*")|strmatch(codtext7,
"*I77.6*")|strmatch(codtext8, "*I77.6*")|strmatch(codtext9, "*I77.6*")|strmatch(codtext10,
"*I77.6*")|strmatch(antecedent1, "*I77.6*")|strmatch(antecedent2, "*I77.6*")|strmatch(antecedent3,
"*I77.6*")|strmatch(antecedent4, "*I77.6*")|strmatch(antecedent5, "*I77.6*")|strmatch(antecedent6,
"*I77.6*")|strmatch(antecedent7, "*I77.6*")|strmatch(antecedent8, "*I77.6*")|strmatch(antecedent9,
"*I77.6*")|strmatch(antecedent10, "*I77.6*")| strmatch(cf1, "*I77.6*")|strmatch(cf2,
"*I77.6*")|strmatch(cf3, "*I77.6*")|strmatch(cf4, "*I77.6*")|strmatch(cf5, "*I77.6*")|strmatch(cf6,
"*I77.6*")|strmatch(cf7, "*I77.6*")|strmatch(cf8, "*I77.6*")|strmatch(cf9, "*I77.6*")|strmatch(cf10,
"*I77.6*")|strmatch(codtext_1, "*I77.6*")|strmatch(codtext_2, "*I77.6*")|strmatch(codtext_3,
"*I77.6*")|strmatch(antecedent_1, "*I77.6*")|strmatch(antecedent_2,
"*I77.6*")|strmatch(antecedent_3, "*I77.6*")|strmatch(contrib_1, "*I77.6*")|strmatch(contrib_2,
"*I77.6*")|strmatch(contrib_3, "*I77.6*")|strmatch(contrib_4, "*I77.6*")

replace vasc_death = 1 if strmatch(codcode, "M313")| strmatch(record_axis_data, "M313")|
strmatch(codtext1, "M31.3")|strmatch(codtext2, "M31.3")|strmatch(codtext3,
"M31.3")|strmatch(codtext4, "M31.3")|strmatch(codtext5, "M31.3")|strmatch(codtext6,
"M31.3")|strmatch(codtext7, "M31.3")|strmatch(codtext8, "M31.3")|strmatch(codtext9,
"M31.3")|strmatch(codtext10, "M31.3")|strmatch(antecedent1, "M31.3")|strmatch(antecedent2,
"M31.3")|strmatch(antecedent3, "M31.3")|strmatch(antecedent4, "M31.3")|strmatch(antecedent5,
"M31.3")|strmatch(antecedent6, "M31.3")|strmatch(antecedent7, "M31.3")|strmatch(antecedent8,
"M31.3")|strmatch(antecedent9, "M31.3")|strmatch(antecedent10, "M31.3")| strmatch(cf1,
"M31.3")|strmatch(cf2, "M31.3")|strmatch(cf3, "M31.3")|strmatch(cf4, "M31.3")|strmatch(cf5,
"M31.3")|strmatch(cf6, "M31.3")|strmatch(cf7, "M31.3")|strmatch(cf8, "M31.3")|strmatch(cf9,
"M31.3")|strmatch(cf10, "M31.3")|strmatch(codtext_1, "M31.3")|strmatch(codtext_2,
"M31.3")|strmatch(codtext_3, "M31.3")|strmatch(antecedent_1, "M31.3")|strmatch(antecedent_2,
"M31.3")|strmatch(antecedent_3, "M31.3")|strmatch(contrib_1, "M31.3")|strmatch(contrib_2,
"M31.3")|strmatch(contrib_3, "M31.3")|strmatch(contrib_4, "M31.3")

replace vasc_death = 1 if strmatch(record_axis_data, "*M313*")| strmatch(codtext1,
"*M31.3*")|strmatch(codtext2, "*M31.3*")|strmatch(codtext3, "*M31.3*")|strmatch(codtext4,
"*M31.3*")|strmatch(codtext5, "*M31.3*")|strmatch(codtext6, "*M31.3*")|strmatch(codtext7,
"*M31.3*")|strmatch(codtext8, "*M31.3*")|strmatch(codtext9, "*M31.3*")|strmatch(codtext10,
"*M31.3*")|strmatch(antecedent1, "*M31.3*")|strmatch(antecedent2,
"*M31.3*")|strmatch(antecedent3, "*M31.3*")|strmatch(antecedent4,
"*M31.3*")|strmatch(antecedent5, "*M31.3*")|strmatch(antecedent6,
"*M31.3*")|strmatch(antecedent7, "*M31.3*")|strmatch(antecedent8,
"*M31.3*")|strmatch(antecedent9, "*M31.3*")|strmatch(antecedent10, "*M31.3*")| strmatch(cf1,
"*M31.3*")|strmatch(cf2, "*M31.3*")|strmatch(cf3, "*M31.3*")|strmatch(cf4,
"*M31.3*")|strmatch(cf5, "*M31.3*")|strmatch(cf6, "*M31.3*")|strmatch(cf7,
"*M31.3*")|strmatch(cf8, "*M31.3*")|strmatch(cf9, "*M31.3*")|strmatch(cf10,
"*M31.3*")|strmatch(codtext_1, "*M31.3*")|strmatch(codtext_2, "*M31.3*")|strmatch(codtext_3,
```

"*M31.3*")|strmatch(antecedent_1, "*M31.3*")|strmatch(antecedent_2,
"*M31.3*")|strmatch(antecedent_3, "*M31.3*")|strmatch(contrib_1, "*M31.3*")|strmatch(contrib_2,
"*M31.3*")|strmatch(contrib_3, "*M31.3*")|strmatch(contrib_4, "*M31.3*")

replace vasc_death = 1 if strmatch(codcode, "M317")| strmatch(record_axis_data, "M317")|
strmatch(codtext1, "M31.7")|strmatch(codtext2, "M31.7")|strmatch(codtext3,
"M31.7")|strmatch(codtext4, "M31.7")|strmatch(codtext5, "M31.7")|strmatch(codtext6,
"M31.7")|strmatch(codtext7, "M31.7")|strmatch(codtext8, "M31.7")|strmatch(codtext9,
"M31.7")|strmatch(codtext10, "M31.7")|strmatch(antecedent1, "M31.7")|strmatch(antecedent2,
"M31.7")|strmatch(antecedent3, "M31.7")|strmatch(antecedent4, "M31.7")|strmatch(antecedent5,
"M31.7")|strmatch(antecedent6, "M31.7")|strmatch(antecedent7, "M31.7")|strmatch(antecedent8,
"M31.7")|strmatch(antecedent9, "M31.7")|strmatch(antecedent10, "M31.7")| strmatch(cf1,
"M31.7")|strmatch(cf2, "M31.7")|strmatch(cf3, "M31.7")|strmatch(cf4, "M31.7")|strmatch(cf5,
"M31.7")|strmatch(cf6, "M31.7")|strmatch(cf7, "M31.7")|strmatch(cf8, "M31.7")|strmatch(cf9,
"M31.7")|strmatch(cf10, "M31.7")|strmatch(codtext_1, "M31.7")|strmatch(codtext_2,
"M31.7")|strmatch(codtext_3, "M31.7")|strmatch(antecedent_1, "M31.7")|strmatch(antecedent_2,
"M31.7")|strmatch(antecedent_3, "M31.7")|strmatch(contrib_1, "M31.7")|strmatch(contrib_2,
"M31.7")|strmatch(contrib_3, "M31.7")|strmatch(contrib_4, "M31.7")

replace vasc_death = 1 if strmatch(record_axis_data, "*M317*")| strmatch(codtext1,
"*M31.7*")|strmatch(codtext2, "*M31.7*")|strmatch(codtext3, "*M31.7*")|strmatch(codtext4,
"*M31.7*")|strmatch(codtext5, "*M31.7*")|strmatch(codtext6, "*M31.7*")|strmatch(codtext7,
"*M31.7*")|strmatch(codtext8, "*M31.7*")|strmatch(codtext9, "*M31.7*")|strmatch(codtext10,
"*M31.7*")|strmatch(antecedent1, "*M31.7*")|strmatch(antecedent2,
"*M31.7*")|strmatch(antecedent3, "*M31.7*")|strmatch(antecedent4,
"*M31.7*")|strmatch(antecedent5, "*M31.7*")|strmatch(antecedent6,
"*M31.7*")|strmatch(antecedent7, "*M31.7*")|strmatch(antecedent8,
"*M31.7*")|strmatch(antecedent9, "*M31.7*")|strmatch(antecedent10, "*M31.7*")| strmatch(cf1,
"*M31.7*")|strmatch(cf2, "*M31.7*")|strmatch(cf3, "*M31.7*")|strmatch(cf4,
"*M31.7*")|strmatch(cf5, "*M31.7*")|strmatch(cf6, "*M31.7*")|strmatch(cf7,
"*M31.7*")|strmatch(cf8, "*M31.7*")|strmatch(cf9, "*M31.7*")|strmatch(cf10,
"*M31.7*")|strmatch(codtext_1, "*M31.7*")|strmatch(codtext_2, "*M31.7*")|strmatch(codtext_3,
"*M31.7*")|strmatch(antecedent_1, "*M31.7*")|strmatch(antecedent_2,
"*M31.7*")|strmatch(antecedent_3, "*M31.7*")|strmatch(contrib_1, "*M31.7*")|strmatch(contrib_2,
"*M31.7*")|strmatch(contrib_3, "*M31.7*")|strmatch(contrib_4, "*M31.7*")

replace vasc_death = 1 if strmatch(codcode, "M300")| strmatch(record_axis_data, "M300")|
strmatch(codtext1, "M30.0")|strmatch(codtext2, "M30.0")|strmatch(codtext3,
"M30.0")|strmatch(codtext4, "M30.0")|strmatch(codtext5, "M30.0")|strmatch(codtext6,
"M30.0")|strmatch(codtext7, "M30.0")|strmatch(codtext8, "M30.0")|strmatch(codtext9,
"M30.0")|strmatch(codtext10, "M30.0")|strmatch(antecedent1, "M30.0")|strmatch(antecedent2,
"M30.0")|strmatch(antecedent3, "M30.0")|strmatch(antecedent4, "M30.0")|strmatch(antecedent5,
"M30.0")|strmatch(antecedent6, "M30.0")|strmatch(antecedent7, "M30.0")|strmatch(antecedent8,
"M30.0")|strmatch(antecedent9, "M30.0")|strmatch(antecedent10, "M30.0")| strmatch(cf1,
"M30.0")|strmatch(cf2, "M30.0")|strmatch(cf3, "M30.0")|strmatch(cf4, "M30.0")|strmatch(cf5,
"M30.0")|strmatch(cf6, "M30.0")|strmatch(cf7, "M30.0")|strmatch(cf8, "M30.0")|strmatch(cf9,
"M30.0")|strmatch(cf10, "M30.0")|strmatch(codtext_1, "M30.0")|strmatch(codtext_2,
"M30.0")|strmatch(codtext_3, "M30.0")|strmatch(antecedent_1, "M30.0")|strmatch(antecedent_2,
"M30.0")|strmatch(antecedent_3, "M30.0")|strmatch(contrib_1, "M30.0")|strmatch(contrib_2,
"M30.0")|strmatch(contrib_3, "M30.0")|strmatch(contrib_4, "M30.0")

replace vasc_death = 1 if strmatch(record_axis_data, "*M300*")| strmatch(codtext1,
"*M30.0*")|strmatch(codtext2, "*M30.0*")|strmatch(codtext3, "*M30.0*")|strmatch(codtext4,
"*M30.0*")|strmatch(codtext5, "*M30.0*")|strmatch(codtext6, "*M30.0*")|strmatch(codtext7,
"*M30.0*")|strmatch(codtext8, "*M30.0*")|strmatch(codtext9, "*M30.0*")|strmatch(codtext10,
"*M30.0*")|strmatch(antecedent1, "*M30.0*")|strmatch(antecedent2,
"*M30.0*")|strmatch(antecedent3, "*M30.0*")|strmatch(antecedent4,
"*M30.0*")|strmatch(antecedent5, "*M30.0*")|strmatch(antecedent6,

"*M30.0*")|strmatch(antecedent7, "*M30.0*")|strmatch(antecedent8,
"*M30.0*")|strmatch(antecedent9, "*M30.0*")|strmatch(antecedent10, "*M30.0*")| strmatch(cf1,
"*M30.0*")|strmatch(cf2, "*M30.0*")|strmatch(cf3, "*M30.0*")|strmatch(cf4,
"*M30.0*")|strmatch(cf5, "*M30.0*")|strmatch(cf6, "*M30.0*")|strmatch(cf7,
"*M30.0*")|strmatch(cf8, "*M30.0*")|strmatch(cf9, "*M30.0*")|strmatch(cf10,
"*M30.0*")|strmatch(codtext_1, "*M30.0*")|strmatch(codtext_2, "*M30.0*")|strmatch(codtext_3,
"*M30.0*")|strmatch(antecedent_1, "*M30.0*")|strmatch(antecedent_2,
"*M30.0*")|strmatch(antecedent_3, "*M30.0*")|strmatch(contrib_1, "*M30.0*")|strmatch(contrib_2,
"*M30.0*")|strmatch(contrib_3, "*M30.0*")|strmatch(contrib_4, "*M30.0*")

replace vasc_death = 1 if strmatch(codcode, "M308")| strmatch(record_axis_data, "M308")|
strmatch(codtext1, "M30.8")|strmatch(codtext2, "M30.8")|strmatch(codtext3,
"M30.8")|strmatch(codtext4, "M30.8")|strmatch(codtext5, "M30.8")|strmatch(codtext6,
"M30.8")|strmatch(codtext7, "M30.8")|strmatch(codtext8, "M30.8")|strmatch(codtext9,
"M30.8")|strmatch(codtext10, "M30.8")|strmatch(antecedent1, "M30.8")|strmatch(antecedent2,
"M30.8")|strmatch(antecedent3, "M30.8")|strmatch(antecedent4, "M30.8")|strmatch(antecedent5,
"M30.8")|strmatch(antecedent6, "M30.8")|strmatch(antecedent7, "M30.8")|strmatch(antecedent8,
"M30.8")|strmatch(antecedent9, "M30.8")|strmatch(antecedent10, "M30.8")| strmatch(cf1,
"M30.8")|strmatch(cf2, "M30.8")|strmatch(cf3, "M30.8")|strmatch(cf4, "M30.8")|strmatch(cf5,
"M30.8")|strmatch(cf6, "M30.8")|strmatch(cf7, "M30.8")|strmatch(cf8, "M30.8")|strmatch(cf9,
"M30.8")|strmatch(cf10, "M30.8")|strmatch(codtext_1, "M30.8")|strmatch(codtext_2,
"M30.8")|strmatch(codtext_3, "M30.8")|strmatch(antecedent_1, "M30.8")|strmatch(antecedent_2,
"M30.8")|strmatch(antecedent_3, "M30.8")|strmatch(contrib_1, "M30.8")|strmatch(contrib_2,
"M30.8")|strmatch(contrib_3, "M30.8")|strmatch(contrib_4, "M30.8")

replace vasc_death = 1 if strmatch(record_axis_data, "*M308*")| strmatch(codtext1,
"*M30.8*")|strmatch(codtext2, "*M30.8*")|strmatch(codtext3, "*M30.8*")|strmatch(codtext4,
"*M30.8*")|strmatch(codtext5, "*M30.8*")|strmatch(codtext6, "*M30.8*")|strmatch(codtext7,
"*M30.8*")|strmatch(codtext8, "*M30.8*")|strmatch(codtext9, "*M30.8*")|strmatch(codtext10,
"*M30.8*")|strmatch(antecedent1, "*M30.8*")|strmatch(antecedent2,
"*M30.8*")|strmatch(antecedent3, "*M30.8*")|strmatch(antecedent4,
"*M30.8*")|strmatch(antecedent5, "*M30.8*")|strmatch(antecedent6,
"*M30.8*")|strmatch(antecedent7, "*M30.8*")|strmatch(antecedent8,
"*M30.8*")|strmatch(antecedent9, "*M30.8*")|strmatch(antecedent10, "*M30.8*")| strmatch(cf1,
"*M30.8*")|strmatch(cf2, "*M30.8*")|strmatch(cf3, "*M30.8*")|strmatch(cf4,
"*M30.8*")|strmatch(cf5, "*M30.8*")|strmatch(cf6, "*M30.8*")|strmatch(cf7,
"*M30.8*")|strmatch(cf8, "*M30.8*")|strmatch(cf9, "*M30.8*")|strmatch(cf10,
"*M30.8*")|strmatch(codtext_1, "*M30.8*")|strmatch(codtext_2, "*M30.8*")|strmatch(codtext_3,
"*M30.8*")|strmatch(antecedent_1, "*M30.8*")|strmatch(antecedent_2,
"*M30.8*")|strmatch(antecedent_3, "*M30.8*")|strmatch(contrib_1, "*M30.8*")|strmatch(contrib_2,
"*M30.8*")|strmatch(contrib_3, "*M30.8*")|strmatch(contrib_4, "*M30.8*")

replace vasc_death = 1 if strmatch(codcode, "M301")| strmatch(record_axis_data, "M301")|
strmatch(codtext1, "M30.1")|strmatch(codtext2, "M30.1")|strmatch(codtext3,
"M30.1")|strmatch(codtext4, "M30.1")|strmatch(codtext5, "M30.1")|strmatch(codtext6,
"M30.1")|strmatch(codtext7, "M30.1")|strmatch(codtext8, "M30.1")|strmatch(codtext9,
"M30.1")|strmatch(codtext10, "M30.1")|strmatch(antecedent1, "M30.1")|strmatch(antecedent2,
"M30.1")|strmatch(antecedent3, "M30.1")|strmatch(antecedent4, "M30.1")|strmatch(antecedent5,
"M30.1")|strmatch(antecedent6, "M30.1")|strmatch(antecedent7, "M30.1")|strmatch(antecedent8,
"M30.1")|strmatch(antecedent9, "M30.1")|strmatch(antecedent10, "M30.1")| strmatch(cf1,
"M30.1")|strmatch(cf2, "M30.1")|strmatch(cf3, "M30.1")|strmatch(cf4, "M30.1")|strmatch(cf5,
"M30.1")|strmatch(cf6, "M30.1")|strmatch(cf7, "M30.1")|strmatch(cf8, "M30.1")|strmatch(cf9,
"M30.1")|strmatch(cf10, "M30.1")|strmatch(codtext_1, "M30.1")|strmatch(codtext_2,
"M30.1")|strmatch(codtext_3, "M30.1")|strmatch(antecedent_1, "M30.1")|strmatch(antecedent_2,
"M30.1")|strmatch(antecedent_3, "M30.1")|strmatch(contrib_1, "M30.1")|strmatch(contrib_2,
"M30.1")|strmatch(contrib_3, "M30.1")|strmatch(contrib_4, "M30.1")

```
replace vasc_death = 1 if strmatch(record_axis_data, "*M301*")| strmatch(codtext1,
"*M30.1*")|strmatch(codtext2, "*M30.1*")|strmatch(codtext3, "*M30.1*")|strmatch(codtext4,
"*M30.1*")|strmatch(codtext5, "*M30.1*")|strmatch(codtext6, "*M30.1*")|strmatch(codtext7,
"*M30.1*")|strmatch(codtext8, "*M30.1*")|strmatch(codtext9, "*M30.1*")|strmatch(codtext10,
"*M30.1*")|strmatch(antecedent1, "*M30.1*")|strmatch(antecedent2,
"*M30.1*")|strmatch(antecedent3, "*M30.1*")|strmatch(antecedent4,
"*M30.1*")|strmatch(antecedent5, "*M30.1*")|strmatch(antecedent6,
"*M30.1*")|strmatch(antecedent7, "*M30.1*")|strmatch(antecedent8,
"*M30.1*")|strmatch(antecedent9, "*M30.1*")|strmatch(antecedent10, "*M30.1*")| strmatch(cf1,
"*M30.1*")|strmatch(cf2, "*M30.1*")|strmatch(cf3, "*M30.1*")|strmatch(cf4,
"*M30.1*")|strmatch(cf5, "*M30.1*")|strmatch(cf6, "*M30.1*")|strmatch(cf7,
"*M30.1*")|strmatch(cf8, "*M30.1*")|strmatch(cf9, "*M30.1*")|strmatch(cf10,
"*M30.1*")|strmatch(codtext_1, "*M30.1*")|strmatch(codtext_2, "*M30.1*")|strmatch(codtext_3,
"*M30.1*")|strmatch(antecedent_1, "*M30.1*")|strmatch(antecedent_2,
"*M30.1*")|strmatch(antecedent_3, "*M30.1*")|strmatch(contrib_1, "*M30.1*")|strmatch(contrib_2,
"*M30.1*")|strmatch(contrib_3, "*M30.1*")|strmatch(contrib_4, "*M30.1*")
```

consider addding: M31.8 & M31.9 => makes no difference

```
browse rootnum lpnum date codcode entity_axis_data record_axis_data multi_cod_format_type
cod_extra_mcod11 rad1_ex0_inj1 cod_extra_rad1 codtext antecedent contrib_factors if rectype == 4 &
vasc_death == 0
```

// death from cardiovascular disease //

```
/*

ICD-9: 410.0 - 410.9, 414.0, 414.1, 414.10, 414.11, 414.12, 414.8, 414.9

ICD-10: I21.0-I21.9, I22.0-I22.9, I23.0-I23.8, I24.0-I24.9, I25.0-I25.9

*/

gen cv_death = 0

replace cv_death = 1 if strmatch(codcode, "4100")| strmatch(codcode, "4101")| strmatch(codcode,
"4102")| strmatch(codcode, "4103")| strmatch(codcode, "4104")| strmatch(codcode, "4105")|
strmatch(codcode, "4106")| strmatch(codcode, "4107")| strmatch(codcode, "4108")|
strmatch(codcode, "4109")| strmatch(record_axis_data, "41000")| strmatch(record_axis_data,
"41010")| strmatch(record_axis_data, "41020")| strmatch(record_axis_data, "41030")|
strmatch(record_axis_data, "41040")| strmatch(record_axis_data, "41050")|
strmatch(record_axis_data, "41060")| strmatch(record_axis_data, "41070")|
strmatch(record_axis_data, "41080")| strmatch(record_axis_data, "41090")

replace cv_death = 1 if strmatch(codcode, "4100*")| strmatch(codcode, "4101*")| strmatch(codcode,
"4102*")| strmatch(codcode, "4103*")| strmatch(codcode, "4104*")| strmatch(codcode, "4105*")|
strmatch(codcode, "4106*")| strmatch(codcode, "4107*")| strmatch(codcode, "4108*")|
strmatch(codcode, "4109*")| strmatch(record_axis_data, "*41000*")| strmatch(record_axis_data,
"*41010*")| strmatch(record_axis_data, "*41020*")| strmatch(record_axis_data, "*41030*")|
strmatch(record_axis_data, "*41040*")| strmatch(record_axis_data, "*41050*")|
strmatch(record_axis_data, "*41060*")| strmatch(record_axis_data, "*41070*")|
strmatch(record_axis_data, "*41080*")| strmatch(record_axis_data, "*41090*")

replace cv_death = 1 if strmatch(codcode, "4140")| strmatch(codcode, "4140")| strmatch(codcode,
"4141")| strmatch(codcode, "4141")| strmatch(codcode, "41410")| strmatch(codcode, "41411")|
strmatch(codcode, "41412")| strmatch(codcode, "4148")| strmatch(codcode, "4149")|
strmatch(record_axis_data, "41400")| strmatch(record_axis_data, "*41400*")|
strmatch(record_axis_data, "41410")| strmatch(record_axis_data, "41410")|
```

```
strmatch(record_axis_data, "41411")| strmatch(record_axis_data, "41412")|
strmatch(record_axis_data, "41480")| strmatch(record_axis_data, "41490")

replace cv_death = 1 if strmatch(codcode, "4140*")| strmatch(codcode, "4140*")| strmatch(codcode,
"4141*")| strmatch(codcode, "4141*")| strmatch(codcode, "41410*")| strmatch(codcode, "41411*")|
strmatch(codcode, "41412*")| strmatch(codcode, "4148*")| strmatch(codcode, "4149*")|
strmatch(record_axis_data, "*41400*")| strmatch(record_axis_data, "*41410*")|
strmatch(record_axis_data, "*41411*")| strmatch(record_axis_data, "*41412*")|
strmatch(record_axis_data, "*41480*")| strmatch(record_axis_data, "*41490*")

replace cv_death = 1 if strmatch(codcode, "4110")| strmatch(codcode, "4110")| strmatch(codcode,
"4111")| strmatch(codcode, "4111")| strmatch(codcode, "41110")| strmatch(codcode, "41111")|
strmatch(codcode, "41112")| strmatch(codcode, "4118")| strmatch(codcode, "4119")|
strmatch(record_axis_data, "41100")| strmatch(record_axis_data, "*41100*")|
strmatch(record_axis_data, "41110")| strmatch(record_axis_data, "41110")|
strmatch(record_axis_data, "41111")| strmatch(record_axis_data, "41112")|
strmatch(record_axis_data, "41180")| strmatch(record_axis_data, "41190")

replace cv_death = 1 if strmatch(codcode, "4110*")| strmatch(codcode, "4110*")| strmatch(codcode,
"4111*")| strmatch(codcode, "4111*")| strmatch(codcode, "41110*")| strmatch(codcode, "41111*")|
strmatch(codcode, "41112*")| strmatch(codcode, "4118*")| strmatch(codcode, "4119*")|
strmatch(record_axis_data, "*41100*")| strmatch(record_axis_data, "*41110*")|
strmatch(record_axis_data, "*41111*")| strmatch(record_axis_data, "*41112*")|
strmatch(record_axis_data, "*41180*")| strmatch(record_axis_data, "*41190*")


replace cv_death = 1 if strmatch(codcode, "4120")| strmatch(codcode, "4120")| strmatch(codcode,
"4121")| strmatch(codcode, "4121")| strmatch(codcode, "41210")| strmatch(codcode, "41211")|
strmatch(codcode, "41212")| strmatch(codcode, "4128")| strmatch(codcode, "4129")|
strmatch(record_axis_data, "41200")| strmatch(record_axis_data, "*41200*")|
strmatch(record_axis_data, "41210")| strmatch(record_axis_data, "41210")|
strmatch(record_axis_data, "41211")| strmatch(record_axis_data, "41212")|
strmatch(record_axis_data, "41280")| strmatch(record_axis_data, "41290")

replace cv_death = 1 if strmatch(codcode, "4120*")| strmatch(codcode, "4120*")| strmatch(codcode,
"4121*")| strmatch(codcode, "4121*")| strmatch(codcode, "41210*")| strmatch(codcode, "41211*")|
strmatch(codcode, "41212*")| strmatch(codcode, "4128*")| strmatch(codcode, "4129*")|
strmatch(record_axis_data, "*41200*")| strmatch(record_axis_data, "*41210*")|
strmatch(record_axis_data, "*41211*")| strmatch(record_axis_data, "*41212*")|
strmatch(record_axis_data, "*41280*")| strmatch(record_axis_data, "*41290*")


/* RULES *

within ICD9, 5 digit

1. if ICD10 => no change

2. if ICD9 & entity_axis_data and record_axis_data don't align as cv_death by codes above, noting that
they are stored as 5 digit codes => no change, cv_death == 0

*/

browse if rectype ==4 & cv_death == 0 & strmatch(codcode, "*410*")

browse if rectype ==4 & cv_death == 0 & strmatch(record_axis_data, "*410*")

browse if rectype ==4 & cv_death == 0 & strmatch(codcode, "*410*")
```

browse rootnum codcode entity_axis_data record_axis_data if rectype ==4 & cv_death == 0 & strmatch(record_axis_data, "*410*")

browse if rectype ==4 & cv_death == 0 & strmatch(codcode, "*414*")

browse if rectype ==4 & cv_death == 0 & strmatch(record_axis_data, "*414*")

* no issues => no changes

browse rootnum lpnum date codcode entity_axis_data record_axis_data multi_cod_format_type cod_extra_mcod11 rad1_ex0_inj1 cod_extra_rad1 codtext antecedent contrib_factors if cv_death == 1 & !(strmatch(codcode, "414*")) & !(strmatch(codcode, "410*"))

* I21.0-I21.9 => I21 used as the stem

replace cv_death = 1 if strmatch(codcode, "I21")|strmatch(record_axis_data, "I21")| strmatch(codtext1, "I21")|strmatch(codtext2, "I21")|strmatch(codtext3, "I21")|strmatch(codtext4, "I21")|strmatch(codtext5, "I21")|strmatch(codtext6, "I21")|strmatch(codtext7, "I21")|strmatch(codtext8, "I21")|strmatch(codtext9, "I21")|strmatch(codtext10, "I21")|strmatch(antecedent1, "I21")|strmatch(antecedent2, "I21")|strmatch(antecedent3, "I21")|strmatch(antecedent4, "I21")|strmatch(antecedent5, "I21")|strmatch(antecedent6, "I21")|strmatch(antecedent7, "I21")|strmatch(antecedent8, "I21")|strmatch(antecedent9, "I21")|strmatch(antecedent10, "I21")| strmatch(cf1, "I21")|strmatch(cf2, "I21")|strmatch(cf3, "I21")|strmatch(cf4, "I21")|strmatch(cf5, "I21")|strmatch(cf6, "I21")|strmatch(cf7, "I21")|strmatch(cf8, "I21")|strmatch(cf9, "I21")|strmatch(cf10, "I21")|strmatch(codtext_1, "I21")|strmatch(codtext_2, "I21")|strmatch(codtext_3, "I21")|strmatch(antecedent_1, "I21")|strmatch(antecedent_2, "I21")|strmatch(antecedent_3, "I21")|strmatch(contrib_1, "I21")|strmatch(contrib_2, "I21")|strmatch(contrib_3, "I21")|strmatch(contrib_4, "I21")

replace cv_death = 1 if strmatch(codcode, "I21*")| strmatch(record_axis_data, "*I21*")| strmatch(codtext1, "*I21*")|strmatch(codtext2, "*I21*")|strmatch(codtext3, "*I21*")|strmatch(codtext4, "*I21*")|strmatch(codtext5, "*I21*")|strmatch(codtext6, "*I21*")|strmatch(codtext7, "*I21*")|strmatch(codtext8, "*I21*")|strmatch(codtext9, "*I21*")|strmatch(codtext10, "*I21*")|strmatch(antecedent1, "*I21*")|strmatch(antecedent2, "*I21*")|strmatch(antecedent3, "*I21*")|strmatch(antecedent4, "*I21*")|strmatch(antecedent5, "*I21*")|strmatch(antecedent6, "*I21*")|strmatch(antecedent7, "*I21*")|strmatch(antecedent8, "*I21*")|strmatch(antecedent9, "*I21*")|strmatch(antecedent10, "*I21*")| strmatch(cf1, "*I21*")|strmatch(cf2, "*I21*")|strmatch(cf3, "*I21*")|strmatch(cf4, "*I21*")|strmatch(cf5, "*I21*")|strmatch(cf6, "*I21*")|strmatch(cf7, "*I21*")|strmatch(cf8, "*I21*")|strmatch(cf9, "*I21*")|strmatch(cf10, "*I21*")|strmatch(codtext_1, "*I21*")|strmatch(codtext_2, "*I21*")|strmatch(codtext_3, "*I21*")|strmatch(antecedent_1, "*I21*")|strmatch(antecedent_2, "*I21*")|strmatch(antecedent_3, "*I21*")|strmatch(contrib_1, "*I21*")|strmatch(contrib_2, "*I21*")|strmatch(contrib_3, "*I21*")|strmatch(contrib_4, "*I21*")

* I22, I23, I24, I25 the same *

replace cv_death = 1 if strmatch(codcode, "I22")| strmatch(record_axis_data, "I22")| strmatch(codtext1, "I22")|strmatch(codtext2, "I22")|strmatch(codtext3, "I22")|strmatch(codtext4, "I22")|strmatch(codtext5, "I22")|strmatch(codtext6, "I22")|strmatch(codtext7, "I22")|strmatch(codtext8, "I22")|strmatch(codtext9, "I22")|strmatch(codtext10, "I22")|strmatch(antecedent1, "I22")|strmatch(antecedent2, "I22")|strmatch(antecedent3, "I22")|strmatch(antecedent4, "I22")|strmatch(antecedent5, "I22")|strmatch(antecedent6, "I22")|strmatch(antecedent7, "I22")|strmatch(antecedent8, "I22")|strmatch(antecedent9, "I22")|strmatch(antecedent10, "I22")| strmatch(cf1, "I22")|strmatch(cf2, "I22")|strmatch(cf3, "I22")|strmatch(cf4, "I22")|strmatch(cf5, "I22")|strmatch(cf6, "I22")|strmatch(cf7, "I22")|strmatch(cf8, "I22")|strmatch(cf9, "I22")|strmatch(cf10, "I22")|strmatch(codtext_1, "I22")|strmatch(codtext_2, "I22")|strmatch(codtext_3, "I22")|strmatch(antecedent_1, "I22")|strmatch(antecedent_2, "I22")|strmatch(antecedent_3, "I22")|strmatch(contrib_1, "I22")|strmatch(contrib_2, "I22")|strmatch(contrib_3, "I22")|strmatch(contrib_4, "I22")

```
replace cv_death = 1 if strmatch(codcode, "I22*")| strmatch(record_axis_data, "*I22*")|
strmatch(codtext1, "*I22*")|strmatch(codtext2, "*I22*")|strmatch(codtext3,
"*I22*")|strmatch(codtext4, "*I22*")|strmatch(codtext5, "*I22*")|strmatch(codtext6,
"*I22*")|strmatch(codtext7, "*I22*")|strmatch(codtext8, "*I22*")|strmatch(codtext9,
"*I22*")|strmatch(codtext10, "*I22*")|strmatch(antecedent1, "*I22*")|strmatch(antecedent2,
"*I22*")|strmatch(antecedent3, "*I22*")|strmatch(antecedent4, "*I22*")|strmatch(antecedent5,
"*I22*")|strmatch(antecedent6, "*I22*")|strmatch(antecedent7, "*I22*")|strmatch(antecedent8,
"*I22*")|strmatch(antecedent9, "*I22*")|strmatch(antecedent10, "*I22*")| strmatch(cf1,
"*I22*")|strmatch(cf2, "*I22*")|strmatch(cf3, "*I22*")|strmatch(cf4, "*I22*")|strmatch(cf5,
"*I22*")|strmatch(cf6, "*I22*")|strmatch(cf7, "*I22*")|strmatch(cf8, "*I22*")|strmatch(cf9,
"*I22*")|strmatch(cf10, "*I22*")|strmatch(codtext_1, "*I22*")|strmatch(codtext_2,
"*I22*")|strmatch(codtext_3, "*I22*")|strmatch(antecedent_1, "*I22*")|strmatch(antecedent_2,
"*I22*")|strmatch(antecedent_3, "*I22*")|strmatch(contrib_1, "*I22*")|strmatch(contrib_2,
"*I22*")|strmatch(contrib_3, "*I22*")|strmatch(contrib_4, "*I22*")

replace cv_death = 1 if strmatch(codcode, "I23")| strmatch(record_axis_data, "I23")|
strmatch(codtext1, "I23")|strmatch(codtext2, "I23")|strmatch(codtext3, "I23")|strmatch(codtext4,
"I23")|strmatch(codtext5, "I23")|strmatch(codtext6, "I23")|strmatch(codtext7,
"I23")|strmatch(codtext8, "I23")|strmatch(codtext9, "I23")|strmatch(codtext10,
"I23")|strmatch(antecedent1, "I23")|strmatch(antecedent2, "I23")|strmatch(antecedent3,
"I23")|strmatch(antecedent4, "I23")|strmatch(antecedent5, "I23")|strmatch(antecedent6,
"I23")|strmatch(antecedent7, "I23")|strmatch(antecedent8, "I23")|strmatch(antecedent9,
"I23")|strmatch(antecedent10, "I23")| strmatch(cf1, "I23")|strmatch(cf2, "I23")|strmatch(cf3,
"I23")|strmatch(cf4, "I23")|strmatch(cf5, "I23")|strmatch(cf6, "I23")|strmatch(cf7, "I23")|strmatch(cf8,
"I23")|strmatch(cf9, "I23")|strmatch(cf10, "I23")|strmatch(codtext_1, "I23")|strmatch(codtext_2,
"I23")|strmatch(codtext_3, "I23")|strmatch(antecedent_1, "I23")|strmatch(antecedent_2,
"I23")|strmatch(antecedent_3, "I23")|strmatch(contrib_1, "I23")|strmatch(contrib_2,
"I23")|strmatch(contrib_3, "I23")|strmatch(contrib_4, "I23")

replace cv_death = 1 if strmatch(codcode, "I23*")| strmatch(record_axis_data, "*I23*")|
strmatch(codtext1, "*I23*")|strmatch(codtext2, "*I23*")|strmatch(codtext3,
"*I23*")|strmatch(codtext4, "*I23*")|strmatch(codtext5, "*I23*")|strmatch(codtext6,
"*I23*")|strmatch(codtext7, "*I23*")|strmatch(codtext8, "*I23*")|strmatch(codtext9,
"*I23*")|strmatch(codtext10, "*I23*")|strmatch(antecedent1, "*I23*")|strmatch(antecedent2,
"*I23*")|strmatch(antecedent3, "*I23*")|strmatch(antecedent4, "*I23*")|strmatch(antecedent5,
"*I23*")|strmatch(antecedent6, "*I23*")|strmatch(antecedent7, "*I23*")|strmatch(antecedent8,
"*I23*")|strmatch(antecedent9, "*I23*")|strmatch(antecedent10, "*I23*")| strmatch(cf1,
"*I23*")|strmatch(cf2, "*I23*")|strmatch(cf3, "*I23*")|strmatch(cf4, "*I23*")|strmatch(cf5,
"*I23*")|strmatch(cf6, "*I23*")|strmatch(cf7, "*I23*")|strmatch(cf8, "*I23*")|strmatch(cf9,
"*I23*")|strmatch(cf10, "*I23*")|strmatch(codtext_1, "*I23*")|strmatch(codtext_2,
"*I23*")|strmatch(codtext_3, "*I23*")|strmatch(antecedent_1, "*I23*")|strmatch(antecedent_2,
"*I23*")|strmatch(antecedent_3, "*I23*")|strmatch(contrib_1, "*I23*")|strmatch(contrib_2,
"*I23*")|strmatch(contrib_3, "*I23*")|strmatch(contrib_4, "*I23*")

replace cv_death = 1 if strmatch(codcode, "I24")| strmatch(record_axis_data, "I24")|
strmatch(codtext1, "I24")|strmatch(codtext2, "I24")|strmatch(codtext3, "I24")|strmatch(codtext4,
"I24")|strmatch(codtext5, "I24")|strmatch(codtext6, "I24")|strmatch(codtext7,
"I24")|strmatch(codtext8, "I24")|strmatch(codtext9, "I24")|strmatch(codtext10,
"I24")|strmatch(antecedent1, "I24")|strmatch(antecedent2, "I24")|strmatch(antecedent3,
"I24")|strmatch(antecedent4, "I24")|strmatch(antecedent5, "I24")|strmatch(antecedent6,
"I24")|strmatch(antecedent7, "I24")|strmatch(antecedent8, "I24")|strmatch(antecedent9,
"I24")|strmatch(antecedent10, "I24")| strmatch(cf1, "I24")|strmatch(cf2, "I24")|strmatch(cf3,
"I24")|strmatch(cf4, "I24")|strmatch(cf5, "I24")|strmatch(cf6, "I24")|strmatch(cf7, "I24")|strmatch(cf8,
"I24")|strmatch(cf9, "I24")|strmatch(cf10, "I24")|strmatch(codtext_1, "I24")|strmatch(codtext_2,
"I24")|strmatch(codtext_3, "I24")|strmatch(antecedent_1, "I24")|strmatch(antecedent_2,
"I24")|strmatch(antecedent_3, "I24")|strmatch(contrib_1, "I24")|strmatch(contrib_2,
"I24")|strmatch(contrib_3, "I24")|strmatch(contrib_4, "I24")
```

```
replace cv_death = 1 if strmatch(codcode, "I24*")| strmatch(record_axis_data, "*I24*")|
strmatch(codtext1, "*I24*")|strmatch(codtext2, "*I24*")|strmatch(codtext3,
"*I24*")|strmatch(codtext4, "*I24*")|strmatch(codtext5, "*I24*")|strmatch(codtext6,
"*I24*")|strmatch(codtext7, "*I24*")|strmatch(codtext8, "*I24*")|strmatch(codtext9,
"*I24*")|strmatch(codtext10, "*I24*")|strmatch(antecedent1, "*I24*")|strmatch(antecedent2,
"*I24*")|strmatch(antecedent3, "*I24*")|strmatch(antecedent4, "*I24*")|strmatch(antecedent5,
"*I24*")|strmatch(antecedent6, "*I24*")|strmatch(antecedent7, "*I24*")|strmatch(antecedent8,
"*I24*")|strmatch(antecedent9, "*I24*")|strmatch(antecedent10, "*I24*")| strmatch(cf1,
"*I24*")|strmatch(cf2, "*I24*")|strmatch(cf3, "*I24*")|strmatch(cf4, "*I24*")|strmatch(cf5,
"*I24*")|strmatch(cf6, "*I24*")|strmatch(cf7, "*I24*")|strmatch(cf8, "*I24*")|strmatch(cf9,
"*I24*")|strmatch(cf10, "*I24*")|strmatch(codtext_1, "*I24*")|strmatch(codtext_2,
"*I24*")|strmatch(codtext_3, "*I24*")|strmatch(antecedent_1, "*I24*")|strmatch(antecedent_2,
"*I24*")|strmatch(antecedent_3, "*I24*")|strmatch(contrib_1, "*I24*")|strmatch(contrib_2,
"*I24*")|strmatch(contrib_3, "*I24*")|strmatch(contrib_4, "*I24*")

replace cv_death = 1 if strmatch(codcode, "I25")| strmatch(record_axis_data, "I25")|
strmatch(codtext1, "I25")|strmatch(codtext2, "I25")|strmatch(codtext3, "I25")|strmatch(codtext4,
"I25")|strmatch(codtext5, "I25")|strmatch(codtext6, "I25")|strmatch(codtext7,
"I25")|strmatch(codtext8, "I25")|strmatch(codtext9, "I25")|strmatch(codtext10,
"I25")|strmatch(antecedent1, "I25")|strmatch(antecedent2, "I25")|strmatch(antecedent3,
"I25")|strmatch(antecedent4, "I25")|strmatch(antecedent5, "I25")|strmatch(antecedent6,
"I25")|strmatch(antecedent7, "I25")|strmatch(antecedent8, "I25")|strmatch(antecedent9,
"I25")|strmatch(antecedent10, "I25")| strmatch(cf1, "I25")|strmatch(cf2, "I25")|strmatch(cf3,
"I25")|strmatch(cf4, "I25")|strmatch(cf5, "I25")|strmatch(cf6, "I25")|strmatch(cf7, "I25")|strmatch(cf8,
"I25")|strmatch(cf9, "I25")|strmatch(cf10, "I25")|strmatch(codtext_1, "I25")|strmatch(codtext_2,
"I25")|strmatch(codtext_3, "I25")|strmatch(antecedent_1, "I25")|strmatch(antecedent_2,
"I25")|strmatch(antecedent_3, "I25")|strmatch(contrib_1, "I25")|strmatch(contrib_2,
"I25")|strmatch(contrib_3, "I25")|strmatch(contrib_4, "I25")

replace cv_death = 1 if strmatch(codcode, "I25*")| strmatch(record_axis_data, "*I25*")|
strmatch(codtext1, "*I25*")|strmatch(codtext2, "*I25*")|strmatch(codtext3,
"*I25*")|strmatch(codtext4, "*I25*")|strmatch(codtext5, "*I25*")|strmatch(codtext6,
"*I25*")|strmatch(codtext7, "*I25*")|strmatch(codtext8, "*I25*")|strmatch(codtext9,
"*I25*")|strmatch(codtext10, "*I25*")|strmatch(antecedent1, "*I25*")|strmatch(antecedent2,
"*I25*")|strmatch(antecedent3, "*I25*")|strmatch(antecedent4, "*I25*")|strmatch(antecedent5,
"*I25*")|strmatch(antecedent6, "*I25*")|strmatch(antecedent7, "*I25*")|strmatch(antecedent8,
"*I25*")|strmatch(antecedent9, "*I25*")|strmatch(antecedent10, "*I25*")| strmatch(cf1,
"*I25*")|strmatch(cf2, "*I25*")|strmatch(cf3, "*I25*")|strmatch(cf4, "*I25*")|strmatch(cf5,
"*I25*")|strmatch(cf6, "*I25*")|strmatch(cf7, "*I25*")|strmatch(cf8, "*I25*")|strmatch(cf9,
"*I25*")|strmatch(cf10, "*I25*")|strmatch(codtext_1, "*I25*")|strmatch(codtext_2,
"*I25*")|strmatch(codtext_3, "*I25*")|strmatch(antecedent_1, "*I25*")|strmatch(antecedent_2,
"*I25*")|strmatch(antecedent_3, "*I25*")|strmatch(contrib_1, "*I25*")|strmatch(contrib_2,
"*I25*")|strmatch(contrib_3, "*I25*")|strmatch(contrib_4, "*I25*")

browse rootnum date codcode codtext antecedent contrib_factors codtext_1 codtext_2 codtext_3
antecedent_1 antecedent_2 antecedent_3 contrib_1 contrib_2 contrib_3 if rectype == 4 & cv_death ==
0

* individual search for I21-I25- nil additional *


// malignancy death


gen malig_death = 0

/*
```

except for 21301, 21302, no malignancy goes to 5 digits

. browse if strmatch(record_axis_data, "*21301*")

. browse if strmatch(record_axis_data, "*21302*")

=> none

*/

* malignancies in codcode *

foreach var of numlist 140/234 {

replace malig_death = 1 if strmatch(codcode, "`var'")

}

foreach var of numlist 1400/2349 {

replace malig_death = 1 if strmatch(codcode, "`var'")

}

foreach var of numlist 140/234 {

replace malig_death = 1 if strmatch(codcode, "`var'*")

}

* record_axis_data

foreach var of numlist 140/234 {

replace malig_death = 1 if strmatch(record_axis_data, "`var'00")| strmatch(record_axis_data, "`var'10")| strmatch(record_axis_data, "`var'20")| strmatch(record_axis_data, "`var'30")| strmatch(record_axis_data, "`var'40")| strmatch(record_axis_data, "`var'50")| strmatch(record_axis_data, "`var'60")| strmatch(record_axis_data, "`var'70")| strmatch(record_axis_data, "`var'80")| strmatch(record_axis_data, "`var'90")

}

foreach var of numlist 140/234 {

replace malig_death = 1 if strmatch(record_axis_data, "*`var'00*")| strmatch(record_axis_data, "*`var'10*")| strmatch(record_axis_data, "*`var'20*")| strmatch(record_axis_data, "*`var'30*")| strmatch(record_axis_data, "*`var'40*")| strmatch(record_axis_data, "*`var'50*")| strmatch(record_axis_data, "*`var'60*")| strmatch(record_axis_data, "*`var'70*")| strmatch(record_axis_data, "*`var'80*")| strmatch(record_axis_data, "*`var'90*")

}

browse rootnum lpnum date codcode entity_axis_data record_axis_data multi_cod_format_type cod_extra_mcod11 rad1_ex0_inj1 cod_extra_rad1 codtext antecedent contrib_factors if rectype == 4 & malig_death == 1

* ICD10 malignancy *

** malignancy in ICD10

codcode

C000 to C979

```
C0* to C9*

foreach var of numlist 0/9 {

replace malig_death = 1 if strmatch(codcode, "C`var'*")

}

foreach var of numlist 0/979{

replace malig_death = 1 if strmatch(codcode, "C`var'*")

}

foreach var of numlist 0/9 {

replace malig_death = 1 if strmatch(record_axis_data, "*C`var'*")| strmatch(codtext1,
"*C`var'*")|strmatch(codtext2, "*C`var'*")|strmatch(codtext3, "*C`var'*")|strmatch(codtext4,
"*C`var'*")|strmatch(codtext5, "*C`var'*")|strmatch(codtext6, "*C`var'*")|strmatch(codtext7,
"*C`var'*")|strmatch(codtext8, "*C`var'*")|strmatch(codtext9, "*C`var'*")|strmatch(codtext10,
"*C`var'*")|strmatch(antecedent1, "*C`var'*")|strmatch(antecedent2,
"*C`var'*")|strmatch(antecedent3, "*C`var'*")|strmatch(antecedent4,
"*C`var'*")|strmatch(antecedent5, "*C`var'*")|strmatch(antecedent6,
"*C`var'*")|strmatch(antecedent7, "*C`var'*")|strmatch(antecedent8,
"*C`var'*")|strmatch(antecedent9, "*C`var'*")|strmatch(antecedent10, "*C`var'*")| strmatch(cf1,
"*C`var'*")|strmatch(cf2, "*C`var'*")|strmatch(cf3, "*C`var'*")|strmatch(cf4, "*C`var'*")|strmatch(cf5,
"*C`var'*")|strmatch(cf6, "*C`var'*")|strmatch(cf7, "*C`var'*")|strmatch(cf8, "*C`var'*")|strmatch(cf9,
"*C`var'*")|strmatch(cf10, "*C`var'*")|strmatch(codtext_1, "*C`var'*")|strmatch(codtext_2,
"*C`var'*")|strmatch(codtext_3, "*C`var'*")|strmatch(antecedent_1,
"*C`var'*")|strmatch(antecedent_2, "*C`var'*")|strmatch(antecedent_3,
"*C`var'*")|strmatch(contrib_1, "*C`var'*")|strmatch(contrib_2, "*C`var'*")|strmatch(contrib_3,
"*C`var'*")|strmatch(contrib_4, "*C`var'*")

}

foreach var of numlist 0/9 {

replace malig_death = 1 if strmatch(record_axis_data, "*c`var'*")| strmatch(codtext1,
"*c`var'*")|strmatch(codtext2, "*c`var'*")|strmatch(codtext3, "*c`var'*")|strmatch(codtext4,
"*c`var'*")|strmatch(codtext5, "*c`var'*")|strmatch(codtext6, "*c`var'*")|strmatch(codtext7,
"*c`var'*")|strmatch(codtext8, "*c`var'*")|strmatch(codtext9, "*c`var'*")|strmatch(codtext10,
"*c`var'*")|strmatch(antecedent1, "*c`var'*")|strmatch(antecedent2,
"*c`var'*")|strmatch(antecedent3, "*c`var'*")|strmatch(antecedent4,
"*c`var'*")|strmatch(antecedent5, "*c`var'*")|strmatch(antecedent6,
"*c`var'*")|strmatch(antecedent7, "*c`var'*")|strmatch(antecedent8,
"*c`var'*")|strmatch(antecedent9, "*c`var'*")|strmatch(antecedent10, "*c`var'*")| strmatch(cf1,
"*c`var'*")|strmatch(cf2, "*c`var'*")|strmatch(cf3, "*c`var'*")|strmatch(cf4, "*c`var'*")|strmatch(cf5,
"*c`var'*")|strmatch(cf6, "*c`var'*")|strmatch(cf7, "*c`var'*")|strmatch(cf8, "*c`var'*")|strmatch(cf9,
"*c`var'*")|strmatch(cf10, "*c`var'*")|strmatch(codtext_1, "*c`var'*")|strmatch(codtext_2,
"*c`var'*")|strmatch(codtext_3, "*c`var'*")|strmatch(antecedent_1,
"*c`var'*")|strmatch(antecedent_2, "*c`var'*")|strmatch(antecedent_3,
"*c`var'*")|strmatch(contrib_1, "*c`var'*")|strmatch(contrib_2, "*c`var'*")|strmatch(contrib_3,
"*c`var'*")|strmatch(contrib_4, "*c`var'*")

}

* D45-D48

foreach var of numlist 45 46 47 48 {

replace malig_death = 1 if strmatch(codcode, "D`var'*")
```

```
}

foreach var of numlist 45 46 47 48 {

replace malig_death = 1 if strmatch(record_axis_data, "*D`var'*")| strmatch(codtext1,
"*D`var'*")|strmatch(codtext2, "*D`var'*")|strmatch(codtext3, "*D`var'*")|strmatch(codtext4,
"*D`var'*")|strmatch(codtext5, "*D`var'*")|strmatch(codtext6, "*D`var'*")|strmatch(codtext7,
"*D`var'*")|strmatch(codtext8, "*D`var'*")|strmatch(codtext9, "*D`var'*")|strmatch(codtext10,
"*D`var'*")|strmatch(antecedent1, "*D`var'*")|strmatch(antecedent2,
"*D`var'*")|strmatch(antecedent3, "*D`var'*")|strmatch(antecedent4,
"*D`var'*")|strmatch(antecedent5, "*D`var'*")|strmatch(antecedent6,
"*D`var'*")|strmatch(antecedent7, "*D`var'*")|strmatch(antecedent8,
"*D`var'*")|strmatch(antecedent9, "*D`var'*")|strmatch(antecedent10, "*D`var'*")| strmatch(cf1,
"*D`var'*")|strmatch(cf2, "*D`var'*")|strmatch(cf3, "*D`var'*")|strmatch(cf4, "*D`var'*")|strmatch(cf5,
"*D`var'*")|strmatch(cf6, "*D`var'*")|strmatch(cf7, "*D`var'*")|strmatch(cf8, "*D`var'*")|strmatch(cf9,
"*D`var'*")|strmatch(cf10, "*D`var'*")|strmatch(codtext_1, "*D`var'*")|strmatch(codtext_2,
"*D`var'*")|strmatch(codtext_3, "*D`var'*")|strmatch(antecedent_1,
"*D`var'*")|strmatch(antecedent_2, "*D`var'*")|strmatch(antecedent_3,
"*D`var'*")|strmatch(contrib_1, "*D`var'*")|strmatch(contrib_2, "*D`var'*")|strmatch(contrib_3,
"*D`var'*")|strmatch(contrib_4, "*D`var'*")

}

foreach var of numlist 45 46 47 48 {

replace malig_death = 1 if strmatch(record_axis_data, "*d`var'*")| strmatch(codtext1,
"*d`var'*")|strmatch(codtext2, "*d`var'*")|strmatch(codtext3, "*d`var'*")|strmatch(codtext4,
"*d`var'*")|strmatch(codtext5, "*d`var'*")|strmatch(codtext6, "*d`var'*")|strmatch(codtext7,
"*d`var'*")|strmatch(codtext8, "*d`var'*")|strmatch(codtext9, "*d`var'*")|strmatch(codtext10,
"*d`var'*")|strmatch(antecedent1, "*d`var'*")|strmatch(antecedent2,
"*d`var'*")|strmatch(antecedent3, "*d`var'*")|strmatch(antecedent4,
"*d`var'*")|strmatch(antecedent5, "*d`var'*")|strmatch(antecedent6,
"*d`var'*")|strmatch(antecedent7, "*d`var'*")|strmatch(antecedent8,
"*d`var'*")|strmatch(antecedent9, "*d`var'*")|strmatch(antecedent10, "*d`var'*")| strmatch(cf1,
"*d`var'*")|strmatch(cf2, "*d`var'*")|strmatch(cf3, "*d`var'*")|strmatch(cf4, "*d`var'*")|strmatch(cf5,
"*d`var'*")|strmatch(cf6, "*d`var'*")|strmatch(cf7, "*d`var'*")|strmatch(cf8, "*d`var'*")|strmatch(cf9,
"*d`var'*")|strmatch(cf10, "*d`var'*")|strmatch(codtext_1, "*d`var'*")|strmatch(codtext_2,
"*d`var'*")|strmatch(codtext_3, "*d`var'*")|strmatch(antecedent_1,
"*d`var'*")|strmatch(antecedent_2, "*d`var'*")|strmatch(antecedent_3,
"*d`var'*")|strmatch(contrib_1, "*d`var'*")|strmatch(contrib_2, "*d`var'*")|strmatch(contrib_3,
"*d`var'*")|strmatch(contrib_4, "*d`var'*")

}


// death from CKD //


*ICD9: 585, 585.0-585.9

*ICD10: N18.0- N18.9 including N18 & 18.90 & 18.91

gen ckd_death = 0

replace ckd_death = 1 if strmatch(codcode, "N18")| strmatch(record_axis_data, "N18")|
strmatch(codtext1, "N18")|strmatch(codtext2, "N18")|strmatch(codtext3, "N18")|strmatch(codtext4,
"N18")|strmatch(codtext5, "N18")|strmatch(codtext6, "N18")|strmatch(codtext7,
"N18")|strmatch(codtext8, "N18")|strmatch(codtext9, "N18")|strmatch(codtext10,
"N18")|strmatch(antecedent1, "N18")|strmatch(antecedent2, "N18")|strmatch(antecedent3,
```

"N18")|strmatch(antecedent4, "N18")|strmatch(antecedent5, "N18")|strmatch(antecedent6, "N18")|strmatch(antecedent7, "N18")|strmatch(antecedent8, "N18")|strmatch(antecedent9, "N18")|strmatch(antecedent10, "N18")| strmatch(cf1, "N18")|strmatch(cf2, "N18")|strmatch(cf3, "N18")|strmatch(cf4, "N18")|strmatch(cf5, "N18")|strmatch(cf6, "N18")|strmatch(cf7, "N18")|strmatch(cf8, "N18")|strmatch(cf9, "N18")|strmatch(cf10, "N18")|strmatch(codtext_1, "N18")|strmatch(codtext_2, "N18")|strmatch(codtext_3, "N18")|strmatch(antecedent_1, "N18")|strmatch(antecedent_2, "N18")|strmatch(antecedent_3, "N18")|strmatch(contrib_1, "N18")|strmatch(contrib_2, "N18")|strmatch(contrib_3, "N18")|strmatch(contrib_4, "N18")

replace ckd_death = 1 if strmatch(codcode, "N18*")| strmatch(record_axis_data, "*N18*")| strmatch(codtext1, "*N18*")|strmatch(codtext2, "*N18*")|strmatch(codtext3, "*N18*")|strmatch(codtext4, "*N18*")|strmatch(codtext5, "*N18*")|strmatch(codtext6, "*N18*")|strmatch(codtext7, "*N18*")|strmatch(codtext8, "*N18*")|strmatch(codtext9, "*N18*")|strmatch(codtext10, "*N18*")|strmatch(antecedent1, "*N18*")|strmatch(antecedent2, "*N18*")|strmatch(antecedent3, "*N18*")|strmatch(antecedent4, "*N18*")|strmatch(antecedent5, "*N18*")|strmatch(antecedent6, "*N18*")|strmatch(antecedent7, "*N18*")|strmatch(antecedent8, "*N18*")|strmatch(antecedent9, "*N18*")|strmatch(antecedent10, "*N18*")| strmatch(cf1, "*N18*")|strmatch(cf2, "*N18*")|strmatch(cf3, "*N18*")|strmatch(cf4, "*N18*")|strmatch(cf5, "*N18*")|strmatch(cf6, "*N18*")|strmatch(cf7, "*N18*")|strmatch(cf8, "*N18*")|strmatch(cf9, "*N18*")|strmatch(cf10, "*N18*")|strmatch(codtext_1, "*N18*")|strmatch(codtext_2, "*N18*")|strmatch(codtext_3, "*N18*")|strmatch(antecedent_1, "*N18*")|strmatch(antecedent_2, "*N18*")|strmatch(antecedent_3, "*N18*")|strmatch(contrib_1, "*N18*")|strmatch(contrib_2, "*N18*")|strmatch(contrib_3, "*N18*")|strmatch(contrib_4, "*N18*")

replace ckd_death = 1 if strmatch(codcode, "585")| strmatch(codcode, "5850")| strmatch(codcode, "5851")| strmatch(codcode, "5852")| strmatch(codcode, "5853")| strmatch(codcode, "5854")| strmatch(codcode, "5855")| strmatch(codcode, "5856")| strmatch(codcode, "58557")| strmatch(codcode, "5858")| strmatch(codcode, "5859")| strmatch(record_axis_data, "58500")| strmatch(record_axis_data, "58510")| strmatch(record_axis_data, "58520")| strmatch(record_axis_data, "58530")| strmatch(record_axis_data, "58540")| strmatch(record_axis_data, "58550")| strmatch(record_axis_data, "58560")| strmatch(record_axis_data, "58570")| strmatch(record_axis_data, "58580")| strmatch(record_axis_data, "58590")

replace ckd_death = 1 if strmatch(codcode, "5850*")| strmatch(codcode, "5851*")| strmatch(codcode, "5852*")| strmatch(codcode, "5853*")| strmatch(codcode, "5854*")| strmatch(codcode, "5855*")| strmatch(codcode, "5856*")| strmatch(codcode, "58557*")| strmatch(codcode, "5858*")| strmatch(codcode, "5859*")| strmatch(record_axis_data, "*58500*")| strmatch(record_axis_data, "*58510*")| strmatch(record_axis_data, "*58520*")| strmatch(record_axis_data, "*58530*")| strmatch(record_axis_data, "*58540*")| strmatch(record_axis_data, "*58550*")| strmatch(record_axis_data, "*58560*")| strmatch(record_axis_data, "*58570*")| strmatch(record_axis_data, "*58580*")| strmatch(record_axis_data, "*58590*")

// death from AKI //

* ICD9: 584.9

* ICD10: N17.9 (other AKI codes N17.0-N17.8 not used in this dataset at all, thus not necessary to consider)

gen aki_death = 0

replace aki_death = 1 if strmatch(codcode, "N179")| strmatch(record_axis_data, "N179")| strmatch(codtext1, "N179")|strmatch(codtext2, "N179")|strmatch(codtext3, "N179")|strmatch(codtext4, "N179")|strmatch(codtext5, "N179")|strmatch(codtext6, "N179")|strmatch(codtext7, "N179")|strmatch(codtext8, "N179")|strmatch(codtext9,

```
"N179")|strmatch(codtext10, "N179")|strmatch(antecedent1, "N179")|strmatch(antecedent2,
"N179")|strmatch(antecedent3, "N179")|strmatch(antecedent4, "N179")|strmatch(antecedent5,
"N179")|strmatch(antecedent6, "N179")|strmatch(antecedent7, "N179")|strmatch(antecedent8,
"N179")|strmatch(antecedent9, "N179")|strmatch(antecedent10, "N179")| strmatch(cf1,
"N179")|strmatch(cf2, "N179")|strmatch(cf3, "N179")|strmatch(cf4, "N179")|strmatch(cf5,
"N179")|strmatch(cf6, "N179")|strmatch(cf7, "N179")|strmatch(cf8, "N179")|strmatch(cf9,
"N179")|strmatch(cf10, "N179")|strmatch(codtext_1, "N179")|strmatch(codtext_2,
"N179")|strmatch(codtext_3, "N179")|strmatch(antecedent_1, "N179")|strmatch(antecedent_2,
"N179")|strmatch(antecedent_3, "N179")|strmatch(contrib_1, "N179")|strmatch(contrib_2,
"N179")|strmatch(contrib_3, "N179")|strmatch(contrib_4, "N179")

replace aki_death = 1 if strmatch(codcode, "N179*")| strmatch(record_axis_data, "*N179*")|
strmatch(codtext1, "*N179*")|strmatch(codtext2, "*N179*")|strmatch(codtext3,
"*N179*")|strmatch(codtext4, "*N179*")|strmatch(codtext5, "*N179*")|strmatch(codtext6,
"*N179*")|strmatch(codtext7, "*N179*")|strmatch(codtext8, "*N179*")|strmatch(codtext9,
"*N179*")|strmatch(codtext10, "*N179*")|strmatch(antecedent1, "*N179*")|strmatch(antecedent2,
"*N179*")|strmatch(antecedent3, "*N179*")|strmatch(antecedent4,
"*N179*")|strmatch(antecedent5, "*N179*")|strmatch(antecedent6,
"*N179*")|strmatch(antecedent7, "*N179*")|strmatch(antecedent8,
"*N179*")|strmatch(antecedent9, "*N179*")|strmatch(antecedent10, "*N179*")| strmatch(cf1,
"*N179*")|strmatch(cf2, "*N179*")|strmatch(cf3, "*N179*")|strmatch(cf4, "*N179*")|strmatch(cf5,
"*N179*")|strmatch(cf6, "*N179*")|strmatch(cf7, "*N179*")|strmatch(cf8, "*N179*")|strmatch(cf9,
"*N179*")|strmatch(cf10, "*N179*")|strmatch(codtext_1, "*N179*")|strmatch(codtext_2,
"*N179*")|strmatch(codtext_3, "*N179*")|strmatch(antecedent_1,
"*N179*")|strmatch(antecedent_2, "*N179*")|strmatch(antecedent_3,
"*N179*")|strmatch(contrib_1, "*N179*")|strmatch(contrib_2, "*N179*")|strmatch(contrib_3,
"*N179*")|strmatch(contrib_4, "*N179*")

replace aki_death = 1 if strmatch(codcode, "5849")| strmatch(record_axis_data, "5849")

replace aki_death = 1 if strmatch(codcode, "5849*")| strmatch(record_axis_data, "*5849*")


// death from infection //

ICD9 chosen using Rassekh 2010 Reclassification of ICD-9 Codes into Meaningful Categories for
Oncology Survivorship Research

ICD10=> list from previous


//////////////////  ICD10 infection codes ///////////////////


gen infection_death = 0

* codcode

foreach var of numlist 0/99 {

replace infection_death = 1 if strmatch(codcode, "A`var'*")

}

foreach var of numlist 0/99 {

replace infection_death = 1 if strmatch(codcode, "B`var'*")

}
```

```
browse rootnum codcode record_axis_data if rectype == 4 & infection_death == 1

foreach var of numlist 0 1 2 41/49 50 51 52 6 6 70 {

replace infection_death = 1 if strmatch(codcode, "G0`var'*")

}

browse rootnum date codcode codtext antecedent contrib_factors codtext_1 codtext_2 codtext_3
antecedent_1 antecedent_2 antecedent_3 contrib_1 contrib_2 contrib_3 if rectype == 4 &
infection_death == 0 & strmatch(codcode, "G*")

foreach var of numlist  3 31 6{

replace infection_death = 1 if strmatch(codcode, "H0`var'*")

}

foreach var of numlist 10 130 131 600 601 602 603 620 621 622 623 660 661 662 663 664 670 671 700
730 750 940{

replace infection_death = 1 if strmatch(codcode, "H`var'*")

}

foreach var of numlist 0 1 2 {

replace infection_death = 1 if strmatch(codcode, "I0`var'*")

}

foreach var of numlist 301 320 321 330 400 {

replace infection_death = 1 if strmatch(codcode, "I`var'*")

}

foreach var of numlist 1/9 {

replace infection_death = 1 if strmatch(codcode, "J0`var'*")

}

foreach var of numlist 10/22 36 390 391 411 418 440 851 852 853 86 860 869{

replace infection_death = 1 if strmatch(codcode, "J`var'*")

}

foreach var of numlist 46 47 {

replace infection_death = 1 if strmatch(codcode, "K0`var'*")

}

foreach var of numlist 113 230 231 351 570 572 574 578 670 671 672 673 678 750 9142 930 931 {

replace infection_death = 1 if strmatch(codcode, "K`var'*")

}

foreach var of numlist 0 1 2 3 50 80/89 {

replace infection_death = 1 if strmatch(codcode, "L0`var'*")

}

foreach var of numlist 0 1 {
```

```
replace infection_death = 1 if strmatch(codcode, "M0`var'*")

}

foreach var of numlist 462 463 490 491 492 600 630 631 632 650 651 710 711 726 730 731 860 861 862
864 865 {

replace infection_death = 1 if strmatch(codcode, "M`var'*")

}

foreach var of numlist 300 308 309 330 340 390 450 459 738 739 74 751 {

replace infection_death = 1 if strmatch(codcode, "N`var'*")

}

foreach var of numlist 572 650 651 75 {

replace infection_death = 1 if strmatch(codcode, "R`var'*")

}

foreach var of numlist 814 826 827 835 836 857{

replace infection_death = 1 if strmatch(codcode, "T`var'*")

}

browse rootnum codcode record_axis_data if rectype == 4 & infection_death == 1

* record_axis_data/text fields

foreach var of numlist 0/99 {

replace infection_death = 1 if strmatch(record_axis_data, "*A`var'*")| strmatch(codtext1,
"*A`var'*")|strmatch(codtext2, "*A`var'*")|strmatch(codtext3, "*A`var'*")|strmatch(codtext4,
"*A`var'*")|strmatch(codtext5, "*A`var'*")|strmatch(codtext6, "*A`var'*")|strmatch(codtext7,
"*A`var'*")|strmatch(codtext8, "*A`var'*")|strmatch(codtext9, "*A`var'*")|strmatch(codtext10,
"*A`var'*")|strmatch(antecedent1, "*A`var'*")|strmatch(antecedent2,
"*A`var'*")|strmatch(antecedent3, "*A`var'*")|strmatch(antecedent4,
"*A`var'*")|strmatch(antecedent5, "*A`var'*")|strmatch(antecedent6,
"*A`var'*")|strmatch(antecedent7, "*A`var'*")|strmatch(antecedent8,
"*A`var'*")|strmatch(antecedent9, "*A`var'*")|strmatch(antecedent10, "*A`var'*")| strmatch(cf1,
"*A`var'*")|strmatch(cf2, "*A`var'*")|strmatch(cf3, "*A`var'*")|strmatch(cf4, "*A`var'*")|strmatch(cf5,
"*A`var'*")|strmatch(cf6, "*A`var'*")|strmatch(cf7, "*A`var'*")|strmatch(cf8, "*A`var'*")|strmatch(cf9,
"*A`var'*")|strmatch(cf10, "*A`var'*")|strmatch(codtext_1, "*A`var'*")|strmatch(codtext_2,
"*A`var'*")|strmatch(codtext_3, "*A`var'*")|strmatch(antecedent_1,
"*A`var'*")|strmatch(antecedent_2, "*A`var'*")|strmatch(antecedent_3,
"*A`var'*")|strmatch(contrib_1, "*A`var'*")|strmatch(contrib_2, "*A`var'*")|strmatch(contrib_3,
"*A`var'*")|strmatch(contrib_4, "*A`var'*")

}

browse rootnum codcode record_axis_data codtext1 codtext2 codtext3 antecedent1 antecedent2
antecedent3 date if rectype == 4 & infection_death == 1

foreach var of numlist 0/99 {

replace infection_death = 1 if strmatch(record_axis_data, "*B`var'*")| strmatch(codtext1,
"*B`var'*")|strmatch(codtext2, "*B`var'*")|strmatch(codtext3, "*B`var'*")|strmatch(codtext4,
"*B`var'*")|strmatch(codtext5, "*B`var'*")|strmatch(codtext6, "*B`var'*")|strmatch(codtext7,
"*B`var'*")|strmatch(codtext8, "*B`var'*")|strmatch(codtext9, "*B`var'*")|strmatch(codtext10,
"*B`var'*")|strmatch(antecedent1, "*B`var'*")|strmatch(antecedent2,
```

```
"*B`var'*")|strmatch(antecedent3, "*B`var'*")|strmatch(antecedent4,
"*B`var'*")|strmatch(antecedent5, "*B`var'*")|strmatch(antecedent6,
"*B`var'*")|strmatch(antecedent7, "*B`var'*")|strmatch(antecedent8,
"*B`var'*")|strmatch(antecedent9, "*B`var'*")|strmatch(antecedent10, "*B`var'*")| strmatch(cf1,
"*B`var'*")|strmatch(cf2, "*B`var'*")|strmatch(cf3, "*B`var'*")|strmatch(cf4, "*B`var'*")|strmatch(cf5,
"*B`var'*")|strmatch(cf6, "*B`var'*")|strmatch(cf7, "*B`var'*")|strmatch(cf8, "*B`var'*")|strmatch(cf9,
"*B`var'*")|strmatch(cf10, "*B`var'*")|strmatch(codtext_1, "*B`var'*")|strmatch(codtext_2,
"*B`var'*")|strmatch(codtext_3, "*B`var'*")|strmatch(antecedent_1,
"*B`var'*")|strmatch(antecedent_2, "*B`var'*")|strmatch(antecedent_3,
"*B`var'*")|strmatch(contrib_1, "*B`var'*")|strmatch(contrib_2, "*B`var'*")|strmatch(contrib_3,
"*B`var'*")|strmatch(contrib_4, "*B`var'*")

}

browse rootnum codcode record_axis_data codtext1 codtext2 codtext3 antecedent1 antecedent2
antecedent3 date if rectype == 4 & infection_death == 1

foreach var of numlist 0 1 2 41/49 50 51 52 6 6 70 {

replace infection_death = 1 if strmatch(record_axis_data, "*G0`var'*")| strmatch(codtext1,
"*G0`var'*")|strmatch(codtext2, "*G0`var'*")|strmatch(codtext3, "*G0`var'*")|strmatch(codtext4,
"*G0`var'*")|strmatch(codtext5, "*G0`var'*")|strmatch(codtext6, "*G0`var'*")|strmatch(codtext7,
"*G0`var'*")|strmatch(codtext8, "*G0`var'*")|strmatch(codtext9, "*G0`var'*")|strmatch(codtext10,
"*G0`var'*")|strmatch(antecedent1, "*G0`var'*")|strmatch(antecedent2,
"*G0`var'*")|strmatch(antecedent3, "*G0`var'*")|strmatch(antecedent4,
"*G0`var'*")|strmatch(antecedent5, "*G0`var'*")|strmatch(antecedent6,
"*G0`var'*")|strmatch(antecedent7, "*G0`var'*")|strmatch(antecedent8,
"*G0`var'*")|strmatch(antecedent9, "*G0`var'*")|strmatch(antecedent10, "*G0`var'*")| strmatch(cf1,
"*G0`var'*")|strmatch(cf2, "*G0`var'*")|strmatch(cf3, "*G0`var'*")|strmatch(cf4,
"*G0`var'*")|strmatch(cf5, "*G0`var'*")|strmatch(cf6, "*G0`var'*")|strmatch(cf7,
"*G0`var'*")|strmatch(cf8, "*G0`var'*")|strmatch(cf9, "*G0`var'*")|strmatch(cf10,
"*G0`var'*")|strmatch(codtext_1, "*G0`var'*")|strmatch(codtext_2, "*G0`var'*")|strmatch(codtext_3,
"*G0`var'*")|strmatch(antecedent_1, "*G0`var'*")|strmatch(antecedent_2,
"*G0`var'*")|strmatch(antecedent_3, "*G0`var'*")|strmatch(contrib_1,
"*G0`var'*")|strmatch(contrib_2, "*G0`var'*")|strmatch(contrib_3, "*G0`var'*")|strmatch(contrib_4,
"*G0`var'*")

}

foreach var of numlist  3 31 6{

replace infection_death = 1 if strmatch(record_axis_data, "*H0`var'*")| strmatch(codtext1,
"*H0`var'*")|strmatch(codtext2, "*H0`var'*")|strmatch(codtext3, "*H0`var'*")|strmatch(codtext4,
"*H0`var'*")|strmatch(codtext5, "*H0`var'*")|strmatch(codtext6, "*H0`var'*")|strmatch(codtext7,
"*H0`var'*")|strmatch(codtext8, "*H0`var'*")|strmatch(codtext9, "*H0`var'*")|strmatch(codtext10,
"*H0`var'*")|strmatch(antecedent1, "*H0`var'*")|strmatch(antecedent2,
"*H0`var'*")|strmatch(antecedent3, "*H0`var'*")|strmatch(antecedent4,
"*H0`var'*")|strmatch(antecedent5, "*H0`var'*")|strmatch(antecedent6,
"*H0`var'*")|strmatch(antecedent7, "*H0`var'*")|strmatch(antecedent8,
"*H0`var'*")|strmatch(antecedent9, "*H0`var'*")|strmatch(antecedent10, "*H0`var'*")| strmatch(cf1,
"*H0`var'*")|strmatch(cf2, "*H0`var'*")|strmatch(cf3, "*H0`var'*")|strmatch(cf4,
"*H0`var'*")|strmatch(cf5, "*H0`var'*")|strmatch(cf6, "*H0`var'*")|strmatch(cf7,
"*H0`var'*")|strmatch(cf8, "*H0`var'*")|strmatch(cf9, "*H0`var'*")|strmatch(cf10,
"*H0`var'*")|strmatch(codtext_1, "*H0`var'*")|strmatch(codtext_2, "*H0`var'*")|strmatch(codtext_3,
"*H0`var'*")|strmatch(antecedent_1, "*H0`var'*")|strmatch(antecedent_2,
"*H0`var'*")|strmatch(antecedent_3, "*H0`var'*")|strmatch(contrib_1,
"*H0`var'*")|strmatch(contrib_2, "*H0`var'*")|strmatch(contrib_3, "*H0`var'*")|strmatch(contrib_4,
"*H0`var'*")
```

```
}

foreach var of numlist 10 130 131 600 601 602 603 620 621 622 623 660 661 662 663 664 670 671 700
730 750 940{

replace infection_death = 1 if strmatch(record_axis_data, "*H`var'*")| strmatch(codtext1,
"*H`var'*")|strmatch(codtext2, "*H`var'*")|strmatch(codtext3, "*H`var'*")|strmatch(codtext4,
"*H`var'*")|strmatch(codtext5, "*H`var'*")|strmatch(codtext6, "*H`var'*")|strmatch(codtext7,
"*H`var'*")|strmatch(codtext8, "*H`var'*")|strmatch(codtext9, "*H`var'*")|strmatch(codtext10,
"*H`var'*")|strmatch(antecedent1, "*H`var'*")|strmatch(antecedent2,
"*H`var'*")|strmatch(antecedent3, "*H`var'*")|strmatch(antecedent4,
"*H`var'*")|strmatch(antecedent5, "*H`var'*")|strmatch(antecedent6,
"*H`var'*")|strmatch(antecedent7, "*H`var'*")|strmatch(antecedent8,
"*H`var'*")|strmatch(antecedent9, "*H`var'*")|strmatch(antecedent10, "*H`var'*")| strmatch(cf1,
"*H`var'*")|strmatch(cf2, "*H`var'*")|strmatch(cf3, "*H`var'*")|strmatch(cf4, "*H`var'*")|strmatch(cf5,
"*H`var'*")|strmatch(cf6, "*H`var'*")|strmatch(cf7, "*H`var'*")|strmatch(cf8, "*H`var'*")|strmatch(cf9,
"*H`var'*")|strmatch(cf10, "*H`var'*")|strmatch(codtext_1, "*H`var'*")|strmatch(codtext_2,
"*H`var'*")|strmatch(codtext_3, "*H`var'*")|strmatch(antecedent_1,
"*H`var'*")|strmatch(antecedent_2, "*H`var'*")|strmatch(antecedent_3,
"*H`var'*")|strmatch(contrib_1, "*H`var'*")|strmatch(contrib_2, "*H`var'*")|strmatch(contrib_3,
"*H`var'*")|strmatch(contrib_4, "*H`var'*")

}

foreach var of numlist 0 1 2 {

replace infection_death = 1 if strmatch(record_axis_data, "*I0`var'*")| strmatch(codtext1,
"*I0`var'*")|strmatch(codtext2, "*I0`var'*")|strmatch(codtext3, "*I0`var'*")|strmatch(codtext4,
"*I0`var'*")|strmatch(codtext5, "*I0`var'*")|strmatch(codtext6, "*I0`var'*")|strmatch(codtext7,
"*I0`var'*")|strmatch(codtext8, "*I0`var'*")|strmatch(codtext9, "*I0`var'*")|strmatch(codtext10,
"*I0`var'*")|strmatch(antecedent1, "*I0`var'*")|strmatch(antecedent2,
"*I0`var'*")|strmatch(antecedent3, "*I0`var'*")|strmatch(antecedent4,
"*I0`var'*")|strmatch(antecedent5, "*I0`var'*")|strmatch(antecedent6,
"*I0`var'*")|strmatch(antecedent7, "*I0`var'*")|strmatch(antecedent8,
"*I0`var'*")|strmatch(antecedent9, "*I0`var'*")|strmatch(antecedent10, "*I0`var'*")| strmatch(cf1,
"*I0`var'*")|strmatch(cf2, "*I0`var'*")|strmatch(cf3, "*I0`var'*")|strmatch(cf4,
"*I0`var'*")|strmatch(cf5, "*I0`var'*")|strmatch(cf6, "*I0`var'*")|strmatch(cf7,
"*I0`var'*")|strmatch(cf8, "*I0`var'*")|strmatch(cf9, "*I0`var'*")|strmatch(cf10,
"*I0`var'*")|strmatch(codtext_1, "*I0`var'*")|strmatch(codtext_2, "*I0`var'*")|strmatch(codtext_3,
"*I0`var'*")|strmatch(antecedent_1, "*I0`var'*")|strmatch(antecedent_2,
"*I0`var'*")|strmatch(antecedent_3, "*I0`var'*")|strmatch(contrib_1, "*I0`var'*")|strmatch(contrib_2,
"*I0`var'*")|strmatch(contrib_3, "*I0`var'*")|strmatch(contrib_4, "*I0`var'*")

}

foreach var of numlist 301 320 321 330 400 {

replace infection_death = 1 if strmatch(record_axis_data, "*I`var'*")| strmatch(codtext1,
"*I`var'*")|strmatch(codtext2, "*I`var'*")|strmatch(codtext3, "*I`var'*")|strmatch(codtext4,
"*I`var'*")|strmatch(codtext5, "*I`var'*")|strmatch(codtext6, "*I`var'*")|strmatch(codtext7,
"*I`var'*")|strmatch(codtext8, "*I`var'*")|strmatch(codtext9, "*I`var'*")|strmatch(codtext10,
"*I`var'*")|strmatch(antecedent1, "*I`var'*")|strmatch(antecedent2, "*I`var'*")|strmatch(antecedent3,
"*I`var'*")|strmatch(antecedent4, "*I`var'*")|strmatch(antecedent5, "*I`var'*")|strmatch(antecedent6,
"*I`var'*")|strmatch(antecedent7, "*I`var'*")|strmatch(antecedent8, "*I`var'*")|strmatch(antecedent9,
"*I`var'*")|strmatch(antecedent10, "*I`var'*")| strmatch(cf1, "*I`var'*")|strmatch(cf2,
"*I`var'*")|strmatch(cf3, "*I`var'*")|strmatch(cf4, "*I`var'*")|strmatch(cf5, "*I`var'*")|strmatch(cf6,
"*I`var'*")|strmatch(cf7, "*I`var'*")|strmatch(cf8, "*I`var'*")|strmatch(cf9, "*I`var'*")|strmatch(cf10,
"*I`var'*")|strmatch(codtext_1, "*I`var'*")|strmatch(codtext_2, "*I`var'*")|strmatch(codtext_3,
"*I`var'*")|strmatch(antecedent_1, "*I`var'*")|strmatch(antecedent_2,
```

```
"*I`var'*")|strmatch(antecedent_3, "*I`var'*")|strmatch(contrib_1, "*I`var'*")|strmatch(contrib_2,
"*I`var'*")|strmatch(contrib_3, "*I`var'*")|strmatch(contrib_4, "*I`var'*")

}

foreach var of numlist 1/9 {

replace infection_death = 1 if strmatch(record_axis_data, "*J0`var'*")| strmatch(codtext1,
"*J0`var'*")|strmatch(codtext2, "*J0`var'*")|strmatch(codtext3, "*J0`var'*")|strmatch(codtext4,
"*J0`var'*")|strmatch(codtext5, "*J0`var'*")|strmatch(codtext6, "*J0`var'*")|strmatch(codtext7,
"*J0`var'*")|strmatch(codtext8, "*J0`var'*")|strmatch(codtext9, "*J0`var'*")|strmatch(codtext10,
"*J0`var'*")|strmatch(antecedent1, "*J0`var'*")|strmatch(antecedent2,
"*J0`var'*")|strmatch(antecedent3, "*J0`var'*")|strmatch(antecedent4,
"*J0`var'*")|strmatch(antecedent5, "*J0`var'*")|strmatch(antecedent6,
"*J0`var'*")|strmatch(antecedent7, "*J0`var'*")|strmatch(antecedent8,
"*J0`var'*")|strmatch(antecedent9, "*J0`var'*")|strmatch(antecedent10, "*J0`var'*")| strmatch(cf1,
"*J0`var'*")|strmatch(cf2, "*J0`var'*")|strmatch(cf3, "*J0`var'*")|strmatch(cf4,
"*J0`var'*")|strmatch(cf5, "*J0`var'*")|strmatch(cf6, "*J0`var'*")|strmatch(cf7,
"*J0`var'*")|strmatch(cf8, "*J0`var'*")|strmatch(cf9, "*J0`var'*")|strmatch(cf10,
"*J0`var'*")|strmatch(codtext_1, "*J0`var'*")|strmatch(codtext_2, "*J0`var'*")|strmatch(codtext_3,
"*J0`var'*")|strmatch(antecedent_1, "*J0`var'*")|strmatch(antecedent_2,
"*J0`var'*")|strmatch(antecedent_3, "*J0`var'*")|strmatch(contrib_1, "*J0`var'*")|strmatch(contrib_2,
"*J0`var'*")|strmatch(contrib_3, "*J0`var'*")|strmatch(contrib_4, "*J0`var'*")

}

foreach var of numlist 10/22 36 390 391 411 418 440 851 852 853 86 860 869{

replace infection_death = 1 if strmatch(record_axis_data, "*J`var'*")| strmatch(codtext1,
"*J`var'*")|strmatch(codtext2, "*J`var'*")|strmatch(codtext3, "*J`var'*")|strmatch(codtext4,
"*J`var'*")|strmatch(codtext5, "*J`var'*")|strmatch(codtext6, "*J`var'*")|strmatch(codtext7,
"*J`var'*")|strmatch(codtext8, "*J`var'*")|strmatch(codtext9, "*J`var'*")|strmatch(codtext10,
"*J`var'*")|strmatch(antecedent1, "*J`var'*")|strmatch(antecedent2,
"*J`var'*")|strmatch(antecedent3, "*J`var'*")|strmatch(antecedent4,
"*J`var'*")|strmatch(antecedent5, "*J`var'*")|strmatch(antecedent6,
"*J`var'*")|strmatch(antecedent7, "*J`var'*")|strmatch(antecedent8,
"*J`var'*")|strmatch(antecedent9, "*J`var'*")|strmatch(antecedent10, "*J`var'*")| strmatch(cf1,
"*J`var'*")|strmatch(cf2, "*J`var'*")|strmatch(cf3, "*J`var'*")|strmatch(cf4, "*J`var'*")|strmatch(cf5,
"*J`var'*")|strmatch(cf6, "*J`var'*")|strmatch(cf7, "*J`var'*")|strmatch(cf8, "*J`var'*")|strmatch(cf9,
"*J`var'*")|strmatch(cf10, "*J`var'*")|strmatch(codtext_1, "*J`var'*")|strmatch(codtext_2,
"*J`var'*")|strmatch(codtext_3, "*J`var'*")|strmatch(antecedent_1, "*J`var'*")|strmatch(antecedent_2,
"*J`var'*")|strmatch(antecedent_3, "*J`var'*")|strmatch(contrib_1, "*J`var'*")|strmatch(contrib_2,
"*J`var'*")|strmatch(contrib_3, "*J`var'*")|strmatch(contrib_4, "*J`var'*")

}

foreach var of numlist 46 47 {

replace infection_death = 1 if strmatch(record_axis_data, "*K0`var'*")| strmatch(codtext1,
"*K0`var'*")|strmatch(codtext2, "*K0`var'*")|strmatch(codtext3, "*K0`var'*")|strmatch(codtext4,
"*K0`var'*")|strmatch(codtext5, "*K0`var'*")|strmatch(codtext6, "*K0`var'*")|strmatch(codtext7,
"*K0`var'*")|strmatch(codtext8, "*K0`var'*")|strmatch(codtext9, "*K0`var'*")|strmatch(codtext10,
"*K0`var'*")|strmatch(antecedent1, "*K0`var'*")|strmatch(antecedent2,
"*K0`var'*")|strmatch(antecedent3, "*K0`var'*")|strmatch(antecedent4,
"*K0`var'*")|strmatch(antecedent5, "*K0`var'*")|strmatch(antecedent6,
"*K0`var'*")|strmatch(antecedent7, "*K0`var'*")|strmatch(antecedent8,
"*K0`var'*")|strmatch(antecedent9, "*K0`var'*")|strmatch(antecedent10, "*K0`var'*")| strmatch(cf1,
"*K0`var'*")|strmatch(cf2, "*K0`var'*")|strmatch(cf3, "*K0`var'*")|strmatch(cf4,
"*K0`var'*")|strmatch(cf5, "*K0`var'*")|strmatch(cf6, "*K0`var'*")|strmatch(cf7,
"*K0`var'*")|strmatch(cf8, "*K0`var'*")|strmatch(cf9, "*K0`var'*")|strmatch(cf10,
```

```
"*K0`var'*")|strmatch(codtext_1, "*K0`var'*")|strmatch(codtext_2, "*K0`var'*")|strmatch(codtext_3,
"*K0`var'*")|strmatch(antecedent_1, "*K0`var'*")|strmatch(antecedent_2,
"*K0`var'*")|strmatch(antecedent_3, "*K0`var'*")|strmatch(contrib_1,
"*K0`var'*")|strmatch(contrib_2, "*K0`var'*")|strmatch(contrib_3, "*K0`var'*")|strmatch(contrib_4,
"*K0`var'*")

}

foreach var of numlist 113 230 231 351 570 572 574 578 670 671 672 673 678 750 9142 930 931 {

replace infection_death = 1 if strmatch(record_axis_data, "*K`var'*")| strmatch(codtext1,
"*K`var'*")|strmatch(codtext2, "*K`var'*")|strmatch(codtext3, "*K`var'*")|strmatch(codtext4,
"*K`var'*")|strmatch(codtext5, "*K`var'*")|strmatch(codtext6, "*K`var'*")|strmatch(codtext7,
"*K`var'*")|strmatch(codtext8, "*K`var'*")|strmatch(codtext9, "*K`var'*")|strmatch(codtext10,
"*K`var'*")|strmatch(antecedent1, "*K`var'*")|strmatch(antecedent2,
"*K`var'*")|strmatch(antecedent3, "*K`var'*")|strmatch(antecedent4,
"*K`var'*")|strmatch(antecedent5, "*K`var'*")|strmatch(antecedent6,
"*K`var'*")|strmatch(antecedent7, "*K`var'*")|strmatch(antecedent8,
"*K`var'*")|strmatch(antecedent9, "*K`var'*")|strmatch(antecedent10, "*K`var'*")| strmatch(cf1,
"*K`var'*")|strmatch(cf2, "*K`var'*")|strmatch(cf3, "*K`var'*")|strmatch(cf4, "*K`var'*")|strmatch(cf5,
"*K`var'*")|strmatch(cf6, "*K`var'*")|strmatch(cf7, "*K`var'*")|strmatch(cf8, "*K`var'*")|strmatch(cf9,
"*K`var'*")|strmatch(cf10, "*K`var'*")|strmatch(codtext_1, "*K`var'*")|strmatch(codtext_2,
"*K`var'*")|strmatch(codtext_3, "*K`var'*")|strmatch(antecedent_1,
"*K`var'*")|strmatch(antecedent_2, "*K`var'*")|strmatch(antecedent_3,
"*K`var'*")|strmatch(contrib_1, "*K`var'*")|strmatch(contrib_2, "*K`var'*")|strmatch(contrib_3,
"*K`var'*")|strmatch(contrib_4, "*K`var'*")

}

foreach var of numlist 0 1 2 3 50 80/89 {

replace infection_death = 1 if strmatch(record_axis_data, "*L0`var'*")| strmatch(codtext1,
"*L0`var'*")|strmatch(codtext2, "*L0`var'*")|strmatch(codtext3, "*L0`var'*")|strmatch(codtext4,
"*L0`var'*")|strmatch(codtext5, "*L0`var'*")|strmatch(codtext6, "*L0`var'*")|strmatch(codtext7,
"*L0`var'*")|strmatch(codtext8, "*L0`var'*")|strmatch(codtext9, "*L0`var'*")|strmatch(codtext10,
"*L0`var'*")|strmatch(antecedent1, "*L0`var'*")|strmatch(antecedent2,
"*L0`var'*")|strmatch(antecedent3, "*L0`var'*")|strmatch(antecedent4,
"*L0`var'*")|strmatch(antecedent5, "*L0`var'*")|strmatch(antecedent6,
"*L0`var'*")|strmatch(antecedent7, "*L0`var'*")|strmatch(antecedent8,
"*L0`var'*")|strmatch(antecedent9, "*L0`var'*")|strmatch(antecedent10, "*L0`var'*")| strmatch(cf1,
"*L0`var'*")|strmatch(cf2, "*L0`var'*")|strmatch(cf3, "*L0`var'*")|strmatch(cf4,
"*L0`var'*")|strmatch(cf5, "*L0`var'*")|strmatch(cf6, "*L0`var'*")|strmatch(cf7,
"*L0`var'*")|strmatch(cf8, "*L0`var'*")|strmatch(cf9, "*L0`var'*")|strmatch(cf10,
"*L0`var'*")|strmatch(codtext_1, "*L0`var'*")|strmatch(codtext_2, "*L0`var'*")|strmatch(codtext_3,
"*L0`var'*")|strmatch(antecedent_1, "*L0`var'*")|strmatch(antecedent_2,
"*L0`var'*")|strmatch(antecedent_3, "*L0`var'*")|strmatch(contrib_1, "*L0`var'*")|strmatch(contrib_2,
"*L0`var'*")|strmatch(contrib_3, "*L0`var'*")|strmatch(contrib_4, "*L0`var'*")

}

foreach var of numlist 0 1 {

replace infection_death = 1 if strmatch(record_axis_data, "*M0`var'*")| strmatch(codtext1,
"*M0`var'*")|strmatch(codtext2, "*M0`var'*")|strmatch(codtext3, "*M0`var'*")|strmatch(codtext4,
"*M0`var'*")|strmatch(codtext5, "*M0`var'*")|strmatch(codtext6, "*M0`var'*")|strmatch(codtext7,
"*M0`var'*")|strmatch(codtext8, "*M0`var'*")|strmatch(codtext9, "*M0`var'*")|strmatch(codtext10,
"*M0`var'*")|strmatch(antecedent1, "*M0`var'*")|strmatch(antecedent2,
"*M0`var'*")|strmatch(antecedent3, "*M0`var'*")|strmatch(antecedent4,
"*M0`var'*")|strmatch(antecedent5, "*M0`var'*")|strmatch(antecedent6,
"*M0`var'*")|strmatch(antecedent7, "*M0`var'*")|strmatch(antecedent8,
```

```
"*M0`var'*")|strmatch(antecedent9, "*M0`var'*")|strmatch(antecedent10, "*M0`var'*")|
strmatch(cf1, "*M0`var'*")|strmatch(cf2, "*M0`var'*")|strmatch(cf3, "*M0`var'*")|strmatch(cf4,
"*M0`var'*")|strmatch(cf5, "*M0`var'*")|strmatch(cf6, "*M0`var'*")|strmatch(cf7,
"*M0`var'*")|strmatch(cf8, "*M0`var'*")|strmatch(cf9, "*M0`var'*")|strmatch(cf10,
"*M0`var'*")|strmatch(codtext_1, "*M0`var'*")|strmatch(codtext_2, "*M0`var'*")|strmatch(codtext_3,
"*M0`var'*")|strmatch(antecedent_1, "*M0`var'*")|strmatch(antecedent_2,
"*M0`var'*")|strmatch(antecedent_3, "*M0`var'*")|strmatch(contrib_1,
"*M0`var'*")|strmatch(contrib_2, "*M0`var'*")|strmatch(contrib_3, "*M0`var'*")|strmatch(contrib_4,
"*M0`var'*")

}

foreach var of numlist 462 463 490 491 492 600 630 631 632 650 651 710 711 726 730 731 860 861 862
864 865 {

replace infection_death = 1 if strmatch(record_axis_data, "*M`var'*")| strmatch(codtext1,
"*M`var'*")|strmatch(codtext2, "*M`var'*")|strmatch(codtext3, "*M`var'*")|strmatch(codtext4,
"*M`var'*")|strmatch(codtext5, "*M`var'*")|strmatch(codtext6, "*M`var'*")|strmatch(codtext7,
"*M`var'*")|strmatch(codtext8, "*M`var'*")|strmatch(codtext9, "*M`var'*")|strmatch(codtext10,
"*M`var'*")|strmatch(antecedent1, "*M`var'*")|strmatch(antecedent2,
"*M`var'*")|strmatch(antecedent3, "*M`var'*")|strmatch(antecedent4,
"*M`var'*")|strmatch(antecedent5, "*M`var'*")|strmatch(antecedent6,
"*M`var'*")|strmatch(antecedent7, "*M`var'*")|strmatch(antecedent8,
"*M`var'*")|strmatch(antecedent9, "*M`var'*")|strmatch(antecedent10, "*M`var'*")| strmatch(cf1,
"*M`var'*")|strmatch(cf2, "*M`var'*")|strmatch(cf3, "*M`var'*")|strmatch(cf4,
"*M`var'*")|strmatch(cf5, "*M`var'*")|strmatch(cf6, "*M`var'*")|strmatch(cf7,
"*M`var'*")|strmatch(cf8, "*M`var'*")|strmatch(cf9, "*M`var'*")|strmatch(cf10,
"*M`var'*")|strmatch(codtext_1, "*M`var'*")|strmatch(codtext_2, "*M`var'*")|strmatch(codtext_3,
"*M`var'*")|strmatch(antecedent_1, "*M`var'*")|strmatch(antecedent_2,
"*M`var'*")|strmatch(antecedent_3, "*M`var'*")|strmatch(contrib_1, "*M`var'*")|strmatch(contrib_2,
"*M`var'*")|strmatch(contrib_3, "*M`var'*")|strmatch(contrib_4, "*M`var'*")

}

foreach var of numlist 300 308 309 330 340 390 450 459 738 739 74 751 {

replace infection_death = 1 if strmatch(record_axis_data, "*N`var'*")| strmatch(codtext1,
"*N`var'*")|strmatch(codtext2, "*N`var'*")|strmatch(codtext3, "*N`var'*")|strmatch(codtext4,
"*N`var'*")|strmatch(codtext5, "*N`var'*")|strmatch(codtext6, "*N`var'*")|strmatch(codtext7,
"*N`var'*")|strmatch(codtext8, "*N`var'*")|strmatch(codtext9, "*N`var'*")|strmatch(codtext10,
"*N`var'*")|strmatch(antecedent1, "*N`var'*")|strmatch(antecedent2,
"*N`var'*")|strmatch(antecedent3, "*N`var'*")|strmatch(antecedent4,
"*N`var'*")|strmatch(antecedent5, "*N`var'*")|strmatch(antecedent6,
"*N`var'*")|strmatch(antecedent7, "*N`var'*")|strmatch(antecedent8,
"*N`var'*")|strmatch(antecedent9, "*N`var'*")|strmatch(antecedent10, "*N`var'*")| strmatch(cf1,
"*N`var'*")|strmatch(cf2, "*N`var'*")|strmatch(cf3, "*N`var'*")|strmatch(cf4, "*N`var'*")|strmatch(cf5,
"*N`var'*")|strmatch(cf6, "*N`var'*")|strmatch(cf7, "*N`var'*")|strmatch(cf8, "*N`var'*")|strmatch(cf9,
"*N`var'*")|strmatch(cf10, "*N`var'*")|strmatch(codtext_1, "*N`var'*")|strmatch(codtext_2,
"*N`var'*")|strmatch(codtext_3, "*N`var'*")|strmatch(antecedent_1,
"*N`var'*")|strmatch(antecedent_2, "*N`var'*")|strmatch(antecedent_3,
"*N`var'*")|strmatch(contrib_1, "*N`var'*")|strmatch(contrib_2, "*N`var'*")|strmatch(contrib_3,
"*N`var'*")|strmatch(contrib_4, "*N`var'*")

}

foreach var of numlist 572 650 651 75 {

replace infection_death = 1 if strmatch(record_axis_data, "*R`var'*")| strmatch(codtext1,
"*R`var'*")|strmatch(codtext2, "*R`var'*")|strmatch(codtext3, "*R`var'*")|strmatch(codtext4,
"*R`var'*")|strmatch(codtext5, "*R`var'*")|strmatch(codtext6, "*R`var'*")|strmatch(codtext7,
```

```
"*R`var'*")|strmatch(codtext8, "*R`var'*")|strmatch(codtext9, "*R`var'*")|strmatch(codtext10,
"*R`var'*")|strmatch(antecedent1, "*R`var'*")|strmatch(antecedent2,
"*R`var'*")|strmatch(antecedent3, "*R`var'*")|strmatch(antecedent4,
"*R`var'*")|strmatch(antecedent5, "*R`var'*")|strmatch(antecedent6,
"*R`var'*")|strmatch(antecedent7, "*R`var'*")|strmatch(antecedent8,
"*R`var'*")|strmatch(antecedent9, "*R`var'*")|strmatch(antecedent10, "*R`var'*")| strmatch(cf1,
"*R`var'*")|strmatch(cf2, "*R`var'*")|strmatch(cf3, "*R`var'*")|strmatch(cf4, "*R`var'*")|strmatch(cf5,
"*R`var'*")|strmatch(cf6, "*R`var'*")|strmatch(cf7, "*R`var'*")|strmatch(cf8, "*R`var'*")|strmatch(cf9,
"*R`var'*")|strmatch(cf10, "*R`var'*")|strmatch(codtext_1, "*R`var'*")|strmatch(codtext_2,
"*R`var'*")|strmatch(codtext_3, "*R`var'*")|strmatch(antecedent_1,
"*R`var'*")|strmatch(antecedent_2, "*R`var'*")|strmatch(antecedent_3,
"*R`var'*")|strmatch(contrib_1, "*R`var'*")|strmatch(contrib_2, "*R`var'*")|strmatch(contrib_3,
"*R`var'*")|strmatch(contrib_4, "*R`var'*")

}

foreach var of numlist 814 826 827 835 836 857{

replace infection_death = 1 if strmatch(record_axis_data, "*T`var'*")| strmatch(codtext1,
"*T`var'*")|strmatch(codtext2, "*T`var'*")|strmatch(codtext3, "*T`var'*")|strmatch(codtext4,
"*T`var'*")|strmatch(codtext5, "*T`var'*")|strmatch(codtext6, "*T`var'*")|strmatch(codtext7,
"*T`var'*")|strmatch(codtext8, "*T`var'*")|strmatch(codtext9, "*T`var'*")|strmatch(codtext10,
"*T`var'*")|strmatch(antecedent1, "*T`var'*")|strmatch(antecedent2,
"*T`var'*")|strmatch(antecedent3, "*T`var'*")|strmatch(antecedent4,
"*T`var'*")|strmatch(antecedent5, "*T`var'*")|strmatch(antecedent6,
"*T`var'*")|strmatch(antecedent7, "*T`var'*")|strmatch(antecedent8,
"*T`var'*")|strmatch(antecedent9, "*T`var'*")|strmatch(antecedent10, "*T`var'*")| strmatch(cf1,
"*T`var'*")|strmatch(cf2, "*T`var'*")|strmatch(cf3, "*T`var'*")|strmatch(cf4, "*T`var'*")|strmatch(cf5,
"*T`var'*")|strmatch(cf6, "*T`var'*")|strmatch(cf7, "*T`var'*")|strmatch(cf8, "*T`var'*")|strmatch(cf9,
"*T`var'*")|strmatch(cf10, "*T`var'*")|strmatch(codtext_1, "*T`var'*")|strmatch(codtext_2,
"*T`var'*")|strmatch(codtext_3, "*T`var'*")|strmatch(antecedent_1,
"*T`var'*")|strmatch(antecedent_2, "*T`var'*")|strmatch(antecedent_3,
"*T`var'*")|strmatch(contrib_1, "*T`var'*")|strmatch(contrib_2, "*T`var'*")|strmatch(contrib_3,
"*T`var'*")|strmatch(contrib_4, "*T`var'*")

}


//////// ICD9 INFECTION CODES /////////


* cod code

* e.g. 001-099

gen infection_death = 0

foreach var of numlist 1/9 {

replace infection_death = 1 if strmatch(codcode, "00`var'*")|strmatch(rad1, "00`var'*")|strmatch(rad2,
"00`var'*")|strmatch(rad3, "00`var'*")|strmatch(rad4, "00`var'*")|strmatch(rad5,
"00`var'*")|strmatch(rad6, "00`var'*")|strmatch(rad7, "00`var'*")|strmatch(rad8,
"00`var'*")|strmatch(rad9, "00`var'*")|strmatch(rad10, "00`var'*")

}

foreach var of numlist 10/99 {

replace infection_death = 1 if strmatch(codcode, "0`var'*")|strmatch(rad1, "0`var'*")|strmatch(rad2,
"0`var'*")|strmatch(rad3, "0`var'*")|strmatch(rad4, "0`var'*")|strmatch(rad5, "0`var'*")|strmatch(rad6,
```

"0`var'*")|strmatch(rad7, "0`var'*")|strmatch(rad8, "0`var'*")|strmatch(rad9, "0`var'*")|strmatch(rad10, "0`var'*")

}

foreach var of numlist 100/136 {

replace infection_death = 1 if strmatch(codcode, "`var'*")|strmatch(rad1, "`var'*")|strmatch(rad2, "`var'*")|strmatch(rad3, "`var'*")|strmatch(rad4, "`var'*")|strmatch(rad5, "`var'*")|strmatch(rad6, "`var'*")|strmatch(rad7, "`var'*")|strmatch(rad8, "`var'*")|strmatch(rad9, "`var'*")|strmatch(rad10, "`var'*")

}

foreach var of numlist 320 321 322 323 324 325 326 382 420 421 422 460 461 462 463 464 465 466 480 481 482 483 484 485 486 487 487 513 590 597 604 681 682 683 684 685 686 711 730 {

replace infection_death = 1 if strmatch(codcode, "`var'*")|strmatch(rad1, "`var'*")|strmatch(rad2, "`var'*")|strmatch(rad3, "`var'*")|strmatch(rad4, "`var'*")|strmatch(rad5, "`var'*")|strmatch(rad6, "`var'*")|strmatch(rad7, "`var'*")|strmatch(rad8, "`var'*")|strmatch(rad9, "`var'*")|strmatch(rad10, "`var'*")

}

foreach var of numlist 3701 3703 3704 3705 3720 3721 3734 3735 3736 3773 3801 3830 3831 3832 4477 5111 5401 5670 5671 5672 5731 5732 5770 5771 5818 5838 5954 5958 5980 6012 6014 6031 6142 6143 6144 6160 6161 6163 6164 6165 7270 7273 7280 7854 7907 7908 {

replace infection_death = 1 if strmatch(codcode, "`var'*")|strmatch(rad1, "`var'*")|strmatch(rad2, "`var'*")|strmatch(rad3, "`var'*")|strmatch(rad4, "`var'*")|strmatch(rad5, "`var'*")|strmatch(rad6, "`var'*")|strmatch(rad7, "`var'*")|strmatch(rad8, "`var'*")|strmatch(rad9, "`var'*")|strmatch(rad10, "`var'*")

}

list rootnum codcode record_axis_data if infection_death == 1

* checking using previous manual codes=> all accounted for OR no longer in the updated dataset- i.e. different controls

// UCOD alone //

browse rootnum date dateofdeath dod dod_a codcode codtext antecedent contrib_factors codtext_1 codtext_2 codtext_3 codtext_1a codtext_2a codtext_3a codtext1 codtext2 codtext3 codtext4 codtext5 codtext6 codtext7 codtext8 codtext9 codtext10 antecedent_1 antecedent_2 antecedent_3 antecedent_1a antecedent_2a antecedent_3a antecedent1 antecedent2 antecedent3 antecedent4 antecedent5 antecedent6 antecedent7 antecedent8 antecedent9 antecedent10 cf1 cf2 cf3 cf4 cf5 cf6 cf7 cf8 cf9 cf10 contrib_1 contrib_2 contrib_3 contrib_1a contrib_2a contrib_3a contrib_4 if rectype == 4

* saved as codcode or codcode_ucod *

gen ucod_vasc = 0

*ICD 9: arteritis 446.5, AAV codes (446.0 & 446.4)

replace ucod_vasc = 1 if strmatch(codcode, "4465*")|strmatch(codcode, "4460*")|strmatch(codcode, "4464*")|strmatch(codcode_ucod, "4465*")|strmatch(codcode_ucod, "4460*")|strmatch(codcode_ucod, "4464*")

*ICD 10: arteritis I77.6, AAV codes (M31.3, M31.7, M30.0, M30.8, M30.1, M30.9)

```
replace ucod_vasc = 1 if strmatch(codcode, "I776*")|strmatch(codcode, "M313*")|strmatch(codcode,
"M317*")|strmatch(codcode, "M300*")| strmatch(codcode, "M308*")|strmatch(codcode,
"M301*")|strmatch(codcode_ucod, "I776*")|strmatch(codcode_ucod,
"M313*")|strmatch(codcode_ucod, "M317*")|strmatch(codcode_ucod, "M300*")|
strmatch(codcode_ucod, "M308*")|strmatch(codcode_ucod, "M301*")

gen ucod_cv = 0

*ICD-9: 410.0 - 410.9, 414.0, 414.1, 414.10, 414.11, 414.12, 414.8, 414.9

replace ucod_cv = 1 if strmatch(codcode, "410*")|strmatch(codcode, "414*")|strmatch(codcode_ucod,
"410*")|strmatch(codcode_ucod, "414*")

*ICD-10: I21.0-I21.9, I22.0-I22.9, I23.0-I23.8, I24.0-I24.9, I25.0-I25.9

replace ucod_cv = 1 if strmatch(codcode, "I21*")| strmatch(codcode, "I22*")| strmatch(codcode,
"I23*")| strmatch(codcode, "I24*")| strmatch(codcode, "I25*")|strmatch(codcode_ucod, "I21*")|
strmatch(codcode_ucod, "I22*")| strmatch(codcode_ucod, "I23*")| strmatch(codcode_ucod, "I24*")|
strmatch(codcode_ucod, "I25*")

gen ucod_malig = 0

foreach var of numlist 140/234 {

replace ucod_malig = 1 if strmatch(codcode, "`var'")|strmatch(codcode_ucod, "`var'")

}

foreach var of numlist 1400/2349 {

replace ucod_malig = 1 if strmatch(codcode, "`var'")|strmatch(codcode_ucod, "`var'")

}

foreach var of numlist 140/234 {

replace ucod_malig = 1 if strmatch(codcode, "`var'*")|strmatch(codcode_ucod, "`var'*")

}

foreach var of numlist 0/9 {

replace ucod_malig = 1 if strmatch(codcode, "C`var'*")|strmatch(codcode_ucod, "C`var'*")

}

foreach var of numlist 0/979{

replace ucod_malig = 1 if strmatch(codcode, "C`var'*")|strmatch(codcode_ucod, "C`var'*")

}

foreach var of numlist 45 46 47 48 {

replace ucod_malig = 1 if strmatch(codcode, "D`var'*")|strmatch(codcode_ucod, "D`var'*")

}

gen ucod_ckd = 0

replace ucod_ckd = 1 if strmatch(codcode, "N18*")| strmatch(codcode_ucod, "N18*")

replace ucod_ckd = 1 if strmatch(codcode, "585*")| strmatch(codcode_ucod, "585*")

gen ucod_aki = 0

replace ucod_aki = 1 if strmatch(codcode, "N179*")|strmatch(codcode_ucod, "N179*")
```

```
replace ucod_aki = 1 if strmatch(codcode, "5849*")|strmatch(codcode_ucod, "5849*")
gen ucod_infection = 0
foreach var of numlist 0/99 {
replace ucod_infection = 1 if strmatch(codcode, "A`var'*")|strmatch(codcode_ucod, "A`var'*")
}
foreach var of numlist 0/99 {
replace ucod_infection = 1 if strmatch(codcode, "B`var'*")|strmatch(codcode_ucod, "B`var'*")
}
foreach var of numlist 0 1 2 41/49 50 51 52 6 6 70 {
replace ucod_infection = 1 if strmatch(codcode, "G0`var'*")|strmatch(codcode_ucod, "G0`var'*")
}
foreach var of numlist  3 31 6{
replace ucod_infection = 1 if strmatch(codcode, "H0`var'*")|strmatch(codcode_ucod, "H0`var'*")
}
foreach var of numlist 10 130 131 600 601 602 603 620 621 622 623 660 661 662 663 664 670 671 700
730 750 940{
replace ucod_infection = 1 if strmatch(codcode, "H`var'*")|strmatch(codcode_ucod, "H`var'*")
}
foreach var of numlist 0 1 2 {
replace ucod_infection = 1 if strmatch(codcode, "I0`var'*")|strmatch(codcode_ucod, "I0`var'*")
}
foreach var of numlist 301 320 321 330 400 {
replace ucod_infection = 1 if strmatch(codcode, "I`var'*")|strmatch(codcode_ucod, "I`var'*")
}
foreach var of numlist 1/9 {
replace ucod_infection = 1 if strmatch(codcode, "J0`var'*")|strmatch(codcode_ucod, "J0`var'*")
}
foreach var of numlist 10/22 36 390 391 411 418 440 851 852 853 86 860 869{
replace ucod_infection = 1 if strmatch(codcode, "J`var'*")|strmatch(codcode_ucod, "J`var'*")
}
foreach var of numlist 46 47 {
replace ucod_infection = 1 if strmatch(codcode, "K0`var'*")|strmatch(codcode_ucod, "K0`var'*")
}
foreach var of numlist 113 230 231 351 570 572 574 578 670 671 672 673 678 750 9142 930 931 {
replace ucod_infection = 1 if strmatch(codcode, "K`var'*")|strmatch(codcode_ucod, "K`var'*")
```

```
}

foreach var of numlist 0 1 2 3 50 80/89 {

replace ucod_infection = 1 if strmatch(codcode, "L0`var'*")|strmatch(codcode_ucod, "L0`var'*")

}

foreach var of numlist 0 1 {

replace ucod_infection = 1 if strmatch(codcode, "M0`var'*")|strmatch(codcode_ucod, "M0`var'*")

}

foreach var of numlist 462 463 490 491 492 600 630 631 632 650 651 710 711 726 730 731 860 861 862
864 865 {

replace ucod_infection = 1 if strmatch(codcode, "M`var'*")|strmatch(codcode_ucod, "M`var'*")

}

foreach var of numlist 300 308 309 330 340 390 450 459 738 739 74 751 {

replace ucod_infection = 1 if strmatch(codcode, "N`var'*")|strmatch(codcode_ucod, "N`var'*")

}

foreach var of numlist 572 650 651 75 {

replace ucod_infection = 1 if strmatch(codcode, "R`var'*")|strmatch(codcode_ucod, "R`var'*")

}

foreach var of numlist 814 826 827 835 836 857{

replace ucod_infection = 1 if strmatch(codcode, "T`var'*")|strmatch(codcode_ucod, "T`var'*")

}

foreach var of numlist 1/9 {

replace ucod_infection = 1 if strmatch(codcode, "00`var'*")|strmatch(codcode_ucod, "00`var'*")

}

foreach var of numlist 10/99 {

replace ucod_infection = 1 if strmatch(codcode, "0`var'*")|strmatch(codcode_ucod, "0`var'*")

}

foreach var of numlist 100/136 {

replace ucod_infection = 1 if strmatch(codcode, "`var'*")|strmatch(codcode_ucod, "`var'*")

}

foreach var of numlist 320 321 322 323 324 325 326 382 420 421 422 460 461 462 463 464 465 466 480
481 482 483 484 485 486 487 487 513 590 597 604 681 682 683 684 685 686 711 730 {

replace ucod_infection = 1 if strmatch(codcode, "`var'*")|strmatch(codcode_ucod, "`var'*")

}

foreach var of numlist 3701 3703 3704 3705 3720 3721 3734 3735 3736 3773 3801 3830 3831 3832
4477 5111 5401 5670 5671 5672 5731 5732 5770 5771 5818 5838 5954 5958 5980 6012 6014 6031
6142 6143 6144 6160 6161 6163 6164 6165 7270 7273 7280 7854 7907 7908 {
```

```
replace ucod_infection = 1 if strmatch(codcode, "`var'*")|strmatch(codcode_ucod, "`var'*")

}

** drop for merge to master file **

save "*** \1. analysis\data\20200915 cause of death finalised.dta"

preserve

keep if rectype == 4

restore

** additional comorbidities as not all accounted for

// cerebrovascular disease

* derived from PlosOne 2015 Validity of acute stroke diagnoses in administrative data

*ICD9: 430-438

*ICD10: I60-I69

gen ucod_stroke = 0

* ICD 9

replace ucod_stroke = 1 if strmatch(codcode, "430*")|strmatch(codcode_ucod,
"430*")|strmatch(codcode, "431*")|strmatch(codcode_ucod, "431*")|strmatch(codcode,
"432*")|strmatch(codcode_ucod, "432*")|strmatch(codcode, "433*")|strmatch(codcode_ucod,
"433*")|strmatch(codcode, "434*")|strmatch(codcode_ucod, "434*")|strmatch(codcode,
"435*")|strmatch(codcode_ucod, "435*")|strmatch(codcode, "436*")|strmatch(codcode_ucod,
"436*")|strmatch(codcode, "437*")|strmatch(codcode_ucod, "437*")|strmatch(codcode,
"438*")|strmatch(codcode_ucod, "438*")

* ICD 10

replace ucod_stroke = 1 if strmatch(codcode, "I60*")|strmatch(codcode, "I61*")|strmatch(codcode,
"I62*")|strmatch(codcode, "I63*")|strmatch(codcode, "I64*")|strmatch(codcode,
"I65*")|strmatch(codcode, "I66*")|strmatch(codcode, "I67*")|strmatch(codcode,
"I68*")|strmatch(codcode, "I69*")|strmatch(codcode_ucod, "I60*")|strmatch(codcode_ucod,
"I61*")|strmatch(codcode_ucod, "I62*")|strmatch(codcode_ucod, "I63*")|strmatch(codcode_ucod,
"I64*")|strmatch(codcode_ucod, "I65*")|strmatch(codcode_ucod, "I66*")|strmatch(codcode_ucod,
"I67*")|strmatch(codcode_ucod, "I68*")|strmatch(codcode_ucod, "I69*")

gen stroke_death = 0

*ICD9

replace stroke_death = 1 if strmatch(codcode, "430*")| strmatch(record_axis_data, "*43000*")

replace stroke_death = 1 if strmatch(codcode, "431*")| strmatch(record_axis_data, "*43100*")

replace stroke_death = 1 if strmatch(codcode, "432*")| strmatch(record_axis_data, "*43200*")|
strmatch(record_axis_data, "*43210*")| strmatch(record_axis_data, "*43290*")

replace stroke_death = 1 if strmatch(codcode, "433*")| strmatch(record_axis_data, "*43300*")|
strmatch(record_axis_data, "*43310*")| strmatch(record_axis_data, "*43320*")|
strmatch(record_axis_data, "*43330*")|strmatch(record_axis_data, "*43380*")|
strmatch(record_axis_data, "*43390*")| strmatch(record_axis_data, "*43301*")|
strmatch(record_axis_data, "*43311*")| strmatch(record_axis_data, "*43321*")|
strmatch(record_axis_data, "*43331*")|strmatch(record_axis_data, "*43381*")|
strmatch(record_axis_data, "*43391*")
```

```
replace stroke_death = 1 if strmatch(codcode, "434*")| strmatch(record_axis_data, "*43400*")|
strmatch(record_axis_data, "*43410*")| strmatch(record_axis_data, "*43490*")|
strmatch(record_axis_data, "*43401*")| strmatch(record_axis_data, "*43411*")|
strmatch(record_axis_data, "*43491*")

replace stroke_death = 1 if strmatch(codcode, "435*")| strmatch(record_axis_data, "*43500*")|
strmatch(record_axis_data, "*43510*")| strmatch(record_axis_data, "*43520*")|
strmatch(record_axis_data, "*43530*")| strmatch(record_axis_data, "*43580*")|
strmatch(record_axis_data, "*43590*")

replace stroke_death = 1 if strmatch(codcode, "436*")| strmatch(record_axis_data, "*43600*")

replace stroke_death = 1 if strmatch(codcode, "437*")| strmatch(record_axis_data, "*43700*")|
strmatch(record_axis_data, "*43710*")| strmatch(record_axis_data, "*43720*")|
strmatch(record_axis_data, "*43730*")| strmatch(record_axis_data, "*43740*")|
strmatch(record_axis_data, "*43750*")| strmatch(record_axis_data, "*43760*")|
strmatch(record_axis_data, "*43770*")| strmatch(record_axis_data,
"*43780*")|strmatch(record_axis_data, "*43790*")

replace stroke_death = 1 if strmatch(codcode, "438*")| strmatch(record_axis_data, "*43800*")

*ICD10

replace stroke_death = 1 if strmatch(codcode, "I60")|strmatch(record_axis_data, "I60")|
strmatch(codtext1, "I60")|strmatch(codtext2, "I60")|strmatch(codtext3, "I60")|strmatch(codtext4,
"I60")|strmatch(codtext5, "I60")|strmatch(codtext6, "I60")|strmatch(codtext7,
"I60")|strmatch(codtext8, "I60")|strmatch(codtext9, "I60")|strmatch(codtext10,
"I60")|strmatch(antecedent1, "I60")|strmatch(antecedent2, "I60")|strmatch(antecedent3,
"I60")|strmatch(antecedent4, "I60")|strmatch(antecedent5, "I60")|strmatch(antecedent6,
"I60")|strmatch(antecedent7, "I60")|strmatch(antecedent8, "I60")|strmatch(antecedent9,
"I60")|strmatch(antecedent10, "I60")| strmatch(cf1, "I60")|strmatch(cf2, "I60")|strmatch(cf3,
"I60")|strmatch(cf4, "I60")|strmatch(cf5, "I60")|strmatch(cf6, "I60")|strmatch(cf7, "I60")|strmatch(cf8,
"I60")|strmatch(cf9, "I60")|strmatch(cf10, "I60")|strmatch(codtext_1, "I60")|strmatch(codtext_2,
"I60")|strmatch(codtext_3, "I60")|strmatch(antecedent_1, "I60")|strmatch(antecedent_2,
"I60")|strmatch(antecedent_3, "I60")|strmatch(contrib_1, "I60")|strmatch(contrib_2,
"I60")|strmatch(contrib_3, "I60")|strmatch(contrib_4, "I60")

replace stroke_death = 1 if strmatch(codcode, "I60*")| strmatch(record_axis_data, "*I60*")|
strmatch(codtext1, "*I60*")|strmatch(codtext2, "*I60*")|strmatch(codtext3,
"*I60*")|strmatch(codtext4, "*I60*")|strmatch(codtext5, "*I60*")|strmatch(codtext6,
"*I60*")|strmatch(codtext7, "*I60*")|strmatch(codtext8, "*I60*")|strmatch(codtext9,
"*I60*")|strmatch(codtext10, "*I60*")|strmatch(antecedent1, "*I60*")|strmatch(antecedent2,
"*I60*")|strmatch(antecedent3, "*I60*")|strmatch(antecedent4, "*I60*")|strmatch(antecedent5,
"*I60*")|strmatch(antecedent6, "*I60*")|strmatch(antecedent7, "*I60*")|strmatch(antecedent8,
"*I60*")|strmatch(antecedent9, "*I60*")|strmatch(antecedent10, "*I60*")| strmatch(cf1,
"*I60*")|strmatch(cf2, "*I60*")|strmatch(cf3, "*I60*")|strmatch(cf4, "*I60*")|strmatch(cf5,
"*I60*")|strmatch(cf6, "*I60*")|strmatch(cf7, "*I60*")|strmatch(cf8, "*I60*")|strmatch(cf9,
"*I60*")|strmatch(cf10, "*I60*")|strmatch(codtext_1, "*I60*")|strmatch(codtext_2,
"*I60*")|strmatch(codtext_3, "*I60*")|strmatch(antecedent_1, "*I60*")|strmatch(antecedent_2,
"*I60*")|strmatch(antecedent_3, "*I60*")|strmatch(contrib_1, "*I60*")|strmatch(contrib_2,
"*I60*")|strmatch(contrib_3, "*I60*")|strmatch(contrib_4, "*I60*")

replace stroke_death = 1 if strmatch(codcode, "I61")|strmatch(record_axis_data, "I61")|
strmatch(codtext1, "I61")|strmatch(codtext2, "I61")|strmatch(codtext3, "I61")|strmatch(codtext4,
"I61")|strmatch(codtext5, "I61")|strmatch(codtext6, "I61")|strmatch(codtext7,
"I61")|strmatch(codtext8, "I61")|strmatch(codtext9, "I61")|strmatch(codtext10,
"I61")|strmatch(antecedent1, "I61")|strmatch(antecedent2, "I61")|strmatch(antecedent3,
"I61")|strmatch(antecedent4, "I61")|strmatch(antecedent5, "I61")|strmatch(antecedent6,
"I61")|strmatch(antecedent7, "I61")|strmatch(antecedent8, "I61")|strmatch(antecedent9,
```

"I61")|strmatch(antecedent10, "I61")| strmatch(cf1, "I61")|strmatch(cf2, "I61")|strmatch(cf3,
"I61")|strmatch(cf4, "I61")|strmatch(cf5, "I61")|strmatch(cf6, "I61")|strmatch(cf7, "I61")|strmatch(cf8,
"I61")|strmatch(cf9, "I61")|strmatch(cf10, "I61")|strmatch(codtext_1, "I61")|strmatch(codtext_2,
"I61")|strmatch(codtext_3, "I61")|strmatch(antecedent_1, "I61")|strmatch(antecedent_2,
"I61")|strmatch(antecedent_3, "I61")|strmatch(contrib_1, "I61")|strmatch(contrib_2,
"I61")|strmatch(contrib_3, "I61")|strmatch(contrib_4, "I61")

replace stroke_death = 1 if strmatch(codcode, "I61*")| strmatch(record_axis_data, "*I61*")|
strmatch(codtext1, "*I61*")|strmatch(codtext2, "*I61*")|strmatch(codtext3,
"*I61*")|strmatch(codtext4, "*I61*")|strmatch(codtext5, "*I61*")|strmatch(codtext6,
"*I61*")|strmatch(codtext7, "*I61*")|strmatch(codtext8, "*I61*")|strmatch(codtext9,
"*I61*")|strmatch(codtext10, "*I61*")|strmatch(antecedent1, "*I61*")|strmatch(antecedent2,
"*I61*")|strmatch(antecedent3, "*I61*")|strmatch(antecedent4, "*I61*")|strmatch(antecedent5,
"*I61*")|strmatch(antecedent6, "*I61*")|strmatch(antecedent7, "*I61*")|strmatch(antecedent8,
"*I61*")|strmatch(antecedent9, "*I61*")|strmatch(antecedent10, "*I61*")| strmatch(cf1,
"*I61*")|strmatch(cf2, "*I61*")|strmatch(cf3, "*I61*")|strmatch(cf4, "*I61*")|strmatch(cf5,
"*I61*")|strmatch(cf6, "*I61*")|strmatch(cf7, "*I61*")|strmatch(cf8, "*I61*")|strmatch(cf9,
"*I61*")|strmatch(cf10, "*I61*")|strmatch(codtext_1, "*I61*")|strmatch(codtext_2,
"*I61*")|strmatch(codtext_3, "*I61*")|strmatch(antecedent_1, "*I61*")|strmatch(antecedent_2,
"*I61*")|strmatch(antecedent_3, "*I61*")|strmatch(contrib_1, "*I61*")|strmatch(contrib_2,
"*I61*")|strmatch(contrib_3, "*I61*")|strmatch(contrib_4, "*I61*")

replace stroke_death = 1 if strmatch(codcode, "I62")|strmatch(record_axis_data, "I62")|
strmatch(codtext1, "I62")|strmatch(codtext2, "I62")|strmatch(codtext3, "I62")|strmatch(codtext4,
"I62")|strmatch(codtext5, "I62")|strmatch(codtext6, "I62")|strmatch(codtext7,
"I62")|strmatch(codtext8, "I62")|strmatch(codtext9, "I62")|strmatch(codtext10,
"I62")|strmatch(antecedent1, "I62")|strmatch(antecedent2, "I62")|strmatch(antecedent3,
"I62")|strmatch(antecedent4, "I62")|strmatch(antecedent5, "I62")|strmatch(antecedent6,
"I62")|strmatch(antecedent7, "I62")|strmatch(antecedent8, "I62")|strmatch(antecedent9,
"I62")|strmatch(antecedent10, "I62")| strmatch(cf1, "I62")|strmatch(cf2, "I62")|strmatch(cf3,
"I62")|strmatch(cf4, "I62")|strmatch(cf5, "I62")|strmatch(cf6, "I62")|strmatch(cf7, "I62")|strmatch(cf8,
"I62")|strmatch(cf9, "I62")|strmatch(cf10, "I62")|strmatch(codtext_1, "I62")|strmatch(codtext_2,
"I62")|strmatch(codtext_3, "I62")|strmatch(antecedent_1, "I62")|strmatch(antecedent_2,
"I62")|strmatch(antecedent_3, "I62")|strmatch(contrib_1, "I62")|strmatch(contrib_2,
"I62")|strmatch(contrib_3, "I62")|strmatch(contrib_4, "I62")

replace stroke_death = 1 if strmatch(codcode, "I62*")| strmatch(record_axis_data, "*I62*")|
strmatch(codtext1, "*I62*")|strmatch(codtext2, "*I62*")|strmatch(codtext3,
"*I62*")|strmatch(codtext4, "*I62*")|strmatch(codtext5, "*I62*")|strmatch(codtext6,
"*I62*")|strmatch(codtext7, "*I62*")|strmatch(codtext8, "*I62*")|strmatch(codtext9,
"*I62*")|strmatch(codtext10, "*I62*")|strmatch(antecedent1, "*I62*")|strmatch(antecedent2,
"*I62*")|strmatch(antecedent3, "*I62*")|strmatch(antecedent4, "*I62*")|strmatch(antecedent5,
"*I62*")|strmatch(antecedent6, "*I62*")|strmatch(antecedent7, "*I62*")|strmatch(antecedent8,
"*I62*")|strmatch(antecedent9, "*I62*")|strmatch(antecedent10, "*I62*")| strmatch(cf1,
"*I62*")|strmatch(cf2, "*I62*")|strmatch(cf3, "*I62*")|strmatch(cf4, "*I62*")|strmatch(cf5,
"*I62*")|strmatch(cf6, "*I62*")|strmatch(cf7, "*I62*")|strmatch(cf8, "*I62*")|strmatch(cf9,
"*I62*")|strmatch(cf10, "*I62*")|strmatch(codtext_1, "*I62*")|strmatch(codtext_2,
"*I62*")|strmatch(codtext_3, "*I62*")|strmatch(antecedent_1, "*I62*")|strmatch(antecedent_2,
"*I62*")|strmatch(antecedent_3, "*I62*")|strmatch(contrib_1, "*I62*")|strmatch(contrib_2,
"*I62*")|strmatch(contrib_3, "*I62*")|strmatch(contrib_4, "*I62*")

replace stroke_death = 1 if strmatch(codcode, "I63")|strmatch(record_axis_data, "I63")|
strmatch(codtext1, "I63")|strmatch(codtext2, "I63")|strmatch(codtext3, "I63")|strmatch(codtext4,
"I63")|strmatch(codtext5, "I63")|strmatch(codtext6, "I63")|strmatch(codtext7,
"I63")|strmatch(codtext8, "I63")|strmatch(codtext9, "I63")|strmatch(codtext10,
"I63")|strmatch(antecedent1, "I63")|strmatch(antecedent2, "I63")|strmatch(antecedent3,
"I63")|strmatch(antecedent4, "I63")|strmatch(antecedent5, "I63")|strmatch(antecedent6,
"I63")|strmatch(antecedent7, "I63")|strmatch(antecedent8, "I63")|strmatch(antecedent9,

"I63")|strmatch(antecedent10, "I63")| strmatch(cf1, "I63")|strmatch(cf2, "I63")|strmatch(cf3,
"I63")|strmatch(cf4, "I63")|strmatch(cf5, "I63")|strmatch(cf6, "I63")|strmatch(cf7, "I63")|strmatch(cf8,
"I63")|strmatch(cf9, "I63")|strmatch(cf10, "I63")|strmatch(codtext_1, "I63")|strmatch(codtext_2,
"I63")|strmatch(codtext_3, "I63")|strmatch(antecedent_1, "I63")|strmatch(antecedent_2,
"I63")|strmatch(antecedent_3, "I63")|strmatch(contrib_1, "I63")|strmatch(contrib_2,
"I63")|strmatch(contrib_3, "I63")|strmatch(contrib_4, "I63")

replace stroke_death = 1 if strmatch(codcode, "I63*")| strmatch(record_axis_data, "*I63*")|
strmatch(codtext1, "*I63*")|strmatch(codtext2, "*I63*")|strmatch(codtext3,
"*I63*")|strmatch(codtext4, "*I63*")|strmatch(codtext5, "*I63*")|strmatch(codtext6,
"*I63*")|strmatch(codtext7, "*I63*")|strmatch(codtext8, "*I63*")|strmatch(codtext9,
"*I63*")|strmatch(codtext10, "*I63*")|strmatch(antecedent1, "*I63*")|strmatch(antecedent2,
"*I63*")|strmatch(antecedent3, "*I63*")|strmatch(antecedent4, "*I63*")|strmatch(antecedent5,
"*I63*")|strmatch(antecedent6, "*I63*")|strmatch(antecedent7, "*I63*")|strmatch(antecedent8,
"*I63*")|strmatch(antecedent9, "*I63*")|strmatch(antecedent10, "*I63*")| strmatch(cf1,
"*I63*")|strmatch(cf2, "*I63*")|strmatch(cf3, "*I63*")|strmatch(cf4, "*I63*")|strmatch(cf5,
"*I63*")|strmatch(cf6, "*I63*")|strmatch(cf7, "*I63*")|strmatch(cf8, "*I63*")|strmatch(cf9,
"*I63*")|strmatch(cf10, "*I63*")|strmatch(codtext_1, "*I63*")|strmatch(codtext_2,
"*I63*")|strmatch(codtext_3, "*I63*")|strmatch(antecedent_1, "*I63*")|strmatch(antecedent_2,
"*I63*")|strmatch(antecedent_3, "*I63*")|strmatch(contrib_1, "*I63*")|strmatch(contrib_2,
"*I63*")|strmatch(contrib_3, "*I63*")|strmatch(contrib_4, "*I63*")

replace stroke_death = 1 if strmatch(codcode, "I64")|strmatch(record_axis_data, "I64")|
strmatch(codtext1, "I64")|strmatch(codtext2, "I64")|strmatch(codtext3, "I64")|strmatch(codtext4,
"I64")|strmatch(codtext5, "I64")|strmatch(codtext6, "I64")|strmatch(codtext7,
"I64")|strmatch(codtext8, "I64")|strmatch(codtext9, "I64")|strmatch(codtext10,
"I64")|strmatch(antecedent1, "I64")|strmatch(antecedent2, "I64")|strmatch(antecedent3,
"I64")|strmatch(antecedent4, "I64")|strmatch(antecedent5, "I64")|strmatch(antecedent6,
"I64")|strmatch(antecedent7, "I64")|strmatch(antecedent8, "I64")|strmatch(antecedent9,
"I64")|strmatch(antecedent10, "I64")| strmatch(cf1, "I64")|strmatch(cf2, "I64")|strmatch(cf3,
"I64")|strmatch(cf4, "I64")|strmatch(cf5, "I64")|strmatch(cf6, "I64")|strmatch(cf7, "I64")|strmatch(cf8,
"I64")|strmatch(cf9, "I64")|strmatch(cf10, "I64")|strmatch(codtext_1, "I64")|strmatch(codtext_2,
"I64")|strmatch(codtext_3, "I64")|strmatch(antecedent_1, "I64")|strmatch(antecedent_2,
"I64")|strmatch(antecedent_3, "I64")|strmatch(contrib_1, "I64")|strmatch(contrib_2,
"I64")|strmatch(contrib_3, "I64")|strmatch(contrib_4, "I64")

replace stroke_death = 1 if strmatch(codcode, "I64*")| strmatch(record_axis_data, "*I64*")|
strmatch(codtext1, "*I64*")|strmatch(codtext2, "*I64*")|strmatch(codtext3,
"*I64*")|strmatch(codtext4, "*I64*")|strmatch(codtext5, "*I64*")|strmatch(codtext6,
"*I64*")|strmatch(codtext7, "*I64*")|strmatch(codtext8, "*I64*")|strmatch(codtext9,
"*I64*")|strmatch(codtext10, "*I64*")|strmatch(antecedent1, "*I64*")|strmatch(antecedent2,
"*I64*")|strmatch(antecedent3, "*I64*")|strmatch(antecedent4, "*I64*")|strmatch(antecedent5,
"*I64*")|strmatch(antecedent6, "*I64*")|strmatch(antecedent7, "*I64*")|strmatch(antecedent8,
"*I64*")|strmatch(antecedent9, "*I64*")|strmatch(antecedent10, "*I64*")| strmatch(cf1,
"*I64*")|strmatch(cf2, "*I64*")|strmatch(cf3, "*I64*")|strmatch(cf4, "*I64*")|strmatch(cf5,
"*I64*")|strmatch(cf6, "*I64*")|strmatch(cf7, "*I64*")|strmatch(cf8, "*I64*")|strmatch(cf9,
"*I64*")|strmatch(cf10, "*I64*")|strmatch(codtext_1, "*I64*")|strmatch(codtext_2,
"*I64*")|strmatch(codtext_3, "*I64*")|strmatch(antecedent_1, "*I64*")|strmatch(antecedent_2,
"*I64*")|strmatch(antecedent_3, "*I64*")|strmatch(contrib_1, "*I64*")|strmatch(contrib_2,
"*I64*")|strmatch(contrib_3, "*I64*")|strmatch(contrib_4, "*I64*")

replace stroke_death = 1 if strmatch(codcode, "I65")|strmatch(record_axis_data, "I65")|
strmatch(codtext1, "I65")|strmatch(codtext2, "I65")|strmatch(codtext3, "I65")|strmatch(codtext4,
"I65")|strmatch(codtext5, "I65")|strmatch(codtext6, "I65")|strmatch(codtext7,
"I65")|strmatch(codtext8, "I65")|strmatch(codtext9, "I65")|strmatch(codtext10,
"I65")|strmatch(antecedent1, "I65")|strmatch(antecedent2, "I65")|strmatch(antecedent3,
"I65")|strmatch(antecedent4, "I65")|strmatch(antecedent5, "I65")|strmatch(antecedent6,
"I65")|strmatch(antecedent7, "I65")|strmatch(antecedent8, "I65")|strmatch(antecedent9,

"I65")|strmatch(antecedent10, "I65")| strmatch(cf1, "I65")|strmatch(cf2, "I65")|strmatch(cf3,
"I65")|strmatch(cf4, "I65")|strmatch(cf5, "I65")|strmatch(cf6, "I65")|strmatch(cf7, "I65")|strmatch(cf8,
"I65")|strmatch(cf9, "I65")|strmatch(cf10, "I65")|strmatch(codtext_1, "I65")|strmatch(codtext_2,
"I65")|strmatch(codtext_3, "I65")|strmatch(antecedent_1, "I65")|strmatch(antecedent_2,
"I65")|strmatch(antecedent_3, "I65")|strmatch(contrib_1, "I65")|strmatch(contrib_2,
"I65")|strmatch(contrib_3, "I65")|strmatch(contrib_4, "I65")

replace stroke_death = 1 if strmatch(codcode, "I65*")| strmatch(record_axis_data, "*I65*")|
strmatch(codtext1, "*I65*")|strmatch(codtext2, "*I65*")|strmatch(codtext3,
"*I65*")|strmatch(codtext4, "*I65*")|strmatch(codtext5, "*I65*")|strmatch(codtext6,
"*I65*")|strmatch(codtext7, "*I65*")|strmatch(codtext8, "*I65*")|strmatch(codtext9,
"*I65*")|strmatch(codtext10, "*I65*")|strmatch(antecedent1, "*I65*")|strmatch(antecedent2,
"*I65*")|strmatch(antecedent3, "*I65*")|strmatch(antecedent4, "*I65*")|strmatch(antecedent5,
"*I65*")|strmatch(antecedent6, "*I65*")|strmatch(antecedent7, "*I65*")|strmatch(antecedent8,
"*I65*")|strmatch(antecedent9, "*I65*")|strmatch(antecedent10, "*I65*")| strmatch(cf1,
"*I65*")|strmatch(cf2, "*I65*")|strmatch(cf3, "*I65*")|strmatch(cf4, "*I65*")|strmatch(cf5,
"*I65*")|strmatch(cf6, "*I65*")|strmatch(cf7, "*I65*")|strmatch(cf8, "*I65*")|strmatch(cf9,
"*I65*")|strmatch(cf10, "*I65*")|strmatch(codtext_1, "*I65*")|strmatch(codtext_2,
"*I65*")|strmatch(codtext_3, "*I65*")|strmatch(antecedent_1, "*I65*")|strmatch(antecedent_2,
"*I65*")|strmatch(antecedent_3, "*I65*")|strmatch(contrib_1, "*I65*")|strmatch(contrib_2,
"*I65*")|strmatch(contrib_3, "*I65*")|strmatch(contrib_4, "*I65*")

replace stroke_death = 1 if strmatch(codcode, "I66")|strmatch(record_axis_data, "I66")|
strmatch(codtext1, "I66")|strmatch(codtext2, "I66")|strmatch(codtext3, "I66")|strmatch(codtext4,
"I66")|strmatch(codtext5, "I66")|strmatch(codtext6, "I66")|strmatch(codtext7,
"I66")|strmatch(codtext8, "I66")|strmatch(codtext9, "I66")|strmatch(codtext10,
"I66")|strmatch(antecedent1, "I66")|strmatch(antecedent2, "I66")|strmatch(antecedent3,
"I66")|strmatch(antecedent4, "I66")|strmatch(antecedent5, "I66")|strmatch(antecedent6,
"I66")|strmatch(antecedent7, "I66")|strmatch(antecedent8, "I66")|strmatch(antecedent9,
"I66")|strmatch(antecedent10, "I66")| strmatch(cf1, "I66")|strmatch(cf2, "I66")|strmatch(cf3,
"I66")|strmatch(cf4, "I66")|strmatch(cf5, "I66")|strmatch(cf6, "I66")|strmatch(cf7, "I66")|strmatch(cf8,
"I66")|strmatch(cf9, "I66")|strmatch(cf10, "I66")|strmatch(codtext_1, "I66")|strmatch(codtext_2,
"I66")|strmatch(codtext_3, "I66")|strmatch(antecedent_1, "I66")|strmatch(antecedent_2,
"I66")|strmatch(antecedent_3, "I66")|strmatch(contrib_1, "I66")|strmatch(contrib_2,
"I66")|strmatch(contrib_3, "I66")|strmatch(contrib_4, "I66")

replace stroke_death = 1 if strmatch(codcode, "I66*")| strmatch(record_axis_data, "*I66*")|
strmatch(codtext1, "*I66*")|strmatch(codtext2, "*I66*")|strmatch(codtext3,
"*I66*")|strmatch(codtext4, "*I66*")|strmatch(codtext5, "*I66*")|strmatch(codtext6,
"*I66*")|strmatch(codtext7, "*I66*")|strmatch(codtext8, "*I66*")|strmatch(codtext9,
"*I66*")|strmatch(codtext10, "*I66*")|strmatch(antecedent1, "*I66*")|strmatch(antecedent2,
"*I66*")|strmatch(antecedent3, "*I66*")|strmatch(antecedent4, "*I66*")|strmatch(antecedent5,
"*I66*")|strmatch(antecedent6, "*I66*")|strmatch(antecedent7, "*I66*")|strmatch(antecedent8,
"*I66*")|strmatch(antecedent9, "*I66*")|strmatch(antecedent10, "*I66*")| strmatch(cf1,
"*I66*")|strmatch(cf2, "*I66*")|strmatch(cf3, "*I66*")|strmatch(cf4, "*I66*")|strmatch(cf5,
"*I66*")|strmatch(cf6, "*I66*")|strmatch(cf7, "*I66*")|strmatch(cf8, "*I66*")|strmatch(cf9,
"*I66*")|strmatch(cf10, "*I66*")|strmatch(codtext_1, "*I66*")|strmatch(codtext_2,
"*I66*")|strmatch(codtext_3, "*I66*")|strmatch(antecedent_1, "*I66*")|strmatch(antecedent_2,
"*I66*")|strmatch(antecedent_3, "*I66*")|strmatch(contrib_1, "*I66*")|strmatch(contrib_2,
"*I66*")|strmatch(contrib_3, "*I66*")|strmatch(contrib_4, "*I66*")

replace stroke_death = 1 if strmatch(codcode, "I67")|strmatch(record_axis_data, "I67")|
strmatch(codtext1, "I67")|strmatch(codtext2, "I67")|strmatch(codtext3, "I67")|strmatch(codtext4,
"I67")|strmatch(codtext5, "I67")|strmatch(codtext6, "I67")|strmatch(codtext7,
"I67")|strmatch(codtext8, "I67")|strmatch(codtext9, "I67")|strmatch(codtext10,
"I67")|strmatch(antecedent1, "I67")|strmatch(antecedent2, "I67")|strmatch(antecedent3,
"I67")|strmatch(antecedent4, "I67")|strmatch(antecedent5, "I67")|strmatch(antecedent6,
"I67")|strmatch(antecedent7, "I67")|strmatch(antecedent8, "I67")|strmatch(antecedent9,

"I67")|strmatch(antecedent10, "I67")| strmatch(cf1, "I67")|strmatch(cf2, "I67")|strmatch(cf3,
"I67")|strmatch(cf4, "I67")|strmatch(cf5, "I67")|strmatch(cf6, "I67")|strmatch(cf7, "I67")|strmatch(cf8,
"I67")|strmatch(cf9, "I67")|strmatch(cf10, "I67")|strmatch(codtext_1, "I67")|strmatch(codtext_2,
"I67")|strmatch(codtext_3, "I67")|strmatch(antecedent_1, "I67")|strmatch(antecedent_2,
"I67")|strmatch(antecedent_3, "I67")|strmatch(contrib_1, "I67")|strmatch(contrib_2,
"I67")|strmatch(contrib_3, "I67")|strmatch(contrib_4, "I67")

replace stroke_death = 1 if strmatch(codcode, "I67*")| strmatch(record_axis_data, "*I67*")|
strmatch(codtext1, "*I67*")|strmatch(codtext2, "*I67*")|strmatch(codtext3,
"*I67*")|strmatch(codtext4, "*I67*")|strmatch(codtext5, "*I67*")|strmatch(codtext6,
"*I67*")|strmatch(codtext7, "*I67*")|strmatch(codtext8, "*I67*")|strmatch(codtext9,
"*I67*")|strmatch(codtext10, "*I67*")|strmatch(antecedent1, "*I67*")|strmatch(antecedent2,
"*I67*")|strmatch(antecedent3, "*I67*")|strmatch(antecedent4, "*I67*")|strmatch(antecedent5,
"*I67*")|strmatch(antecedent6, "*I67*")|strmatch(antecedent7, "*I67*")|strmatch(antecedent8,
"*I67*")|strmatch(antecedent9, "*I67*")|strmatch(antecedent10, "*I67*")| strmatch(cf1,
"*I67*")|strmatch(cf2, "*I67*")|strmatch(cf3, "*I67*")|strmatch(cf4, "*I67*")|strmatch(cf5,
"*I67*")|strmatch(cf6, "*I67*")|strmatch(cf7, "*I67*")|strmatch(cf8, "*I67*")|strmatch(cf9,
"*I67*")|strmatch(cf10, "*I67*")|strmatch(codtext_1, "*I67*")|strmatch(codtext_2,
"*I67*")|strmatch(codtext_3, "*I67*")|strmatch(antecedent_1, "*I67*")|strmatch(antecedent_2,
"*I67*")|strmatch(antecedent_3, "*I67*")|strmatch(contrib_1, "*I67*")|strmatch(contrib_2,
"*I67*")|strmatch(contrib_3, "*I67*")|strmatch(contrib_4, "*I67*")

replace stroke_death = 1 if strmatch(codcode, "I68")|strmatch(record_axis_data, "I68")|
strmatch(codtext1, "I68")|strmatch(codtext2, "I68")|strmatch(codtext3, "I68")|strmatch(codtext4,
"I68")|strmatch(codtext5, "I68")|strmatch(codtext6, "I68")|strmatch(codtext7,
"I68")|strmatch(codtext8, "I68")|strmatch(codtext9, "I68")|strmatch(codtext10,
"I68")|strmatch(antecedent1, "I68")|strmatch(antecedent2, "I68")|strmatch(antecedent3,
"I68")|strmatch(antecedent4, "I68")|strmatch(antecedent5, "I68")|strmatch(antecedent6,
"I68")|strmatch(antecedent7, "I68")|strmatch(antecedent8, "I68")|strmatch(antecedent9,
"I68")|strmatch(antecedent10, "I68")| strmatch(cf1, "I68")|strmatch(cf2, "I68")|strmatch(cf3,
"I68")|strmatch(cf4, "I68")|strmatch(cf5, "I68")|strmatch(cf6, "I68")|strmatch(cf7, "I68")|strmatch(cf8,
"I68")|strmatch(cf9, "I68")|strmatch(cf10, "I68")|strmatch(codtext_1, "I68")|strmatch(codtext_2,
"I68")|strmatch(codtext_3, "I68")|strmatch(antecedent_1, "I68")|strmatch(antecedent_2,
"I68")|strmatch(antecedent_3, "I68")|strmatch(contrib_1, "I68")|strmatch(contrib_2,
"I68")|strmatch(contrib_3, "I68")|strmatch(contrib_4, "I68")

replace stroke_death = 1 if strmatch(codcode, "I68*")| strmatch(record_axis_data, "*I68*")|
strmatch(codtext1, "*I68*")|strmatch(codtext2, "*I68*")|strmatch(codtext3,
"*I68*")|strmatch(codtext4, "*I68*")|strmatch(codtext5, "*I68*")|strmatch(codtext6,
"*I68*")|strmatch(codtext7, "*I68*")|strmatch(codtext8, "*I68*")|strmatch(codtext9,
"*I68*")|strmatch(codtext10, "*I68*")|strmatch(antecedent1, "*I68*")|strmatch(antecedent2,
"*I68*")|strmatch(antecedent3, "*I68*")|strmatch(antecedent4, "*I68*")|strmatch(antecedent5,
"*I68*")|strmatch(antecedent6, "*I68*")|strmatch(antecedent7, "*I68*")|strmatch(antecedent8,
"*I68*")|strmatch(antecedent9, "*I68*")|strmatch(antecedent10, "*I68*")| strmatch(cf1,
"*I68*")|strmatch(cf2, "*I68*")|strmatch(cf3, "*I68*")|strmatch(cf4, "*I68*")|strmatch(cf5,
"*I68*")|strmatch(cf6, "*I68*")|strmatch(cf7, "*I68*")|strmatch(cf8, "*I68*")|strmatch(cf9,
"*I68*")|strmatch(cf10, "*I68*")|strmatch(codtext_1, "*I68*")|strmatch(codtext_2,
"*I68*")|strmatch(codtext_3, "*I68*")|strmatch(antecedent_1, "*I68*")|strmatch(antecedent_2,
"*I68*")|strmatch(antecedent_3, "*I68*")|strmatch(contrib_1, "*I68*")|strmatch(contrib_2,
"*I68*")|strmatch(contrib_3, "*I68*")|strmatch(contrib_4, "*I68*")

replace stroke_death = 1 if strmatch(codcode, "I69")|strmatch(record_axis_data, "I69")|
strmatch(codtext1, "I69")|strmatch(codtext2, "I69")|strmatch(codtext3, "I69")|strmatch(codtext4,
"I69")|strmatch(codtext5, "I69")|strmatch(codtext6, "I69")|strmatch(codtext7,
"I69")|strmatch(codtext8, "I69")|strmatch(codtext9, "I69")|strmatch(codtext10,
"I69")|strmatch(antecedent1, "I69")|strmatch(antecedent2, "I69")|strmatch(antecedent3,
"I69")|strmatch(antecedent4, "I69")|strmatch(antecedent5, "I69")|strmatch(antecedent6,
"I69")|strmatch(antecedent7, "I69")|strmatch(antecedent8, "I69")|strmatch(antecedent9,

"I69")|strmatch(antecedent10, "I69")| strmatch(cf1, "I69")|strmatch(cf2, "I69")|strmatch(cf3, "I69")|strmatch(cf4, "I69")|strmatch(cf5, "I69")|strmatch(cf6, "I69")|strmatch(cf7, "I69")|strmatch(cf8, "I69")|strmatch(cf9, "I69")|strmatch(cf10, "I69")|strmatch(codtext_1, "I69")|strmatch(codtext_2, "I69")|strmatch(codtext_3, "I69")|strmatch(antecedent_1, "I69")|strmatch(antecedent_2, "I69")|strmatch(antecedent_3, "I69")|strmatch(contrib_1, "I69")|strmatch(contrib_2, "I69")|strmatch(contrib_3, "I69")|strmatch(contrib_4, "I69")

replace stroke_death = 1 if strmatch(codcode, "I69*")| strmatch(record_axis_data, "*I69*")| strmatch(codtext1, "*I69*")|strmatch(codtext2, "*I69*")|strmatch(codtext3, "*I69*")|strmatch(codtext4, "*I69*")|strmatch(codtext5, "*I69*")|strmatch(codtext6, "*I69*")|strmatch(codtext7, "*I69*")|strmatch(codtext8, "*I69*")|strmatch(codtext9, "*I69*")|strmatch(codtext10, "*I69*")|strmatch(antecedent1, "*I69*")|strmatch(antecedent2, "*I69*")|strmatch(antecedent3, "*I69*")|strmatch(antecedent4, "*I69*")|strmatch(antecedent5, "*I69*")|strmatch(antecedent6, "*I69*")|strmatch(antecedent7, "*I69*")|strmatch(antecedent8, "*I69*")|strmatch(antecedent9, "*I69*")|strmatch(antecedent10, "*I69*")| strmatch(cf1, "*I69*")|strmatch(cf2, "*I69*")|strmatch(cf3, "*I69*")|strmatch(cf4, "*I69*")|strmatch(cf5, "*I69*")|strmatch(cf6, "*I69*")|strmatch(cf7, "*I69*")|strmatch(cf8, "*I69*")|strmatch(cf9, "*I69*")|strmatch(cf10, "*I69*")|strmatch(codtext_1, "*I69*")|strmatch(codtext_2, "*I69*")|strmatch(codtext_3, "*I69*")|strmatch(antecedent_1, "*I69*")|strmatch(antecedent_2, "*I69*")|strmatch(antecedent_3, "*I69*")|strmatch(contrib_1, "*I69*")|strmatch(contrib_2, "*I69*")|strmatch(contrib_3, "*I69*")|strmatch(contrib_4, "*I69*")

"*I26*")|strmatch(antecedent_3, "*I26*")|strmatch(contrib_1, "*I26*")|strmatch(contrib_2, "*I26*")|strmatch(contrib_3, "*I26*")|strmatch(contrib_4, "*I26*")

// respiratory disease (non-infectious)

* all respiratory conditions excluding the infection codes within the respiratory section; pulmonary haemorrahge added (786.3 & R04.2, R04.8, R04.9)

gen resp_death = 0

gen ucod_resp = 0

ICD9 these are the infection codes->

3 digit:

460 461 462 463 464 465 466 480 481 482 483 484 485 486 487 487 513

4 digit:

5111

foreach var of numlist 467/479 488/510 512 514/519 {

replace ucod_resp = 1 if strmatch(codcode, "`var'*")|strmatch(codcode_ucod, "`var'*")

}

foreach var of numlist 5118 5119 7863 {

replace ucod_resp = 1 if strmatch(codcode, "`var'*")|strmatch(codcode_ucod, "`var'*")

}

foreach var of numlist 467/479 488/510 512 514/519 {

replace resp_death = 1 if strmatch(codcode, "`var'*")|strmatch(rad1, "`var'*")|strmatch(rad2, "`var'*")|strmatch(rad3, "`var'*")|strmatch(rad4, "`var'*")|strmatch(rad5, "`var'*")|strmatch(rad6,

"`var'*")|strmatch(rad7, "`var'*")|strmatch(rad8, "`var'*")|strmatch(rad9, "`var'*")|strmatch(rad10, "`var'*")

}

foreach var of numlist 5118 5119 7863 {

replace resp_death = 1 if strmatch(codcode, "`var'*")|strmatch(rad1, "`var'*")|strmatch(rad2, "`var'*")|strmatch(rad3, "`var'*")|strmatch(rad4, "`var'*")|strmatch(rad5, "`var'*")|strmatch(rad6, "`var'*")|strmatch(rad7, "`var'*")|strmatch(rad8, "`var'*")|strmatch(rad9, "`var'*")|strmatch(rad10, "`var'*")

}

// UCOD

foreach var of numlist 23/35 37/38 392/399 40 42/43 45/84 850 90/99{

replace ucod_resp = 1 if strmatch(codcode, "J`var'*")|strmatch(codcode_ucod, "J`var'*")

}

// contrib cause

foreach var of numlist 23/35 37/38 392/399 40 42/43 45/84 850 90/99{

replace resp_death = 1 if strmatch(codcode, "J`var'*")|strmatch(codcode_ucod, "J`var'*")

}

foreach var of numlist 23/35 37/38 392/399 40 42/43 45/84 850 90/99{

replace resp_death = 1 if strmatch(record_axis_data, "*J`var'*")| strmatch(codtext1, "*J`var'*")|strmatch(codtext2, "*J`var'*")|strmatch(codtext3, "*J`var'*")|strmatch(codtext4, "*J`var'*")|strmatch(codtext5, "*J`var'*")|strmatch(codtext6, "*J`var'*")|strmatch(codtext7, "*J`var'*")|strmatch(codtext8, "*J`var'*")|strmatch(codtext9, "*J`var'*")|strmatch(codtext10, "*J`var'*")|strmatch(antecedent1, "*J`var'*")|strmatch(antecedent2, "*J`var'*")|strmatch(antecedent3, "*J`var'*")|strmatch(antecedent4, "*J`var'*")|strmatch(antecedent5, "*J`var'*")|strmatch(antecedent6, "*J`var'*")|strmatch(antecedent7, "*J`var'*")|strmatch(antecedent8, "*J`var'*")|strmatch(antecedent9, "*J`var'*")|strmatch(antecedent10, "*J`var'*")| strmatch(cf1, "*J`var'*")|strmatch(cf2, "*J`var'*")|strmatch(cf3, "*J`var'*")|strmatch(cf4, "*J`var'*")|strmatch(cf5, "*J`var'*")|strmatch(cf6, "*J`var'*")|strmatch(cf7, "*J`var'*")|strmatch(cf8, "*J`var'*")|strmatch(cf9, "*J`var'*")|strmatch(cf10, "*J`var'*")|strmatch(codtext_1, "*J`var'*")|strmatch(codtext_2, "*J`var'*")|strmatch(codtext_3, "*J`var'*")|strmatch(antecedent_1, "*J`var'*")|strmatch(antecedent_2, "*J`var'*")|strmatch(antecedent_3, "*J`var'*")|strmatch(contrib_1, "*J`var'*")|strmatch(contrib_2, "*J`var'*")|strmatch(contrib_3, "*J`var'*")|strmatch(contrib_4, "*J`var'*")

}

replace resp_death = 1 if strmatch(codcode, "R042")|strmatch(record_axis_data, "R042")| strmatch(codtext1, "R042")|strmatch(codtext2, "R042")|strmatch(codtext3, "R042")|strmatch(codtext4, "R042")|strmatch(codtext5, "R042")|strmatch(codtext6, "R042")|strmatch(codtext7, "R042")|strmatch(codtext8, "R042")|strmatch(codtext9, "R042")|strmatch(codtext10, "R042")|strmatch(antecedent1, "R042")|strmatch(antecedent2, "R042")|strmatch(antecedent3, "R042")|strmatch(antecedent4, "R042")|strmatch(antecedent5, "R042")|strmatch(antecedent6, "R042")|strmatch(antecedent7, "R042")|strmatch(antecedent8, "R042")|strmatch(antecedent9, "R042")|strmatch(antecedent10, "R042")| strmatch(cf1, "R042")|strmatch(cf2, "R042")|strmatch(cf3, "R042")|strmatch(cf4, "R042")|strmatch(cf5, "R042")|strmatch(cf6, "R042")|strmatch(cf7, "R042")|strmatch(cf8, "R042")|strmatch(cf9, "R042")|strmatch(cf10, "R042")|strmatch(codtext_1, "R042")|strmatch(codtext_2, "R042")|strmatch(codtext_3, "R042")|strmatch(antecedent_1, "R042")|strmatch(antecedent_2,

```
"R042")|strmatch(antecedent_3, "R042")|strmatch(contrib_1, "R042")|strmatch(contrib_2,
"R042")|strmatch(contrib_3, "R042")|strmatch(contrib_4, "R042")

replace resp_death = 1 if strmatch(codcode, "R042*")| strmatch(record_axis_data, "*R042*")|
strmatch(codtext1, "*R042*")|strmatch(codtext2, "*R042*")|strmatch(codtext3,
"*R042*")|strmatch(codtext4, "*R042*")|strmatch(codtext5, "*R042*")|strmatch(codtext6,
"*R042*")|strmatch(codtext7, "*R042*")|strmatch(codtext8, "*R042*")|strmatch(codtext9,
"*R042*")|strmatch(codtext10, "*R042*")|strmatch(antecedent1, "*R042*")|strmatch(antecedent2,
"*R042*")|strmatch(antecedent3, "*R042*")|strmatch(antecedent4, "*R042*")|strmatch(antecedent5,
"*R042*")|strmatch(antecedent6, "*R042*")|strmatch(antecedent7, "*R042*")|strmatch(antecedent8,
"*R042*")|strmatch(antecedent9, "*R042*")|strmatch(antecedent10, "*R042*")| strmatch(cf1,
"*R042*")|strmatch(cf2, "*R042*")|strmatch(cf3, "*R042*")|strmatch(cf4, "*R042*")|strmatch(cf5,
"*R042*")|strmatch(cf6, "*R042*")|strmatch(cf7, "*R042*")|strmatch(cf8, "*R042*")|strmatch(cf9,
"*R042*")|strmatch(cf10, "*R042*")|strmatch(codtext_1, "*R042*")|strmatch(codtext_2,
"*R042*")|strmatch(codtext_3, "*R042*")|strmatch(antecedent_1, "*R042*")|strmatch(antecedent_2,
"*R042*")|strmatch(antecedent_3, "*R042*")|strmatch(contrib_1, "*R042*")|strmatch(contrib_2,
"*R042*")|strmatch(contrib_3, "*R042*")|strmatch(contrib_4, "*R042*")

replace resp_death = 1 if strmatch(codcode, "R048")|strmatch(record_axis_data, "R048")|
strmatch(codtext1, "R048")|strmatch(codtext2, "R048")|strmatch(codtext3,
"R048")|strmatch(codtext4, "R048")|strmatch(codtext5, "R048")|strmatch(codtext6,
"R048")|strmatch(codtext7, "R048")|strmatch(codtext8, "R048")|strmatch(codtext9,
"R048")|strmatch(codtext10, "R048")|strmatch(antecedent1, "R048")|strmatch(antecedent2,
"R048")|strmatch(antecedent3, "R048")|strmatch(antecedent4, "R048")|strmatch(antecedent5,
"R048")|strmatch(antecedent6, "R048")|strmatch(antecedent7, "R048")|strmatch(antecedent8,
"R048")|strmatch(antecedent9, "R048")|strmatch(antecedent10, "R048")| strmatch(cf1,
"R048")|strmatch(cf2, "R048")|strmatch(cf3, "R048")|strmatch(cf4, "R048")|strmatch(cf5,
"R048")|strmatch(cf6, "R048")|strmatch(cf7, "R048")|strmatch(cf8, "R048")|strmatch(cf9,
"R048")|strmatch(cf10, "R048")|strmatch(codtext_1, "R048")|strmatch(codtext_2,
"R048")|strmatch(codtext_3, "R048")|strmatch(antecedent_1, "R048")|strmatch(antecedent_2,
"R048")|strmatch(antecedent_3, "R048")|strmatch(contrib_1, "R048")|strmatch(contrib_2,
"R048")|strmatch(contrib_3, "R048")|strmatch(contrib_4, "R048")

replace resp_death = 1 if strmatch(codcode, "R048*")| strmatch(record_axis_data, "*R048*")|
strmatch(codtext1, "*R048*")|strmatch(codtext2, "*R048*")|strmatch(codtext3,
"*R048*")|strmatch(codtext4, "*R048*")|strmatch(codtext5, "*R048*")|strmatch(codtext6,
"*R048*")|strmatch(codtext7, "*R048*")|strmatch(codtext8, "*R048*")|strmatch(codtext9,
"*R048*")|strmatch(codtext10, "*R048*")|strmatch(antecedent1, "*R048*")|strmatch(antecedent2,
"*R048*")|strmatch(antecedent3, "*R048*")|strmatch(antecedent4, "*R048*")|strmatch(antecedent5,
"*R048*")|strmatch(antecedent6, "*R048*")|strmatch(antecedent7, "*R048*")|strmatch(antecedent8,
"*R048*")|strmatch(antecedent9, "*R048*")|strmatch(antecedent10, "*R048*")| strmatch(cf1,
"*R048*")|strmatch(cf2, "*R048*")|strmatch(cf3, "*R048*")|strmatch(cf4, "*R048*")|strmatch(cf5,
"*R048*")|strmatch(cf6, "*R048*")|strmatch(cf7, "*R048*")|strmatch(cf8, "*R048*")|strmatch(cf9,
"*R048*")|strmatch(cf10, "*R048*")|strmatch(codtext_1, "*R048*")|strmatch(codtext_2,
"*R048*")|strmatch(codtext_3, "*R048*")|strmatch(antecedent_1, "*R048*")|strmatch(antecedent_2,
"*R048*")|strmatch(antecedent_3, "*R048*")|strmatch(contrib_1, "*R048*")|strmatch(contrib_2,
"*R048*")|strmatch(contrib_3, "*R048*")|strmatch(contrib_4, "*R048*")

replace resp_death = 1 if strmatch(codcode, "R049")|strmatch(record_axis_data, "R049")|
strmatch(codtext1, "R049")|strmatch(codtext2, "R049")|strmatch(codtext3,
"R049")|strmatch(codtext4, "R049")|strmatch(codtext5, "R049")|strmatch(codtext6,
"R049")|strmatch(codtext7, "R049")|strmatch(codtext8, "R049")|strmatch(codtext9,
"R049")|strmatch(codtext10, "R049")|strmatch(antecedent1, "R049")|strmatch(antecedent2,
"R049")|strmatch(antecedent3, "R049")|strmatch(antecedent4, "R049")|strmatch(antecedent5,
"R049")|strmatch(antecedent6, "R049")|strmatch(antecedent7, "R049")|strmatch(antecedent8,
"R049")|strmatch(antecedent9, "R049")|strmatch(antecedent10, "R049")| strmatch(cf1,
"R049")|strmatch(cf2, "R049")|strmatch(cf3, "R049")|strmatch(cf4, "R049")|strmatch(cf5,
"R049")|strmatch(cf6, "R049")|strmatch(cf7, "R049")|strmatch(cf8, "R049")|strmatch(cf9,
```

"R049")|strmatch(cf10, "R049")|strmatch(codtext_1, "R049")|strmatch(codtext_2, "R049")|strmatch(codtext_3, "R049")|strmatch(antecedent_1, "R049")|strmatch(antecedent_2, "R049")|strmatch(antecedent_3, "R049")|strmatch(contrib_1, "R049")|strmatch(contrib_2, "R049")|strmatch(contrib_3, "R049")|strmatch(contrib_4, "R049")

replace resp_death = 1 if strmatch(codcode, "R049*")| strmatch(record_axis_data, "*R049*")| strmatch(codtext1, "*R049*")|strmatch(codtext2, "*R049*")|strmatch(codtext3, "*R049*")|strmatch(codtext4, "*R049*")|strmatch(codtext5, "*R049*")|strmatch(codtext6, "*R049*")|strmatch(codtext7, "*R049*")|strmatch(codtext8, "*R049*")|strmatch(codtext9, "*R049*")|strmatch(codtext10, "*R049*")|strmatch(antecedent1, "*R049*")|strmatch(antecedent2, "*R049*")|strmatch(antecedent3, "*R049*")|strmatch(antecedent4, "*R049*")|strmatch(antecedent5, "*R049*")|strmatch(antecedent6, "*R049*")|strmatch(antecedent7, "*R049*")|strmatch(antecedent8, "*R049*")|strmatch(antecedent9, "*R049*")|strmatch(antecedent10, "*R049*")| strmatch(cf1, "*R049*")|strmatch(cf2, "*R049*")|strmatch(cf3, "*R049*")|strmatch(cf4, "*R049*")|strmatch(cf5, "*R049*")|strmatch(cf6, "*R049*")|strmatch(cf7, "*R049*")|strmatch(cf8, "*R049*")|strmatch(cf9, "*R049*")|strmatch(cf10, "*R049*")|strmatch(codtext_1, "*R049*")|strmatch(codtext_2, "*R049*")|strmatch(codtext_3, "*R049*")|strmatch(antecedent_1, "*R049*")|strmatch(antecedent_2, "*R049*")|strmatch(antecedent_3, "*R049*")|strmatch(contrib_1, "*R049*")|strmatch(contrib_2, "*R049*")|strmatch(contrib_3, "*R049*")|strmatch(contrib_4, "*R049*")

Appendix 2 Rituximab for the maintenance of remission in AAV Delphi exercise- cumulative summary of participant responses

Delphi exercise- guidance for the use of rituximab in the maintenance of remission in AAV

Structure of guidelines

1. When should rituximab be used for the maintenance of remission in AAV?
    a. GPA/MPA – new and relapsing patients
    b. EGPA patients
2. What rituximab maintenance regimen should be used for AAV?
    a. Dose and dosing intervals
    b. Management of relapse despite maintenance rituximab
    c. Extended rituximab maintenance therapy
    d. Role of biomarkers in rituximab maintenance therapy
3. Concomitant therapy
    a. Concomitant immunosuppressive agents/disease modifying anti-rheumatic drugs
    b. Glucocorticoids
4. Prophylaxis
    a. Co-trimoxazole
    b. Vaccination
5. Adverse effects with treatment
    a. Hypogammaglobulinaemia
        i. threshold for referral for clinical immunology investigations
        ii. further rituximab in the setting of hypogammaglobulinaemia
    b. Late onset neutropenia and further rituximab
6. Research agenda

Face-to-face meeting

This was altered in the following ways to reflect changes from round 2

- removal of subcategories of relapse on maintenance rituximab (2b)

- factors determining duration of therapy has been replaced by extended rituximab maintenance therapy.

- duration will now be moved to be incorporated into 2a

No specific changes recommended at face-to-face

1. **When should rituximab be used for the maintenance of remission in AAV?**
    a. **GPA/MPA – new and relapsing patients**
    b. **EGPA patients**

Delphi round 1

- RTX maintenance therapy is used in:
    - Patients who have completed RTX induction therapy (no respondent indicated that CYC, MTX or MMF induction was followed by RTX maintenance)
    - newly diagnosed patients by 10 of 16 respondents
        - with CYC refractory disease, contraindication to CYC or caution with CYC (elderly/frail pt)- 5/16
        - intolerance of AZA and MMF- 1/16
    - relapsing patients by 8/9 (relapsing patients specified as a category by 9 respondents)
        - after second relapse- 1/9
        - RTX used only after relapse- 5/9
- In EGPA:
    - 13/19 use the same approach
    - 6/19 noted that more steroid is generally required to maintain disease control

Delphi round 2

In response to the following questions regarding maintenance rituximab therapy for GPA and MPA:

- Rituximab maintenance can be considered following:
    - Cyclophosphamide induction: 16/19 (84%)
        - Specified as not first line (1)
    - Rituximab induction: 19/19 (100%)
- Rituximab maintenance should be considered in:
    - Newly diagnosed patients: 14/19 (74%)
        - Specified as not first line (2)
    - Relapsing patients: 19/19 (100%)

Delphi Round 3/Face-to-face meeting

Proposed statements accepted unchanged.

Draft statement

We recommend the use of rituximab for the maintenance of remission in patients with GPA and MPA following rituximab induction. Rituximab maintenance can also be considered after cyclophosphamide induction.

Despite limited evidence regarding the use of rituximab for the maintenance of remission in EGPA, we advise a similar approach to GPA and MPA. Overall response to rituximab may differ to GPA and MPA, and steroid withdrawal may be more challenging.

2. What rituximab maintenance regimen should be used for AAV?

a) Dosing and dosing intervals

Delphi Round 1

Dosing:

- 1 g dosing is used by 16/19 respondents
    - 750 mg/m^2 up to 1g is used by 1/19
- 500 mg dosing used by 2/19 respondents

Intervals:

- Fixed interval dosing is preferred/used by 16/19 respondents
- 1 indicated that after first relapse, B cell markers +/- ANCA influences re-dosing; after >1 relapse, fixed interval dosing is employed
- 1 respondent uses a combination of clinical response, B cell markers and ANCA to guide redosing

Duration:

- 16/17 routinely use a total of 2 years of rituximab, of whom:
    - 1 extends to 3 years if annual rituximab has been used
    - 7 consider >2 years in specific subgroups, determined by a combination of clinical disease characteristics, ANCA and/or B cell markers

Delphi Round 2

As fixed interval dosing was the preferred option for maintenance of remission, clarification was sought to confirm the preferred dose to be administered every 6 months:

- 500 mg: 2/19 (11%)
- 1000 mg: 16/19 (84%)
- Weight based dosing: 2/19 (11%)
    - 750 mg/m^2 to a maximum of 1000 mg was favoured by 1 respondent

- 500 mg for individuals weighing < 60 kg was specified by 1 respondent who selected 1000 mg dosing as 'standard'

- Age based dosing: 3/19 (16%) (each used different cut-off points):
  - > 65 yo with significant comorbidities/concern re: frailty
  - > 80 yo
  - > 85 yo

Delphi Round 3/Face-to-face meeting

- Proposed statement accepted unchanged.

Round 4

- Edit for clarity: responses in all rounds state 500 mg or 1g dosing, dosing in statement amended

Draft statement

We recommend fixed interval dosing with rituximab 500 mg – 1 g (or equivalent) administered 6 monthly for a period of 2 years. This approach should be individualised, particularly in children and older individuals with comorbidities where concerns regarding adverse effects exist. There is an ongoing relapse risk after rituximab withdrawal and patients should be monitored accordingly.

b) Management of relapse despite maintenance rituximab

Delphi round 3/face-to-face

Proposed statement:

"Optimal duration and infusion intervals beyond 2 years are yet to be determined. This approach should be individualised, ideally with the use of a maximal interval duration that maintains disease remission, and regular reassessment prior to each infusion to confirm benefit of ongoing treatment."

- No clear consensus on statement in wider group discussion
- In small group face-to-face discussions
  - Acknowledgement that there is very limited evidence in this setting (one observational cohort uses 4 monthly rituximab, altered to 6 monthly after 2 years indefinitely)
  - statement re-worded to 'minimise total rituximab exposure' => draft statement following face-to-face meeting

    "Optimal duration and infusion regimens beyond 2 years are yet to be determined. This approach should be individualised, aiming to minimise total rituximab exposure whilst maintaining disease remission. Regular reassessment should be performed prior to each infusion to evaluate the balance of risks and benefits of ongoing treatment."

Delphi round 4

- grammatical edit 'changes to treatment' added to sentence

Draft statement

Changes to treatment in refractory disease or relapse despite induction and rituximab maintenance therapy should be determined according to disease severity and organ involvement.

A guide to treatment decisions is presented. [flowchart]

c) extended rituximab maintenance therapy

Delphi round 2

In response to round 1, opinions for when extended duration therapy should be considered were sought:

- **>1 previous relapse 9/19 (47%)**
  - Major only- 4/8
  - Any (major and minor)- 4/8
- **Previous relapse after rituximab cessation 17/19 (89%)**
  - Major only- 6/17
  - **Any (major and minor)- 11/17**
- Persistent ANCA after 2 years of rituximab maintenance 3/19 (16%)
- Biomarkers during follow-up: 5/19 (26%)
  - ANCA return or increase 4/5
  - B cell return 3/5
- Previous high GC burden 5/19 (26%)
- **Previous life/organ threatening disease with short/limited prodrome 11/19 (58%)**
- Overall high risk 10/19 (53%); individual responses:
  - PR3
  - GPA
  - Relapsing, PR3 ever, granulomatous disease, persistent ANCA
  - Normal renal function, severe sinus disease, cessation of GC, rising ANCA
  - Multiple previous relapses, difficult ENT/granulomatous disease, PR3
  - Nasal limited disease
  - GPA, PR3, ENT involvement
  - Severe disease, especially aggressive disease whilst on therapy, persistent ANCA, GPA
  - Recurrent relapse off treatment, concerns about compliance with other (oral) immunosuppression, intolerance of other therapies
  - Combination: PR3, multiple relapses, B cells
- Other:
  - Clinically silent disease e.g. CNS lesions
  - Patient preference

- High level of damage accrued due to previous multiple relapses e.g. ENT destruction
- individuals with relative contraindication to GCs which would be required for treatment of relapse (e.g. DM, severe OP, obesity or in whom another relapse may lead to irreversible loss of organ function e.g. precipitate the need for dialysis, long term oxygen therapy)
- poor renal function to prevent renal relapse

Delphi Round 3/face-to-face meeting

- importance of subgroup who have borderline organ function and at risk of relapse raised, amendment to statement to incorporate this subgroup

Delphi Round 4

- responses regarding high risk groups taken into consideration with evidence regarding high risk groups and reworded with further detail added.
- owing to some confusion, statement reworded to separate timing adjustment based on time from rituximab cessation to relapse

Draft statement

In selected patients, if relapse risk remains high after 2 years of maintenance therapy, extended duration therapy could be considered. This includes patients who relapse after a prior course of rituximab maintenance, with persistent elevation or return of ANCA, or where the consequence of relapse would be organ or life threatening.

Delphi round 2: protocol preferences for extended maintenance therapy

18 respondents:

Dosing specified by 10

- 1g: 9/10 (90%)
  - Reduced to 500 mg if IgG <6: 1/8
- 500 mg – 1000 mg: 1/10 (10%)

Duration specified by 15

- 5 years: 6 (40%)
- 4 years: 4 (27%)
- Indefinite: 3 (20%)
- “1 year of remission”: 1 (7%)
- Reassessed yearly: 1 (7%)

Pattern specified by 18

- Fixed interval: 15/18 (83%)
    - Biomarkers considered by 2/15
    - Time from last rituximab to relapse considered by 3/15
    - Option to reduce to dosing only with clinical relapse (where issues with neutropenia, hypogammaglobulinaemia, infections have occurred) by 1/15
- Stretching intervals: 2/18 (11%)
- Watch and wait followed by patient disease dependent time interval: 1/18 (6%)
- Biomarker driven (MPO): 1/18 (6%)

Frequency specified by 17

- 6/12ly: 10/17 (59%)
    - 6-9 m (1); 6-12 (2)
    - Change to disease driven if adverse effects: 1
- 12/12ly: 4/17 (24%)
    - 9-12 m (1)
    - Shortened if time from previous rtx to relapse shorter than 12/12 (1)
- Stretching: 2/17 (12%)
- Patient disease driven: 4/17 (24%)

Influences on dosing/intervals

- ANCA: 6
- B cells: 6
- Clinical symptoms: 7

Cessation where adverse effects (hypogammagalobulinaemia and/or recurrent infections) develop specified by 6/18 (33%).

Change to clinical symptom driven 'on-demand' dosing in patients with previous late onset neutropenia, hypogammaglobulinaemia, or recurrent infection specified by 1/18 (6%).

Delphi Round 3

Proposed draft statement: "Optimal duration and infusion intervals beyond 2 years are yet to be determined. This approach should be individualised, ideally with the use of a maximal interval duration that maintains disease remission, and regular reassessment prior to each infusion to confirm benefit of ongoing treatment."

- No clear consensus on statement in wider group discussion
- In small group face-to-face discussions
    - Acknowledgement that there is very limited evidence in this setting (one observational cohort uses 4 monthly rituximab, altered to 6 monthly after 2 years indefinitely)

- statement re-worded to ‘minimise total rituximab exposure’ => draft statement reworded

  “Optimal duration and infusion regimens beyond 2 years are yet to be determined. This approach should be individualised, aiming to minimise total rituximab exposure whilst maintaining disease remission. Regular reassessment should be performed prior to each infusion to evaluate the balance of risks and benefits of ongoing treatment.”

Round 4

Statement proposed: “Optimal treatment approaches beyond 2 years are yet to be determined. Up to 1 g every 6 to 12 months, adjusted based on time from previous treatment cessation to flare of disease could be considered, for up to 5 years.”

- 14/14 respondents agreed to statement
- Dosing amended for consistency with previous statement.

Draft statement

Optimal treatment approaches beyond 2 years are yet to be determined. 500 mg – 1 g every 6 to 12 months for up to 5 years could be considered. In patients with prior relapse after maintenance rituximab cessation, this could be adjusted based on time from treatment cessation to disease relapse.

d) **Role of biomarkers in rituximab maintenance therapy**

Delphi round 1

The role of biomarkers was raised in the comments and discussed as potential influencers of treatment frequency and duration, though not used/recommended by the majority of respondents.

To guide dosing interval within 2 years (19 responses):

- 5 influenced by ANCA
- 4 influenced by B cell markers

To guide duration of therapy beyond 2 years (17 responses):

- 4 used a combination of clinical assessment, ANCA and/or B cell markers

Delphi round 2

Questions on decision on **extended** rituximab-

ANCA:

- Patients with history of PR3-ANCA identified as 'high risk subgroup', contributing to decisions re: extended rituximab maintenance duration- 4/19 (21%)
- Persistent ANCA after 2 years of rituximab maintenance identified as a factor contributing to decisions re: extended rituximab maintenance duration- 3/19 (16%)

B cell return: 3/19 (17%) considered this a factor contributing to decision re: extended rituximab maintenance

During extended rituximab use-

ANCA or B cell markers or "biomarkers" were noted to influence the treatment regimen in extended rituximab therapy in 8/18 (44%) respondents

- ANCA (6)
- B cells (6)
- Undefined (1)

Delphi round 3/face-to-face meeting

- Proposed draft statement: "Further research is needed to consider the role of ANCA and B cell return in guiding treatment in AAV".
- Suggested change terminology to 'biomarkers'

Draft statement

Further research is needed to consider the role of biomarkers (e.g. ANCA and B cell return) in guiding rituximab maintenance therapy in AAV.

3. Concomitant therapy

a. Concomitant immunosuppressive agents/disease modifying anti-rheumatic drugs

Delphi round 1

Traditional DMARDs were not generally used in conjunction with RTX

- 5/19 respondents discussed situations with use of concomitant therapy
    - 1- ongoing disease activity despite steroids and rtx
    - 1- high risk of relapse
    - 1- retro-orbital disease
    - 2- where rtx was added to existing conventional DMARD (and subsequently weaned if disease control obtained)

Delphi Round 2

Strategies for concomitant DMARD therapy:

- Cease with rituximab commencement- 11/19 (58%)
- Cease with after disease control established- 13/19 (68%)
- Overlap: 6/19 (32%)

Delphi round 3/face-to-face meeting

- In pre-UKIVAS and wider group discussion, concern raised regarding recommendation for cessation of DMARD
    - Suggested review of data from Cleveland clinic Azar A&R 2014
        - Assessment of concomitant DMARD/RTX performed in 89 patients who did not receive pre-emptive/regular RTX maintenance therapy. Comparison of 47 patients who received RTX induction followed by glucocorticoid + MTX or AZA or MMF vs 42 patients who received RTX induction followed by glucocorticoid, demonstrating prolonged disease-free remission in patients receiving a maintenance agent (MTX/AZA/MMF) with glucocorticoid. This study does not discuss concomitant therapy with RTX maintenance.
- Further concern was raised regarding heightened infection risk in patients with AAV and the potential contribution of concomitant therapy to this
- In small group face-to-face, no amendment to statement was made as statement allows for time frame to be determined by treating clinician, and observational cohorts using pre-emptive rituximab strategies have not routinely used concomitant therapy, and have typically withdrawn concomitant agents where they have been present.

Round 4

- 13/14 respondents agreed to statement, therefore this remains unchanged after round 4 responses

Draft statement

Where rituximab is commenced in a patient already receiving a DMARD for remission maintenance (e.g. azathioprine, methotrexate or mycophenolate), we recommend that existing DMARDs be withdrawn.

3. Concomitant therapy

b. Glucocorticoids

Delphi round 1

Glucocorticoid (prednisolone used by all)

- Continuation of prednisolone at 5 mg/d or lower for at least 2 years was specified by 4/19 respondents

- Aim for prednisolone wean to cessation or cessation within 12 months was specified by 6/19
- Aim for prednisolone wean or cessation between 12 and 24 months was specified by 3/19
- Aim for prednisolone withdrawal without specific time scale

Delphi round 2

Given spread of responses from round 1, further question posed to clarify timing of GC withdrawal.

Where there is successful control of disease activity with rituximab maintenance therapy, glucocorticoid tapering strategies should aim for complete withdrawal after (first rituximab or disease control) in:

- 6 months: 10/19 (53%) agreed
- 12 months: 8/19 (42%) agreed
- Overlap: 2/19 (11%)
- Disagreed to both: 2/19 (11%)
  - 1- related to wording & stated 'not in all cases'
  - 1- 'complete steroid withdrawal risks disease flares'

Delphi round 3/face-to-face meeting

- Proposed draft statement: "With successful control of disease activity, glucocorticoid tapering strategies should aim for complete withdrawal."
- In small group face-to-face, preference to provide a timeframe. Acknowledging the split between responses, 6-12 months suggested.
- Terminology has been further altered from 'withdrawal' to 'cessation'
- Following face-to-face meeting, disease remission has been replaced with 'rituximab commencement'

Draft statement

Glucocorticoid tapering strategies should aim for complete cessation 6-12 months after rituximab commencement.

4. **Prophylaxis**
   a. **Pneumocystis jirovecii prophylaxis**

Delphi round 1

- Co-trimoxazole is used routinely during rituximab induction therapy by 16/19 respondents

    - 4 continued for the duration of rituximab therapy until B cell repopulation or recovery of lymphopenia
- subgroups for continuation of use beyond induction
    - infective prophylaxis
        - IgG < 6 – 2 respondents
    - Relapse prevention
        - Nasal/ENT disease (continuation beyond induction treatment prophylaxis)- 5 respondents
        - GPA- 1 respondent

Delphi round 2

Given the degree of consensus, a draft statement was proposed.

"Co-trimoxazole should be prescribed in all patients receiving rituximab maintenance therapy."

- 15/18 (78%) agreed
    - 2 suggested a duration: 6 months; 6 months, factoring use of other immunosuppressive agents and CD4 counts
- 4/18 (22%) disagreed:
    - 1 indicated statement was too rigid (e.g. in the setting of contraindications)
    - 1 indicated only used if high dose steroids, concomitant immunosuppressive therapies used, or low CD4
    - 1 indicated only used in patients at high risk of infection
    - 1 indicated uncertainty regarding the evidence to support this

Delphi round 3

- in small group face-to-face, prior comment from 1 respondent to maintain consistency with SMPC/SPC raised to ensure any changes acknowledge this (statements have been consistent with this); agreed that evidence for PCP prophylaxis remains
- responses from round 2 reviewed; limited evidence supporting use acknowledged, blurb to discussing timing (at least 6 months) with longer durations to be considered in patients with ongoing lymphopenia, CD4 T cell lymphopenia, and concomitant immunosuppression with glucocorticoids or DMARDs)
- Proposed statement accepted unchanged

Delphi Round 4

- A few respondents queried duration of PJP prophylaxis- further literature review was therefore conducted (see separate document) and statement amended.

Draft statement

Pneumocystis jirovecii prophylaxis is recommended in all patients receiving rituximab therapy.

4. Prophylaxis

b. Vaccination

Delphi round 1

- Where this was discussed in some detail, consensus was that standard 'immunosuppression' vaccination advice applied- influenza, pneumococcal, no live vaccines, with understanding that consideration needed to be taken into the timing of vaccinations and the potential for inefficacy.

- Influenza vaccination recommendation- 11/18
- Pneumococcal vaccination recommendation- 8/18
- Tetanus vaccination recommendation- 1/18
- Haemophilus vaccination recommendation- 1/18
- Avoid live vaccination (VZV vac taken as equivalent) recommendation- 8/18
- Timing of vaccinations
    - Aim for at least 4/52 before rituximab: 6/18
    - Aim for 4/12 after rituximab: 2/18

Delphi round 2

Given the degree of consensus regarding need for vaccination, a draft statement was proposed.

"Influenza and pneumococcal vaccinations should be recommended to all patients. Live vaccinations should be avoided. Additional vaccinations should be considered according to local guidelines."

- 19/19 (100%) agreed
    - Haemophilus vaccination queried
    - Timing queried by 3
    - VZV vaccination queried- though with potential future introduction of Shingrix, ?may not require specific recommendation

Delphi round 3

- Previous proposed statements:

  Influenza and pneumococcal vaccinations should be recommended to all patients. Live vaccinations should be avoided. Additional vaccinations should be considered according to local guidelines.

  Although vaccinations are ideally provided at least 1 month prior to rituximab infusion, timing should not preclude vaccination.

- Removal of 'Additional vaccinations should be considered according to local guidelines.'

Draft statement

Influenza and pneumococcal vaccinations should be recommended to all patients. Live vaccinations should be avoided.

Although vaccinations are ideally provided at least 1 month prior to rituximab infusion, timing should not preclude vaccination.

5. **Adverse effects with treatment**
    a. **Hypogammaglobulinaemia**
        i. **threshold for referral for clinical immunology investigations**

Delphi round 1

- Immunoglobulins routinely assessed pre-rituximab- 17/18
- Immunoglobulins routinely assessed in follow-up- 18/19

- Hypogammaglobulinaemia, severe hypogammaglobulinaemia or symptomatic hypogammaglobulinaemia were noted as a contraindications or caution to rituximab maintenance by 10/19 respondents
- Hypogammaglobulinaemia was noted to influence ongoing prescription of maintenance rituximab by 15/18

Delphi round 2

Given the degree of consensus, a draft statement was proposed.

"In the setting of rituximab maintenance therapy:

1. Immunoglobulins should be monitored in all patients
2. Further investigation and referral for Immunology review should be considered in the setting of:
    a. recurrent infections; OR
    b. IgG <3"

- 16/19 (84%) agreed
    - 1 noted that age appropriate cut-offs should be used in children
    - 2 raised caveat of severity and/or nature of infections raise
    - 1 commented on the use of antibiotic prophylaxis prior to immunoglobulin replacement
- 1 abstained- no local specialist immunology service
- 2 disagreed
    - "investigate if infections- try to keep IgG above 3.5 by not overtreated with rituximab- refer to consider IVIG replacement"
    - "refer only if recurrent of infections, regardless of IgG level"

Delphi round 3/face-to-face

- Following round 2, monitoring of IG prior to each infusion statement removed and remains as “immunoglobulins should be monitored in all patients”
- Removal of “immunology review” in view of limited clinical immunology service in selected regions.
- Antibiotic prophylaxis, IG replacement and immunology review to be discussed in blurb

Draft statement

In the setting of rituximab maintenance therapy:

1. Immunoglobulins should be monitored in all patients
2. Further investigation is recommended in the setting of:
    a. Recurrent or atypical infections; OR
    b. IgG <3 (In children, IgG less than the age appropriate lower limit of normal should be used.)

5. Adverse effects with treatment

a. Hypogammaglobulinaemia

i. further rituximab in the setting of hypogammaglobulinaemia

Delphi round 2

Comment received by 2 respondents.

Delphi round 3

- Parallel administration of rituximab and immunoglobulin replacement should be considered in patients with hypogammaglobulinaemia and a clinically important response to rituximab is anticipated.
- replacement of “should” with “could”

Draft statement

Parallel administration of rituximab and immunoglobulin replacement could be considered in patients with hypogammaglobulinaemia and a clinically important response to rituximab is anticipated.

b. Late onset neutropenia and further rituximab

Delphi round 1

- Late onset neutropenia influenced ongoing rituximab used for 2/18 respondents
- Raised in comments for recommendation

Delphi round 2

Following review of the literature, a draft statement was proposed.

“Clinicians and patients should be aware of the possibility of late onset neutropenia with rituximab use. A history of late onset neutropenia does not prohibit future rituximab use.”

- Agreed 16/19 (84%)
- Disagreed/abstained 3/19 (16%)
    - “needs careful consideration and advice particularly if severe sepsis previously” personal experience of high recurrence, “further clarity about the appropriate action including guidance on the period during which the neutrophil count should be monitored more closely and thresholds for intervention when this has occurred previously.”
    - “would be wary of ongoing use”
    - “helpful to define level of neutropenia/any associated infections? Absolute cut-off versus cautions for use”

One respondent:

"In my experience the risk of recurrence of this is high and I think further clarity about the appropriate action including guidance on the period during which the neutrophil count should be monitored more closely and thresholds for intervention when this has occurred previously."

One respondent:

“discussion of risk-benefit assessment in patients who have had symptomatic/febrile neutropenic episodes”

Draft statement

Clinicians and patients should be aware of the possibility of late onset neutropenia with rituximab use. A history of uncomplicated late onset neutropenia does not prohibit future rituximab use.

6. Research agenda
    a) Rituximab alternatives: subcutaneous rituximab, biosimilars, ofatumumab, belimumab

b) Cost effectiveness analysis in view of reducing cost
c) Effects on health related quality of life
d) B cell dysfunction in AAV
e) Biomarkers in AAV including ANCA, CD19, CD27 for risk of relapse
f) Paediatric patients with AAV
g) Fertility and pregnancy
h) Progressive multifocal leukoencephalopathy risk

Appendix 3 Manuscript: Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis

EXTENDED REPORT

Trimethoprim–sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis

Andreas Kronbichler,[1,2] Julia Kerschbaum,[2] Seerapani Gopaluni,[1] Joanna Tieu,[1] Federico Alberici,[1,3] Rachel Bronwen Jones,[1] Rona M Smith,[1] David R W Jayne[1,4]

Handling editor Josef S Smolen

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-212861).

[1]Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge, UK
[2]Department of Internal Medicine IV (Nephrology and Hypertension), Anichstraße, Innsbruck, Austria
[3]Renal Medicine and Vasculitis Clinic, San Carlo Borromeo Hospital, Milan, Italy
[4]Department of Medicine, University of Cambridge, Cambridge, UK

Correspondence to
Dr Andreas Kronbichler, Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK; andreas.kronbichler@i-med.ac.at

Parts of this work were presented during the 52nd ERA-EDTA Congress 2015 (London, UK) and during the ASN Kidney Week 2016 (Chicago, USA).

Received 16 December 2017
Accepted 11 June 2018
Published Online First 27 June 2018

To cite: Kronbichler A, Kerschbaum J, Gopaluni S, *et al*. *Ann Rheum Dis* 2018;**77**:1440–1447.

ABSTRACT

Objective We aimed to assess risk factors for the development of severe infection in patients with antineutrophil cytoplasm antibody-associated vasculitis (AAV) receiving rituximab.

Methods 192 patients with AAV were identified. Univariate and multivariate analyses were performed to identify risk factors for severe infection following rituximab. Severe infections were classified as grade ≥3 as proposed by the Common Terminology Criteria for Adverse Events V.4.0.

Results 95 severe infections were recorded in 49 (25.52%) patients, corresponding to an event rate of 26.06 per 100 person-years. The prophylactic use of trimethoprim–sulfamethoxazole was associated with a lower frequency of severe infections (HR 0.30, 95% CI 0.13 to 0.69), while older age (HR 1.03, 95% CI 1.01 to 1.05), endobronchial involvement (HR 2.21, 95% CI 1.14 to 4.26), presence of chronic obstructive pulmonary disease (HR 6.30, 95% CI 1.08 to 36.75) and previous alemtuzumab use (HR 3.97, 95% CI 1.50 to 10.54) increased the risk. When analysis was restricted to respiratory tract infections (66.3% of all infections), endobronchial involvement (HR 4.27, 95% CI 1.81 to 10.06), severe bronchiectasis (HR 6.14, 95% CI 1.18 to 31.91), higher neutrophil count (HR 1.19, 95% CI 1.06 to 1.33) and major relapse (HR 3.07, 95% CI 1.30 to 7.23) as indication for rituximab use conferred a higher risk, while refractory disease (HR 0.25, 95% CI 0.07 to 0.90) as indication had a lower frequency of severe infections.

Conclusions We found severe infections in one quarter of patients with AAV receiving rituximab. Trimethoprim–sulfamethoxazole prophylaxis reduced the risk, while especially bronchiectasis and endobronchial involvement are risk factors for severe respiratory infections.

INTRODUCTION

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) encompasses three entities, namely granulomatosis with polyangiitis (GPA, previously Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, previously Churg-Strauss Syndrome). The availability of ANCA facilitates diagnosis and treatment strategies, and has led to a better prognosis over recent decades.[1] Nevertheless, comorbidities attributable to the persistence of the disease or side effects of treatment remain a challenge. Forty-eight per cent of deaths occurring during the first year are caused by infections and remain a major cause of mortality thereafter.[2] Infectious complications have been studied especially in cyclophosphamide-treated patients. Several risk factors have been identified, including treatment intensity (cumulative steroid and cyclophosphamide dose), reduced creatinine clearance (estimated glomerular filtration rate (eGFR) of ≤30 mL/min) or dialysis dependency, older age and pulmonary involvement.[3] Rituximab showed similar efficacy compared with a cyclophosphamide-based treatment in the induction of remission in two randomised controlled trials. However, rituximab did not show a reduced rate of severe infections compared with cyclophosphamide.[4 5] Patients recruited into trials may have a lower adverse event rate due to rigorous monitoring and selection of patients according to exclusion criteria,[6] and the rate of side effects might be even higher in routine practice. Several observational studies have reported severe/life-threatening infectious complications following rituximab, including cases with *Pneumocystis jirovecii*, *Pseudomonas aeruginosa*, pulmonary aspergillosis and progressive multifocal leukoencephalopathy.[7–9] While *P. jirovecii* prophylaxis is widely accepted in patients receiving cyclophosphamide (CYC), no such recommendations exist for patients receiving rituximab.

This study investigated the frequency of severe/life-threatening infections in 192 patients with AAV treated with rituximab. It also aimed to identify risk factors for severe infection in this patient population.

METHODS

Study population

This study included patients with AAV older than 18 years who were referred for rituximab to two tertiary care specialist centres, Addenbrooke's Hospital (Cambridge, UK) and the Medical University Innsbruck (Innsbruck, Austria), between 2004 and 2014. Diagnosis of AAV was established according to the European Medicines Agency (EMA) algorithm.[10] Follow-up of patients began at the time of rituximab administration and ended on the date of death, the date patients were lost to follow-up, 2 years after first rituximab

administration or on 1 January 2015, whichever occurred first. This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. The Institutional Review Board of both university hospitals approved the use of anonymised patient data for research purposes.

Clinical data

The following data were obtained from the respective electronic medical records of the patients: demography (age, gender), diagnosis, date of diagnosis, time to rituximab, ANCA serotype, disease phenotype, organ involvement, prior immunosuppressive therapies, cumulative cyclophosphamide exposure (in grams), immunosuppression during the year before rituximab, concomitant treatment, laboratory values (serum creatinine, C reactive protein (CRP), erythrocyte sedimentation rate (ESR), neutrophils, white blood count (WBC), lymphocytes, CD3/CD4/CD8/CD19/CD56 counts, immunoglobulins), indication for the use of rituximab (see online supplementary appendix), comorbidities (including chronic obstructive pulmonary disease, diabetes mellitus, hypertension, chronic heart failure), smoking history, antibiotic prophylaxis (trimethoprim–sulfamethoxazole or others) and the occurrence of severe/life-threatening infections (grade ≥3), as classified by the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0 (see online supplementary appendix).[11] Hypogammaglobulinaemia was defined as a IgG level of below 7 g/L. Patients with incomplete or missing medical records were excluded from further analyses. The cumulative doses of rituximab during follow-up were determined.

Statistical analysis

Categorical variables were compared using the χ^2 test (or Fisher's exact test, when appropriate), and metric variables were compared using the Mann-Whitney U test. Metric variables are shown as median (and minimum to maximum), and nominal variables are shown as per cent (%). Both univariate and multivariate Cox regression analyses were performed to determine significant risk factors for severe/life-threatening and respiratory infections. The occurrence of at least one episode of severe/life-threatening infection during the follow-up period of 24 months was the outcome of interest. Kaplan-Meier plots and log-rank test were performed to assess univariate associations. All variables showing significant association with the dependent variable in the univariate Cox regression analysis were entered into a multivariate Cox regression model. A backward selection procedure was then used (with p values greater than 0.100 as the removal criterion, using Wald's test). Neutrophils correlated with WBC, CRP and ESR and sinusitis correlated with ear, nose and throat (ENT) involvement, thus only neutrophils at baseline and sinusitis were included in multivariate analysis. Results are expressed as HRs with 95% CIs. All statistical analyses were performed with SPSS Statistics V.21.0 (IBM).

RESULTS

Patient characteristics

The total number of patients included in the analysis was 192 (134 with GPA, 28 with MPA and 30 with EGPA). Mean duration of initial diagnosis to initiation of rituximab was 4.33 years. Patients were followed for a mean time of 22.67 months from the time of rituximab initiation (mean rituximab dose 4.75 g). Forty-nine patients presented with 95 infectious complications classified as CTCAE V.4.0 ≥3. In detail, 71 episodes were CTCAE V.4.0 grade 3, 23 as grade 4 and 1 as grade 5 (multiorgan failure as a consequence of sepsis related to an urinary tract infection). The overall event rate was 26.06 per 100 person-years. Twenty-five per cent of the observed infections occurred during the first 4 months of follow-up, while 50% and 80% were observed after 12 and 18 months, respectively. Antibiotic prophylaxis with trimethoprim–sulfamethoxazole was administered in 73 out of 192 (38.02%). During the follow-up period, seven fatalities were recorded. Baseline characteristics of patients with severe infections and those without are depicted in table 1.

Infections

Respiratory tract infection was the most common infectious complication (n=63), followed by urinary tract (n=12), gastrointestinal tract (n=8), mastoiditis/otitis externa (n=4), skin (n=3), sepsis/septicaemia with unidentified site of infection (n=1), catheter-associated exit site infections (n=1), orbital mass infection (n=1), lacrimal gland abscess (n=1) and eye (n=1) (online supplementary table S1). Moreover, in cases with a positive microbial result, opportunistic pathogens were seen, including *P. aeruginosa* (n=4), *Staphylococcus aureus* including methicillin-resistant strains (n=4), *Escherichia coli* (n=3), *Clostridium difficile* (n=2), *P. jirovecii* (n=1), *Legionella pneumophila* (n=1) and invasive aspergillosis (n=1). In addition, one case of *Campylobacter jejuni* gastroenteritis was observed (online supplementary table S1 and online supplementary table S2).

Rituximab treatment and risk of infections

To identify specific risk factors associated with the development of infectious complications, univariate analysis was performed. Older patients (HR 1.02, 95% CI 1.00 to 1.04), patients with endobronchial involvement (HR 2.44, 95% CI 1.38 to 4.32) and severe bronchiectasis (HR 4.79, 95% CI 1.47 to 15.59) were at increased risk for severe infections. Patients presenting with sinusitis (HR 0.48, 95% CI 0.27 to 0.84) or in general ENT involvement (HR 0.46, 95% CI 0.26 to 0.82) had fewer severe infections. While there was no correlation with serum creatinine, higher eGFR (HR 0.99, 95% CI 0.98 to 1.00) emerged as a protective factor. Higher ESR (HR 1.11, 95% CI 1.03 to 1.20), WBC (HR 1.06, 95% CI 1.01 to 1.10), higher steroid doses (HR 1.02, 95% CI 1.01 to 1.04) and an IgG decline ≥30% (HR 1.88, 95% CI 1.04 to 3.39) at baseline were predictors of severe infections. Concomitant comorbidities, such as chronic obstructive pulmonary disease (COPD, HR 16.07, 95% CI 4.41 to 58.49), diabetes (HR 2.35, 95% CI 1.14 to 4.85) and reduced left ventricular ejection fraction/previous myocardial infarction (HR 2.21, 95% CI 1.07 to 4.56) emerged as risk factors. Treatment with alemtuzumab (ALM) ever before rituximab was associated with an increased risk (HR 2.49, 95% CI 1.05 to 5.91). Antibiotic prophylaxis to prevent *P. jirovecii* infections with trimethoprim–sulfamethoxazole reduced the risk of severe infections (HR 0.45, 95% CI 0.23 to 0.88). A multivariate logistic regression analysis revealed that the use of trimethoprim–sulfamethoxazole as prophylactic antibiotic measure had an impact on reduction of severe infections (HR 0.30, 95% CI 0.13 to 0.69). Moreover, the use of trimethoprim–sulfamethoxazole significantly reduced the time to first significant infection (p=0.016) (table 2 and figure 1). Moreover, older age (HR 1.03, 95% CI 1.01 to 1.05), endobronchial involvement (HR 2.21, 95% CI 1.15 to 4.26), COPD (HR 6.30, 95% CI 1.08 to 36.75) and ALM treatment before rituximab (HR 3.97, 95% CI 1.50 to 10.54) emerged as independent risk factors to develop severe infections following rituximab (table 2).

Table 1 Baseline characteristics of patients having severe infections versus those without severe infections

	No severe infection (n=143)	Severe infection (n=49)	P values
Demographics			
Age (years)	56 (16–85)	60 (22–82)	**0.023**
Gender (male, %)	45	41	0.573
Type of vasculitis (%)			0.407
GPA	71	65	
MPA	13	20	
EGPA	16	14	
Symptoms (%)			
B-symptoms (night sweat, fever, unintentional weight loss)	21	14	0.353
Neuropathy	27	24	0.774
Sinusitis	72	53	**0.015**
Deafness/mastoiditis/otitis media	31	22	0.266
Arthralgia	45	33	0.117
Organ involvement (%)			
CNS	7	7	1
Subglottic/tracheal stenosis	12	14	0.661
Skin	18	14	0.533
Kidney	44	51	0.398
Eye	29	17	0.112
Others	7	8	1
ENT	79	61	**0.014**
Lung	54	65	0.162
Imaging findings (%)			
Pulmonary cavities	24	26	0.75
Endobronchial	20	41	**0.004**
Severe bronchiectasis	1	8	0.054
Disease activity measures			
BVAS	6 (0–28)	6 (0–18)	0.602
DEI	6 (2–12)	6 (2–10)	0.848
Laboratory values			
Creatinine (µmol/L)	86 (45–1451)	98 (49–879)	**0.027**
eGFR (MDRD/Modification of Diet in Renal Disease equation) mL/min/1.73 m^2	75 (3–163)	60 (5–155)	**0.002**
CRP (0–6 mg/L)	5.0 (0.7–215.0)	14.0 (1.0–215.0)	**0.001**
ESR (5–15 in the 1st hour)	16 (2–116)	22 (1–109)	**0.006**
Neutrophils (2–8×10^9/L)	7.1 (2.0–18.6)	8.3 (2.4–21.4)	**0.025**
WBC (4–11×10^9/L)	9.4 (3.6–42.0)	10.7 (3.3–24.4)	**0.006**
Lymphocytes (1–4.5×10^9/L)	1.0 (0.1–3.7)	1.0 (0.4–4.5)	0.145
CD19 (0.1–0.5)	0.04 (0.00–0.80)	0.03 (0.00–0.77)	0.781
CD3 (0.7–2.1)	0.82 (0.05–7.20)	0.70 (0.21–3.32)	0.246
CD4 (0.3–1.4)	0.48 (0.03–1.98)	0.38 (0.11–2.80)	0.303
CD8 (0.2–0.9)	0.29 (0.02–1.93)	0.20 (0.07–0.95)	0.414
CD56 (0.12–0.88)	0.11 (0.00–0.70)	0.15 (0.00–0.80)	0.09
IgG (6–13 g/L)	9.0 (2.8–22.6)	8.8 (3.0–18.9)	0.823
IgG decline ≥30% (%)	20	35	**0.041**
Hypogammaglobulinaemia (%)	13	16	0.593
IgM (0.4–2.2 g/L)	0.7 (0.3–2.6)	0.7 (0.3–2.0)	0.398
IgA (0.8–3.7 g/L)	1.8 (0.4–5.3)	2.1 (0.5–4.3)	0.715
ANCA-positive (%)	73	76	0.703
Comorbidities (%)			
COPD	1	6	0.053
Diabetes	6	18	**0.021**
Hypertension	37	33	0.557
Myocardial infarction/reduced LVEF	8	18	**0.036**
Indication (%)			
Minor relapse	41	29	0.114
Major relapse	27	39	0.13

Continued

Table 1 Continued

	No severe infection (n=143)	Severe infection (n=49)	P values
Maintenance	78	82	0.622
Refractory disease	31	27	0.516
Steroid sparing	17	22	0.375
1st line	5	10	0.187
Premedication (last 12 months)			
CYC (g)	0 (0–45)	0 (0–22)	0.632
MMF (g)	0 (0–1080)	15 (0–1080)	0.798
AZA (g)	0 (0–81)	0 (0–72)	0.036
MTX (mg)	0 (0–1286)	0 (0–1286)	0.739
IVIG (ever) (%)	4	12	0.128
Anti-TNF (ever) (%)	3	5	0.65
PLEX (ever) (%)	9	7	1
ALM (ever) (%)	5	14	0.079
Medication used concurrently with RTX			
Steroids (mg)	15 (0–60)	15 (5–60)	0.087
Trimethoprim–sulfamethoxazole (%)	43	22	**0.009**
Other antibiotic prophylaxis (%)	9	16	0.172

Metric variables are shown as median and (minimum–maximum), nominal variables are shown as %. Statistics tests are χ quadrate test/Fisher's exact test and Mann-Whitney U test where appropriate. The respective reference ranges, if applicable, are given in parentheses. P values indicating significant changes are highlighted in bold font.
ALM, alemtuzumab; ANCA, antineutrophil cytoplasm antibody; AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score; CD, cluster of differentiation; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; CYC, cyclophosphamide; DEI, Disease Extent Index; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear, nose and throat; ESR, erythrocyte sedimentation rate; GPA, granulomatosis with polyangiitis; IVIG, intravenous immunoglobulins; LVEF, left ventricular ejection fraction; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; PLEX, plasma exchange; RTX, rituximab; TNF, tumour necrosis factor; WBC, white blood count.

Risk for lower respiratory tract infections after rituximab

Since respiratory tract infections were the leading cause of infectious complications (n=63), we aimed to identify factors predicting the risk. Nine patients underwent bronchoscopy and most of them had at least two respiratory tract infections (7/9). Patients with preserved eGFR (HR 0.99, 95% CI 0.98 to 1.00), presenting with sinusitis (HR 0.47, 95% CI 0.23 to 0.98) and ENT involvement (HR 0.43, 95% CI 0.20 to 0.87) as well as receiving rituximab for refractory disease (HR 0.35, 95% CI 0.12 to 0.99), had a lower likelihood to develop severe pulmonary infections. In contrast, lung involvement (HR 2.53, 95% CI 1.08 to 5.93) and in particular endobronchial involvement (HR 4.30, 95% CI 2.06 to 8.94) and severe bronchiectasis (HR 7.48, 95% CI 2.22 to 25.16) emerged as risk factors. Higher CRP (HR 1.01, 95% CI 1.00 to 1.01), ESR (HR 1.02, 95% CI 1.00 to 1.03), neutrophils (HR 1.15, 95% CI 1.15) and WBC (HR 1.07, 95% CI 1.01 to 1.12) at baseline were associated with severe pulmonary infections. Moreover, those with concomitant COPD (HR 19.75, 95% CI 5.23 to 74.63), major relapse as indication (HR 2.65, 95% CI 1.28 to 5.49) and higher steroid doses (HR 1.02, 95% CI 1.00 to 1.04) had more pulmonary infections. Multivariate analysis retained endobronchial involvement (HR 4.30, 95% CI 2.06 to 8.94), severe bronchiectasis (HR 7.48, 95% CI 2.22 to 25.16), neutrophil count at baseline (HR 1.19, 95% CI 1.06 to 1.33) and major relapse (HR 2.65, 95% CI 1.28 to 5.49) as independent risk factors, while rituximab use in the setting of refractory disease was negatively associated with severe pulmonary infections (HR 0.35, 95% CI 0.12 to 0.99) (online supplementary table S3).

Prescription pattern and side effects of trimethoprim–sulfamethoxazole

The dose of trimethoprim–sulfamethoxazole used as a prophylaxis was not consistent. Most patients received 480 mg on alternate days (38.36%), followed by 960 mg on alternate days (21.92%) and 960 mg twice daily (12.33%, further details see online supplementary table S4). Among differences in the prescription pattern, a diagnosis of GPA, ENT involvement including sinusitis and deafness, mastoiditis and otitis media were associated with a more frequent prescription. Lower CD4 T-cell count as well as cyclophosphamide in the year before and a higher concomitant steroid use led to trimethoprim–sulfamethoxazole prescription (online supplementary table S5). Next, we assessed side effects of trimethoprim–sulfamethoxazole focusing on recently reported adverse events in rheumatological indications.[12] Trimethoprim–sulfamethoxazole was stopped in five patients due to haematopoietic complications in three (lymphopenia, pancytopenia, neutropenia), sore mouth in one and abnormal liver function test in the remainder. In general, trimethoprim–sulfamethoxazole prophylaxis was maintained for 14.67 months.

DISCUSSION

Comorbidities, either attributable to active disease or immunosuppression, remain a major issue in the management of AAV. An analysis of the early EUVAS trials revealed that infections contributed to the majority (28/59, 48%) of deaths within the first year of trial inclusion, whereas it is among the three leading causes thereafter (15/74, 20%). A direct effect of induction treatment was proposed to be causative of severe infections within the first year.[2] A recent study analysing the Chapel Hill cohort highlighted that infections were responsible for a high proportion of deaths within the first year (4/31, 13%), while active disease (29%) was the leading cause in a large cohort comprising 421 patients with a follow-up of at least 1 year.[13] Differences in the treatment modalities may have accounted for the differences leading to fatal infections in diverse cohorts. The methylprednisolone versus plasma exchange (MEPEX) trial (one of the early European Vasculitis Society (EUVAS) trials) randomised patients

Table 2 Univariate and multivariate analysis of risk factors for severe or life-threatening infection following rituximab treatment during 24 months of follow-up

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P values	HR	95% CI	P values
Demographics						
Age (years)	1.02	1.00 to 1.04	**0.031**	1.03	1.01 to 1.05	0.012
Gender (male)	0.88	0.50 to 1.55	0.647			
Type of vasculitis						
GPA	Reference	–	–			
MPA	1.59	0.78 to 3.23	0.203			
EGPA	0.95	0.42 to 2.15	0.899			
Symptoms/manifestations						
B-symptoms (night sweat, fever, unintentional weight loss)	0.67	0.28 to 1.58	0.355			
Neuropathy	0.89	0.46 to 1.70	0.72			
Sinusitis	0.48	0.27 to 0.84	**0.01**			
Deafness/mastoiditis/otitis media	0.69	0.35 to 1.35	0.275			
Arthralgia	0.63	0.35 to 1.14	0.127			
Organ involvement						
CNS	1.12	0.35 to 3.63	0.85			
Subglottic/tracheal stenosis	1.14	0.51 to 2.54	0.746			
Skin	0.74	0.33 to 1.64	0.45			
Kidney	1.27	0.72 to 2.21	0.411			
Eye	0.52	0.23 to 1.17	0.113			
Others	0.82	0.26 to 2.65	0.745			
ENT	0.46	0.26 to 0.82	**0.008**			
Lung	1.57	0.87 to 2.82	0.136			
Imaging findings						
Pulmonary cavities	1.11	0.56 to 2.21	0.765			
Endobronchial	2.44	1.38 to 4.32	**0.002**	2.21	1.14 to 4.26	0.018
Severe bronchiectasis	4.79	1.47 to 15.59	**0.009**			
Disease activity measures						
BVAS	1.01	0.95 to 1.07	0.811			
DEI	0.98	0.84 to 1.15	0.840			
Laboratory values						
Creatinine	1	1.00 to 1.00	0.141			
eGFR (MDRD equation) mL/min/1.73 m^2	0.99	0.98 to 1.00	**0.011**			
CRP	1.01	1.00 to 1.01	0.061			
ESR	1.01	1.00 to 1.02	**0.014**			
Neutrophils	1.11	1.03 to 1.20	**0.005**			
WBC	1.06	1.01 to 1.10	**0.013**			
Lymphocytes	0.73	0.48 to 1.11	0.142			
CD19	1.17	0.11 to 12.51	0.896			
CD3	0.75	0.45 to 1.25	0.27			
CD4	0.74	0.34 to 1.61	0.44			
CD8	0.58	0.16 to 2.09	0.407			
CD56	2.75	0.34 to 22.10	0.341			
IgG	1.02	0.93 to 1.12	0.663			
IgG decline ≥30 %	1.88	1.04 to 3.39	**0.036**			
Hypogammaglobulinaemia	1.22	0.54 to 2.74	0.633			
IgM	0.72	0.38 to 1.35	0.304			
IgA	1.11	0.80 to 1.54	0.535			
ANCA positive	1.11	0.58 to 2.14	0.744			
Comorbidities						
COPD	16.07	4.41 to 58.49	**<0.001**	6.3	1.08 to 36.75	0.041
Diabetes	2.35	1.14 to 4.85	**0.021**			
Hypertension	0.79	0.44 to 1.44	0.445			
Myocardial infarction/reduced LVEF	2.21	1.07 to 4.56	**0.032**			
Indication						

Continued

Table 2 Continued

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P values	HR	95% CI	P values
Minor relapse	0.6	0.32 to 1.11	0.102			
Major relapse	1.63	0.92 to 2.90	0.097			
Maintenance	1.15	0.56 to 2.37	0.708			
Refractory disease	0.8	0.42 to 1.51	0.491			
Steroid sparing	1.37	0.70 to 2.68	0.36			
1st line	1.95	0.77 to 4.91	0.159			
Premedication (last 12 months)						
CYC (g)	0.97	0.90 to 1.04	0.389			
MMF (g)	1	1.00 to 1.00	0.273			
AZA (g)	0.97	0.95 to 1.00	0.066			
MTX (mg)	1	1.00 to 1.00	0.979			
IVIG (ever)	2.4	0.94 to 6.12	0.067			
Anti-TNF (ever)	1.41	0.34 to 5.84	0.636			
PLEX (ever)	0.75	0.23 to 2.42	0.629			
ALM (ever)	2.49	1.05 to 5.91	**0.039**	3.97	1.50 to 10.54	0.006
Medication used concurrently with RTX						
Steroids (mg)	1.02	1.01 to 1.04	**0.006**			
Trimethoprim–sulfamethoxazole	0.45	0.23 to 0.88	**0.02**	0.3	0.13 to 0.69	0.005
Other antibiotic prophylaxis	1.63	0.76 to 3.47	0.209			

Demographics of the respective patients, the form of ANCA-associated vasculitis, symptoms, laboratory values, comorbidities, indication for rituximab use, the premedication and the concomitant therapy are given. P values indicating significant changes are highlighted in bold font.

ALM, alemtuzumab; ANCA, antineutrophil cytoplasm antibody; AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score; CD, cluster of differentiation; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; CYC, cyclophosphamide; DEI, Disease Extent Index; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ear, nose and throat; ESR, erythrocyte sedimentation rate; GPA, granulomatosis with polyangiitis; IVIG, intravenous immunoglobulins; LVEF, left ventricular ejection fraction; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; PLEX, plasma exchange; RTX, rituximab; TNF, tumour necrosis factor; WBC, white blood count.

either to plasma exchange or high-dose methylprednisolone alongside standard induction therapy reported 19 deaths (out of 137 patients) related to infections within the first year.[14]

Little is known about infections in patients with AAV treated with rituximab. In the first 6 months, the rate of severe infections (defined as grade ≥3 CTCAE V.3.0 event) was 7% in the group of patients receiving either rituximab or standard of care in the RAVE trial.[4] Over 18 months, 12% in the rituximab and 11% of participants in the standard of care group had at least one episode of grade ≥3 infections.[6] In the RITUXVAS trial, a higher occurrence of severe infectious complications was observed in both treatment arms. While the rate of severe infections was 18% in both arms, the number of patients presenting with non-severe infections was higher (18% vs 9%) in the rituximab group.[5] In general, patients with vasculitis may carry an increased risk to develop severe infections following rituximab administration. In patients with rheumatoid arthritis (RA), long-term follow-up of a global clinical trial programme revealed a serious infection event rate of 3.76 per 100 person-years. In contrast to our findings, opportunistic infections remained rare during follow-up with an event rate of 0.05 events per 100 patient-years in the RA cohort.[15]

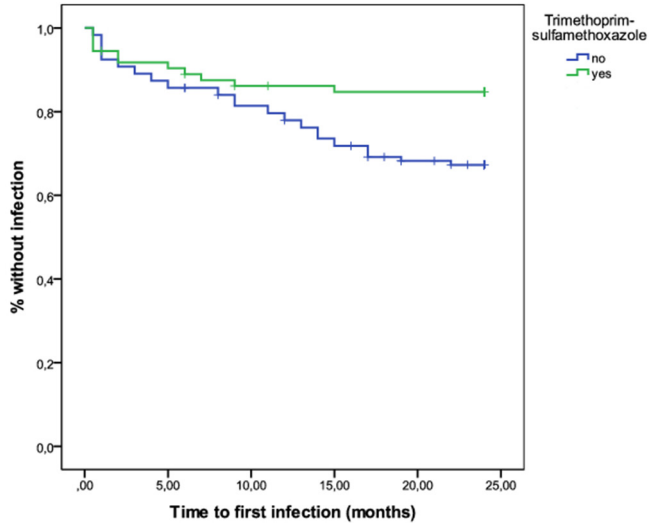


Figure 1 Kaplan-Meier curve of patients presenting with severe infections and either receiving trimethoprim–sulfamethoxazole or prophylaxis or not.

The current European League Against Rheumatism/European Renal Association - European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of AAV encourage *P. jirovecii* prophylaxis in patients receiving cyclophosphamide.[16] However, no concrete recommendation concerning rituximab is given. In the updated EMA label, prophylaxis is recommended during and following rituximab, as appropriate.[17] In this study, the frequency of *P. jirovecii* infection was low (n=1). This frequency is in line with a study reporting one case of *P. jirovecii* in patients receiving mainly cyclophosphamide as induction treatment.[13] Currently, it is uncertain if patients with AAV receiving rituximab benefit from *P. jirovecii* prophylaxis since the reported frequency of severe adverse events attributable to trimethoprim–sulfamethoxazole is high in patients with systemic autoimmune diseases, with some fatalities.[12 18] A randomised controlled trial investigating the role of trimethoprim–sulfamethoxazole in therapeutic dosage (960 mg twice a day for 2 years) found a reduction in respiratory

tract infections and a trend towards fewer non-respiratory tract infections (p=0.05) compared with placebo.[19] This is in line with our study confirming a protective effect of prophylactic trimethoprim–sulfamethoxazole use on the risk to develop severe infections. Thus, it may be appropriate to conclude that trimethoprim–sulfamethoxazole may reduce *P. jirovecii* pneumonia and also reduces overall infective risk and prophylaxis should be initiated in patients with AAV receiving rituximab. In our cohort, patients tolerating trimethoprim–sulfamethoxazole remained on prophylaxis during the 2-year period (mean 14.67 months). Five patients stopped trimethoprim–sulfamethoxazole due to adverse events.

The reported occurrence of severe infections in observational studies of AAV varies (frequency 20%–60%)[3] influenced by follow-up times, prophylactic measures and the impact of different criteria for infections. In our study, 26.06% patients presented with at least one severe infection. The observed frequency is higher compared with both Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis (RAVE) and Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis (RITUXVAS) trials. This may be explained by the scheduled rigorous study visits, allowing for early detection of infection and prescription of antimicrobials, or the selection of a lower risk cohort for the clinical trials. However, the frequency of observed severe infections is similar to other observational studies reported to date.[7 8 20] Older age was an independent risk factor for infections in the pre-rituximab era.[3] We observed an association between age and severe infections in our cohort. Patients with lung involvement and concomitant COPD may be particularly vulnerable to severe infections. Endobronchial involvement and COPD were risk factors for infections and endobronchial involvement alongside severe bronchiectasis predictors of severe pulmonary infections. In patients with AAV on immunosuppressive treatment, most severe infections are located in the respiratory tract.[13 21 22] In rituximab-treated patients, 20 out of 30 infectious complications were restricted to the upper and lower respiratory tract during a follow-up period of 230.4 patient-years.[8] Respiratory tract infections were the leading cause of severe infections in our cohort as well.

Compared with a matched background population, patients with AAV are at an increased risk of severe infections, including non-specific (HR 4.55), Gram-negative (HR 3.49) and *S. aureus* septicaemia (HR 3.40), pneumonia (HR 3.27), acute upper respiratory tract infections (HR 8.88), *C. difficile* infection (HR 5.35) and skin infections (HR 5.35).[23] Interestingly, no difference related to infectious complications was observed when an early cohort was compared with a recent cohort.[23] Another study corroborated an impact of *S. aureus* in patients with AAV, being the most prevalent causative organism (34% of 249 positive cultures). Among 85 positive cultures, 18 (21%) of *S. aureus* isolates were grown despite trimethoprim–sulfamethoxazole prophylaxis. Moreover, 14% of infections caused by *S. aureus* were severe.[13] In contrast, our study found a broad spectrum of opportunistic pathogens and *P. aeruginosa* as well as *S. aureus* (four severe infections, each) were the leading causative organism, followed by *E. coli* (three severe infections). The spectrum of isolates is in line with a recent study reporting the efficacy and safety profile of rituximab in induction and maintenance of remission. Out of 12 severe infections, four led to fatality in four subjects with either coma (meningitis) or respiratory failure (pneumonitis with detection of *P. aeruginosa* or *P. jirovecii*).[7] Both *S. aureus* and Gram-negative bacteria may have a direct impact on disease onset or relapse,[24] which is a potential explanation for the high number of infections caused by these pathogens.

Most infections occur within the first months of treatment. McGregor *et al* showed the highest risk of infections during the first 3 months of follow-up and in general severe infections within the first 12 months were associated with death (19% vs 4%).[13] A recent registry analysis highlighted that a high proportion of severe infections occurred during the first 6 months of follow-up (38.4%).[23] In contrast, severe infections occurred during the whole observational period in our cohort of rituximab-treated patients. In retrospective studies, hypogammaglobulinaemia was a frequently observed complication of rituximab with the need of IgG replacement due to recurrent infections in 4.2% of the patients.[25] Univariate analysis revealed an association between IgG decline of at least 30% from baseline in patients with severe infections. This may indicate that this subgroup of patients with a drop in IgG levels may be specifically prone towards infections.

In conclusion, we found severe infections occurring in approximately one quarter of patients in a 2-year observation period after rituximab therapy for AAV. There was a reduction of severe infections when trimethoprim–sulfamethoxazole prophylaxis was used. Respiratory tract infections were the leading cause of severe infections. We found an association of endobronchial involvement, bronchiectasis and rituximab use for major relapses with severe respiratory tract infections. While these results require confirmation, they support routine use of trimethoprim–sulfamethoxazole in rituximab-treated patients.

Contributors AK, SG and JT retrieved data. Analysis was performed by AK, JK and SG. All authors contributed to the analysis or interpretation of data and critical revision of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer The funding bodies did not have any contribution in collection, analysis, interpretation of data presented or writing of the manuscript.

Competing interests AK has received travel support from Roche/Genentech. DRWJ has received research grants and consulting fees from Roche/Genentech and Terumo BCT and is supported by the Cambridge Biomedical Research Centre.

Patient consent Not required.

Ethics approval Both universities waive specific IRB approval for retrospective analyses.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Jayne D, Rasmussen N. Twenty-five years of European Union collaboration in ANCA-associated vasculitis research. *Nephrol Dial Transplant* 2015;30(Suppl 1):i1–7.
2 Flossmann O, Berden A, de Groot K, *et al*. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011;70:488–94.
3 Kronbichler A, Jayne DR, Mayer G. Frequency, risk factors and prophylaxis of infection in ANCA-associated vasculitis. *Eur J Clin Invest* 2015;45:346–68.
4 Stone JH, Merkel PA, Spiera R, *et al*. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010;363:221–32.
5 Jones RB, Tervaert JW, Hauser T, *et al*. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010;363:211–20.
6 Specks U, Merkel PA, Seo P, *et al*. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013;369:417–27.
7 Charles P, Néel A, Tieulié N, *et al*. Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients. *Rheumatology* 2014;53:532–9.

8 Cartin-Ceba R, Golbin JM, Keogh KA, *et al*. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. *Arthritis Rheum* 2012;64:3770–8.
9 Brunetta P, Martin C, Lehane PB, *et al*. *Two Case Reports of Progressive Multifocal Leukoencephalopathy (PML) in Granulomatosis Polyangiitis (GPA) Treated With Rituximab. 17th International ANCA and Vasculitis Workshop 2015*. London, United Kingdom.
10 Watts R, Lane S, Hanslik T, *et al*. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis* 2007;66:222–7.
11 Institute NC. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009 https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.
12 Park JW, Curtis JR, Moon J, *et al*. Prophylactic effect of trimethoprim–sulfamethoxazole for Pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids. *Ann Rheum Dis* 2018;77:644–9.
13 McGregor JG, Negrete-Lopez R, Poulton CJ, *et al*. Adverse events and infectious burden, microbes and temporal outline from immunosuppressive therapy in antineutrophil cytoplasmic antibody-associated vasculitis with native renal function. *Nephrol Dial Transplant* 2015;30(Suppl 1):i171–81.
14 Jayne DR, Gaskin G, Rasmussen N, *et al*. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007;18:2180–8.
15 van Vollenhoven RF, Fleischmann RM, Furst DE, *et al*. Longterm safety of rituximab: final report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 years. *J Rheumatol* 2015;42:1761–6.
16 Yates M, Watts RA, Bajema IM, *et al*. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* 2016;75:1583–94.
17 Summary of product characteristics rituximab. 2017 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf.
18 Utsunomiya M, Dobashi H, Odani T, *et al*. Optimal regimens of sulfamethoxazole–trimethoprim for chemoprophylaxis of Pneumocystis pneumonia in patients with systemic rheumatic diseases: results from a non-blinded, randomized controlled trial. *Arthritis Res Ther* 2017;19:7.
19 Stegeman CA, Tervaert JW, de Jong PE, *et al*. Trimethoprim–sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. *N Engl J Med* 1996;335:16–20.
20 Calich AL, Puéchal X, Pugnet G, *et al*. Rituximab for induction and maintenance therapy in granulomatosis with polyangiitis (Wegener's). Results of a single-center cohort study on 66 patients. *J Autoimmun* 2014;50:135–41.
21 Goupil R, Brachemi S, Nadeau-Fredette AC, *et al*. Lymphopenia and treatment-related infectious complications in ANCA-associated vasculitis. *Clin J Am Soc Nephrol* 2013;8:416–23.
22 Harper L, Savage CO. ANCA-associated renal vasculitis at the end of the twentieth century—a disease of older patients. *Rheumatology* 2005;44:495–501.
23 Mohammad AJ, Segelmark M, Smith R, *et al*. Severe infection in antineutrophil cytoplasmic antibody-associated vasculitis. *J Rheumatol* 2017;44:1468–75.
24 Kronbichler A, Kerschbaum J, Mayer G. The influence and role of microbial factors in autoimmune kidney diseases: a systematic review. *J Immunol Res* 2015;2015:1–13.
25 Roberts DM, Jones RB, Smith RM, *et al*. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. *J Autoimmun* 2015;57:60–5.

Appendix 4 Manuscript: Long-term maintenance rituximab for ANCA-associated vasculitis: relapse and infection prediction models

RHEUMATOLOGY

Rheumatology 2021;60:1491–1501
doi:10.1093/rheumatology/keaa541
Advance Access publication 3 November 2020

Original article

Long-term maintenance rituximab for ANCA-associated vasculitis: relapse and infection prediction models

Mark E. McClure [1,2,*], Yajing Zhu[3,*], Rona M. Smith [1], Seerapani Gopaluni[1,2], Joanna Tieu[1], Tasneem Pope[2], Karl Emil Kristensen[1], David R. W. Jayne[1,2], Jessica Barrett[3,†] and Rachel B. Jones[1,†]

Abstract

Objectives. Following a maintenance course of rituximab (RTX) for ANCA-associated vasculitis (AAV), relapses occur on cessation of therapy, and further dosing is considered. This study aimed to develop relapse and infection risk prediction models to help guide decision making regarding extended RTX maintenance therapy.

Methods. Patients with a diagnosis of AAV who received 4–8 grams of RTX as maintenance treatment between 2002 and 2018 were included. Both induction and maintenance doses were included; most patients received standard departmental protocol consisting of 2× 1000 mg 2 weeks apart, followed by 1000 mg every 6 months for 2 years. Patients who continued on repeat RTX dosing long-term were excluded. Separate risk prediction models were derived for the outcomes of relapse and infection.

Results. A total of 147 patients were included in this study with a median follow-up of 63 months [interquartile range (IQR): 34–93]. Relapse: At time of last RTX, the model comprised seven predictors, with a corresponding C-index of 0.54. Discrimination between individuals using this model was not possible; however, discrimination could be achieved by grouping patients into low- and high-risk groups. When the model was applied 12 months post last RTX, the ability to discriminate relapse risk between individuals improved (C-index 0.65), and once again, clear discrimination was observed between patients from low- and high-risk groups. Infection: At time of last RTX, five predictors were retained in the model. The C-index was 0.64 allowing discrimination between low and high risk of infection groups. At 12 months post RTX, the C-index for the model was 0.63. Again, clear separation of patients from two risk groups was observed.

Conclusion. While our models had insufficient power to discriminate risk between individual patients they were able to assign patients into risk groups for both relapse and infection. The ability to identify risk groups may help in decisions regarding the potential benefit of ongoing RTX treatment. However, we caution the use of these prediction models until prospective multi-centre validation studies have been performed.

Key words: ANCA, vasculitis, rituximab, relapse, infection, prediction

CLINICAL SCIENCE

Rheumatology key messages

- Benefits of relapse prevention with long-term RTX must be weighed against the risk of RTX-induced immunodeficiency.
- These prediction models can identify risk groups for both relapse and infection outcomes following RTX.
- The ability to assign patients into risk groups may help with decisions regarding ongoing treatment.

[1]Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, UK, [2]Department of Medicine, University of Cambridge, Cambridge, UK and [3]MRC Biostatistics Unit, University of Cambridge, Cambridge, UK

Submitted 27 February 2020; accepted 14 July 2020

Correspondence to: Mark E. McClure, Department of Medicine, University of Cambridge, Level 5, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK. E-mail: mm2238@cam.ac.uk

*McClure and Zhu who contributed equally as first authors.

†Barret and Jones who contributed equally as senior authors.

Introduction

ANCA-associated vasculitis (AAV) is an organ and life-threatening multisystem autoimmune disease that often follows a relapsing and remitting course. B cell-derived ANCAs are implicated in the pathogenesis [1] and evidence from randomized trials supports the use of rituximab (RTX), an anti-CD20 monoclonal antibody that depletes B cells, as both a remission induction and maintenance agent [2–4]. Fixed-interval repeat-dose RTX infusions over a 2-year period is a commonly used approach to maintain remission and prevent relapses [2, 5]. However, after a maintenance course of RTX, relapses occur on cessation of therapy, and further dosing is considered where the benefits of relapse prevention must be weighed against the risk of RTX-induced immunodeficiency and susceptibility to infections.

Patient-specific and disease-specific characteristics exist that can influence an individual's risk of relapse and risk of infectious complications [6–8]. For instance, a consistent finding from observational studies and clinical trials is that having circulating ANCAs against proteinase 3 (PR3) rather than myeloperoxidase (MPO) is a significant risk for relapsing disease [9, 10]. The disease phenotype also influences relapse risk as patients with granulomatosis with polyangiitis (GPA) tend to have more relapses than patients with microscopic polyangiitis (MPA), as do those with involvement of the upper and lower airways. In addition, patients who have had previous relapses, tend to relapse again, and some studies have shown increased relapse risk in patients with better renal function, persistent ANCA positivity and nasal colonization of *Staphylococcus Aureus* [6, 11, 12]. Prior and current immunosuppressive treatments, both in terms of the agent used and the duration of therapy, may also influence relapse risk [6].

Elderly patients are at increased risk of infectious complications associated with immunosuppressive therapy, as are those with impaired renal function, lung damage and diabetes [13–15]. An over-suppressed immune system may be indicated by leukopenia and hypogammaglobulinaemia; the former being more commonly associated with CYC use, whereas the latter has been seen in patients with AAV, both prior to and in association with RTX use [16–18]. Overall immunosuppressive burden including the use of other agents such as prednisolone, CYC and mycophenolate may contribute to hypogammaglobulinaemia. However, there is not a clear association between cumulative RTX exposure, low immunoglobulin levels and infection risk, suggesting complex interplay of many patient, disease and treatment related factors [19]. This heterogeneity between individual patients makes predicting the occurrence and severity of RTX-induced hypogammaglobulinaemia challenging.

In clinical practice, clinicians must weigh up potential relapse and infection risk factors when deciding whether or not an individual patient will benefit from ongoing RTX treatment. Although previous observational studies and clinical trials have identified risk factors for relapse and infection, this is the first study to attempt to generate risk prediction models to help guide decision making regarding extended RTX maintenance therapy in AAV beyond a 2-year RTX treatment course.

Methods

All patients with a diagnosis of AAV (GPA or MPA) who received between 4 and 8 g of RTX at Addenbrooke's Hospital (Cambridge, UK) between January 2002 and January 2018 were included in this study. Both induction and maintenance doses were included; most patients received standard departmental protocol consisting of $2\times$ 1000 mg 2 weeks apart, followed by 1000 mg every 6 months for 2 years; however, 21 (14%) patients were participants in the RITAZAREM trial, in which they received 4 weekly doses of 375 mg/m^2 followed by 1000 mg every 4 months for 20 months. Patients who received ongoing fixed-interval RTX beyond 2 years from the initial induction dose for high perceived relapse risk were excluded ($n = 47$). Concomitant use of CYC or another immunosuppressant including azathioprine, methotrexate, or mycophenolate mofetil was permitted; however, in the majority immunosuppression was discontinued at RTX initiation. Clinical and laboratory data were collected retrospectively using electronic patient records. In accordance with the UK National Health Service Research Ethics Committee guidelines, ethics approval was not required because this work comprises retrospective data, and all treatment decisions were made before our evaluation.

Definitions

Predictors

Diagnosis of clinical phenotype (GPA *vs* MPA) followed the definitions from the Chapel Hill Consensus Conference, 2012 [20]. ANCA positivity was defined based on the reference ranges provided by the manufacturer ($>$1.9 iU/l for PR3-ANCA, $>$3.4 iU/l for MPO-ANCA) using commercial EliA fluoro enzyme immune assay test reagents and the Phadia instrument 2500/5000. B cell return was defined as detectable CD19+ cells in the blood ($\geq 0.01 \times 10^9$/l). The Disease Extent Index [21] was used to score disease activity and organ involvement at time of first RTX dose. Involvement of each organ system scores 2 points; constitutional symptoms score 1 point (total possible score = 21). A patient was classified as having diabetes if the diagnosis was documented in their medical notes or the patient was taking long-term anti-diabetic medications. Structural lung disease was defined as the presence of either obstructive lung disease (endobronchial stenosis, bronchiectasis, emphysema) or restrictive lung disease (fibrosis; not pleural disease). Age was dichotomized at 60 for the relapse models (the median age) and at 70 for infection

models (chosen as older patients are known to have a greater risk of infection [22]). The threshold for infectious events during RTX treatment was defined as either one serious infection (requiring intravenous antibiotics and/or hospital admission) or at least three non-serious infections (requirement of oral antimicrobials in the community). A complete list of all candidate predictors entered into the original models is shown in Tables 1 and 2.

Outcomes

Relapse: time to first relapse was defined as the occurrence of any new manifestations attributable to active vasculitis that required escalation of immunosuppressive therapy beyond a temporary increase in oral corticosteroids in a patient previously in remission. Infection: a clinically relevant definition for infectious events was chosen, which included the composite of either time to first serious infection or third non-serious infection.

Statistical analysis

Full details of the statistical methods can be found in the supplementary materials section (Introduction, Supplementary Figs S1–3, Supplementary Tables S1–3, all available at *Rheumatology* online). From the time of the last dose of RTX, separate risk prediction models were derived for the outcomes of relapse and infection. Time to relapse was censored by death or last follow-up. Time to infection was censored by death, last follow-up or relapse (due to confounding effect of additional immunosuppression). Multivariable Cox proportional hazards models were fitted to each outcome using clinically relevant baseline predictors. Continuous predictors were normalized to improve the stability of estimated coefficients. Proportional hazards assumptions were assessed using Schoenfeld residual plots. Due to a relatively small amount of missing values across all predictors, complete-case analyses were performed.

The predictive performance of each model was assessed using the C-index and the calibration slope. The C-index [23] captures the ability of a model to distinguish between high-risk and low-risk patients (0.5 represents no discrimination and 1 represents perfect discrimination). The calibration slope reflects the agreement between observed and estimated risk (ideal is 1; values below 1 represent over-fitting). When dealing with relatively small sample sizes, it makes more sense to use all of the available data in both training and testing a model rather than splitting the dataset into independent training and test sets, as this would reduce the ability to develop reliable prediction models. Thus, a non-parametric bootstrap procedure (1000 iterations for each analysis), incorporating the variable selection using backwards elimination, was used to correct for over-optimism from assessing predictive performance on the same dataset used to fit the model. Optimism-corrected validation statistics were computed (Supplementary Table S2, available at *Rheumatology* online), and the final model was derived by multiplying the estimated coefficients by a shrinkage factor.

Prediction models for both relapse and infection were then refitted at 12 months following the last dose of RTX. These models used all of the same baseline variables; however, the model for relapse included updated values for serum creatinine (continuous) and ANCA status (positive or negative), as well as the return of B cells within 12 months (binary). Updated values for the infection model at 12 months included serum creatinine, serum immunoglobulin G (IgG) level and total lymphocyte count, each as a continuous variable. Missing values of the latter two variables (>30%) were imputed using their baseline values (correlation is 0.78).

Risk scores were calculated by multiplying 1 or 0 (for binary variables) or the actual value (for continuous variables) by the $\log^{10}$ of the hazard ratio for each variable. The sum of the risk scores for each model represents the linear predictor for the outcome, i.e. an individual's risk score. Risk groups could be assigned by dividing the distribution of all linear predictors by the median (low- and high-risk groups).

Patient population, definition of predictors and outcomes and statistical analysis were planned a priori with the exception of the infection outcome, which was modified post hoc to include the third non-serious infection (in a composite infection outcome) as a meaningful measure of infection-related morbidity after a relatively low event rate was identified with serious infection alone. A power analysis was not conducted because all eligible patients attending the clinic were included in the study.

All analyses were performed in R version 3.5.3 (packages: rms [24] and survminer [25]) with fully reproducible scripts (supplementary, github, available at *Rheumatology* online).

Results

One hundred and forty-seven patients were included in this study with a median follow-up after last RTX of 63 months (IQR: 34–93). Eighty patients experienced a relapse, with a median time to relapse of 45 (IQR: 23–97) months following last RTX. There were 88 infectious events (26 had a serious infection; 62 had ≥3 non-serious infections) with a median time to infection of 44 (IQR: 23–88) months. Ten relapses and 8 infectious events occurred within 12 months, and 7 patients had <12 months follow-up. Therefore, the relapse and infection risk assessment at 12 months post RTX was performed on 130 patients and 122 patients, respectively (see Supplementary Fig. S1, available at *Rheumatology* online, for more details). Clinically relevant predictors are summarized in Table 1 for relapse and Table 2 for infection. Proportional hazard assumption was checked for all models (Supplementary Fig. S2, available at *Rheumatology* online).

Table 1 Candidate predictors for relapse (at time of last RTX and 12 months after the last RTX)

Predictors of relapse	Prediction at time of last RTX			Updated prediction 12 months post last RTX		
	Total (*N* = 147)	No relapse (*N* = 67)	Relapse (*N* = 80)	Total (*N* = 130)	No relapse (*N* = 60)	Relapse (*N* = 70)
Gender, *n* (%)						
Female	76 (52)	34 (51)	42 (52)	70 (54)	32 (53)	38 (54)
Male	71 (48)	33 (49)	38 (48)	60 (46)	28 (47)	32 (46)
Age strata, *n* (%)						
<60	74 (50)	31 (46)	43 (54)	64 (49)	27 (45)	37 (53)
≥60	73 (50)	36 (54)	37 (46)	66 (51)	33 (55)	33 (47)
Disease subtype, *n* (%)						
GPA	122 (83)	51 (76)	71 (88)	107 (82)	45 (75)	62 (88)
MPA	25 (13)	16 (24)	9 (12)	23 (18)	15 (25)	8 (12)
ANCA subtype, *n* (%)						
Negative	8 (5)	4 (6)	4 (5)	8 (6)	4 (7)	4 (6)
MPO	23 (16)	14 (21)	9 (11)	21 (16)	13 (22)	8 (11)
PR3	116 (79)	49 (73)	67 (84)	101 (78)	43 (72)	58 (83)
ANCA positive at end RTX, *n* (%)						
No	104 (71)	49 (73)	55 (69)	–	–	–
Yes	43 (29)	18 (27)	25 (31)	–	–	–
Indication for RTX, *n* (%)						
New disease/refractory	39 (27)	18 (27)	21 (26)	35 (27)	16 (27)	19 (27)
Relapse	108 (73)	49 (73)	59 (74)	95 (73)	44 (73)	51 (73)
ENT involvement, *n* (%)						
No	34 (23)	26 (39)	8 (10)	31 (24)	24 (40)	7 (10)
Yes	113 (77)	41 (61)	72 (90)	99 (76)	36 (60)	63 (90)
Serum creatinine at end RTX, μmol/l						
Median (IQR)	82 (67, 111)	80 (65, 115)	83 (69, 108)	–	–	–
Concomitant CYC or oral IS, *n* (%)						
No	133 (90)	60 (90)	73 (91)	116 (89)	53 (88)	63 (90)
Yes	14 (10)	7 (10)	7 (9)	14 (11)	7 (12)	7 (10)
Cumulative RTX, g						
Median (IQR)	6.0 (5.0, 6.0)	6.0 (5.0, 6.0)	6.0 (5.0, 6.25)	6.0 (5.0, 6.0)	6.0 (5.0, 6.0)	6.0 (5.0, 6.75)
Cumulative CYC prior to 1st RTX, g						
Median (IQR)	6.0 (0.0, 10.0)	4.5 (0.0, 9.0)	7.2 (0.0, 12.0)	6.0 (0.0, 10.0)	4.5 (0.0, 9.0)	7.2 (0.0, 12.0)
Steroid dose at end RTX, mg/day						
Median (IQR)	1.0 (0.0, 5.0)	0.0 (0.0, 5.0)	1.25 (0.0, 5.0)	–	–	–
ANCA status 12 months post last RTX, *n* (%)				**(*N* = 117)**	**(*N* = 55)**	**(*N* = 62)**
Negative	–	–	–	81 (69)	45 (82)	36 (58)
Persistently positive	–	–	–	23 (18)	7 (12)	16 (23)
Negative–positive switch	–	–	–	13 (11)	3 (5)	10 (16)
B cell return within 12 months, *n* (%)				**(*N* = 97)**	**(*N* = 47)**	**(*N* = 50)**
No	–	–	–	41 (42)	25 (53)	16 (32)
Yes				56 (58)	22 (47)	34 (68)
Serum creatinine 12 months post last RTX, μmol/l				**(*N* = 125)**	**(*N* = 57)**	**(*N* = 68)**
Median (IQR)	–	–	–	84 (71, 111)	83 (66, 115)	85 (74, 107)
Steroid dose 12 months post last RTX, mg/day				**(*N* = 130)**	**(*N* = 60)**	**(*N* = 70)**
Median (IQR)	–	–	–	0.75 (0.0, 5.0)	0.0 (0.0, 5.0)	1.75 (0.0, 5.0)

RTX, rituximab; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; ENT, ear, nose and throat; IS, immunosuppression; IQR, interquartile range.

Table 2 Candidate predictors for infection (at time of last RTX and 12 months after the last RTX)

Predictors of infection	Prediction at time of last RTX			Updated prediction 12 months post last RTX		
	Total (*N* = 147)	No infection (*N* = 59)	Infection (*N* = 88)	Total (*N* = 122)	No infection (*N* = 54)	Infection (*N* = 68)
Gender, *n* (%)						
Female	76 (52)	23 (39)	53 (60)	63 (52)	21 (39)	42 (62)
Male	71 (48)	36 (61)	35 (40)	59 (48)	33 (61)	26 (38)
Age strata, *n* (%)						
<70	110 (75)	40 (68)	70 (80)	91 (75)	37 (69)	54 (79)
≥70	37 (25)	19 (32)	18 (20)	31 (25)	17 (31)	14 (21)
Structural lung disease, *n* (%)						
No	107 (73)	51 (86)	56 (64)	92 (75)	47 (87)	45 (66)
Yes	40 (27)	8 (14)	32 (36)	30 (25)	7 (13)	23 (34)
Diabetes, *n* (%)						
No	120 (82)	54 (92)	66 (75)	102 (84)	50 (93)	52 (76)
Yes	27 (18)	5 (8)	22 (25)	20 (16)	4 (7)	16 (24)
Cumulative CYC prior to 1st RTX, g						
Median (IQR)	6.0 (0.0, 10.0)	5.0 (0.0, 9.0)	7.0 (0.0, 12.0)	6.0 (0.0, 10.0)	5.0 (0.0, 9.0)	7.0 (0.0, 11.2)
Concomitant CYC or oral IS, *n* (%)						
No	133 (90)	55 (93)	78 (89)	109 (89)	51 (94)	58 (85)
Yes	14 (10)	4 (7)	10 (11)	13 (11)	3 (6)	10 (15)
Cumulative RTX, g						
Median (IQR)	6.0 (5.0, 6.0)	6.0 (5.0, 6.5)	6.0 (5.0, 6.0)	6.0 (5.0, 6.0)	6.0 (5.0, 6.7)	6.0 (5.0, 6.0)
Steroid dose at end RTX, mg/day						
Median (IQR)	1.0 (0.0, 5.0)	0.0 (0.0, 5.0)	1.7 (0.0, 5.0)	0.7 (0.0, 5.0)	0.0 (0.0, 5.0)	1.2 (0.0, 5.0)
On antibiotic prophylaxis at end RTX, *n* (%)						
No	84 (57)	30 (51)	54 (61)	67 (55)	26 (48)	41 (60)
Yes	63 (43)	29 (49)	34 (39)	55 (45)	28 (52)	27 (40)
Infections during RTX, *n* (%)[a]						
No	128 (87)	55 (93)	73 (83)	112 (92)	50 (93)	62 (91)
Yes	19 (13)	4 (7)	15 (17)	10 (8)	4 (7)	6 (9)
Serum creatinine at end RTX, μmol/l						
Median (IQR)	82 (67, 111)	81 (67, 142)	83 (68, 105)	–	–	–
Nadir serum IgG level during RTX, g/l						
Median (IQR)	6.50 (5.43, 8.10)	7.00 (5.60, 8.41)	6.40 (5.10, 7.80)	6.60 (5.47, 8.39)	7.00 (5.55, 8.42)	6.4 (5.2, 7.9)
Serum IgG level at end RTX, g/l						
Median (IQR)	7.2 (5.9, 9.1)	7.8 (6.4, 9.7)	6.9 (5.7, 8.6)	–	–	–
Total lymphocyte count at end RTX, $\times 10^9$/l	**(*N* = 143)**	**(*N* = 58)**	**(*N* = 85)**	**(*N* = 119)**	**(*N* = 53)**	**(*N* = 66)**
Median (IQR)	1.3 (0.9, 1.6)	1.2 (0.8, 1.5)	1.3 (0.9, 1.7)	1.26 (0.9, 1.6)	1.1 (0.8, 1.5)	1.37 (1.0, 1.7)
Serum creatinine 12 months post RTX, μmol/l				**(*N* = 119)**	**(*N* = 51)**	**(*N* = 68)**
Median (IQR)	–	–	–	84 (70, 111)	85 (67, 142)	84 (72, 99)
Serum IgG level 12 months post RTX, g/l				**(*N* = 94)**	**(*N* = 38)**	**(*N* = 56)**
Median (IQR)	–	–	–	7.2 (5.9, 9.5)	7.7 (6.6, 9.7)	6.7 (5.7, 9.3)
Total lymphocyte count 12 months post RTX, $\times 10^9$/l				**(*N* = 86)**	**(*N* = 35)**	**(*N* = 51)**
Median (IQR)	–	–	–	1.3 (1.0, 1.6)	1.2 (0.8, 1.5)	1.4 (1.1, 1.9)

[a]Clinically relevant infections = ≥1 serious or ≥3 non-serious infections. RTX, rituximab; ENT, ear nose and throat; IS, immunosuppression; IQR, interquartile range.

Relapse

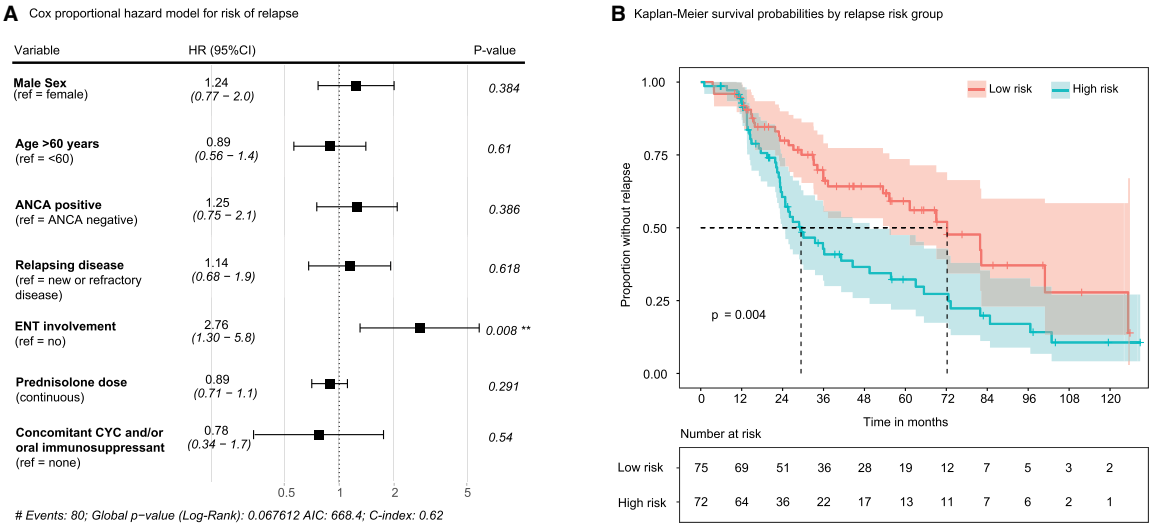
At time of last RTX, 11 baseline predictors were entered into the original model, of which 7 were retained in the final model. ANCA subtype, serum creatinine at end of RTX, cumulative RTX dose and cumulative CYC exposure before first RTX treatment were dropped in the bootstrap backwards elimination procedure (Supplementary Table S1, available at *Rheumatology* online). ENT involvement was found to be associated with a higher risk of relapse [unshrunken hazard ratio (HR) = 2.76 (95% CI: 1.3, 5.8); $P = 0.008$] and the contribution (unshrunken coefficients) of other predictors are shown in Fig. 1A. The optimism-corrected C-index was low (C-index = 0.54), indicating that discrimination between individuals was poor; however, discrimination could be achieved by grouping patients into low-risk and high-risk groups, which have a median time to relapse of 72.2 months and 29.4 months, respectively (Fig. 1B).

For prediction performed 12 months post last RTX, ANCA positivity became a strong predictor of a relapse at this time point [unshrunken HR = 2.73 (95% CI: 1.56, 4.80); $P < 0.001$] while gender, age group, concomitant CYC (or oral immunosuppressant) and return of B cells were dropped from the model due to their limited contribution (Fig. 2A). As a result, the ability of the updated model to discriminate relapse risk between individual patients improved (optimism corrected C-index = 0.65). Furthermore, grouping of patients into low and high risk of relapse was possible with clear separation highlighting the ability of the model to discriminate between these groups. Median time to relapse was 69.6 months and 22 months for the low- and high-risk group, respectively (Fig. 2B). Both relapse models (Supplementary Table S3, available at *Rheumatology* online) were well calibrated (Supplementary Figs S3 A1, A3, A5; B1, B3, B5, available at *Rheumatology* online).

Infection

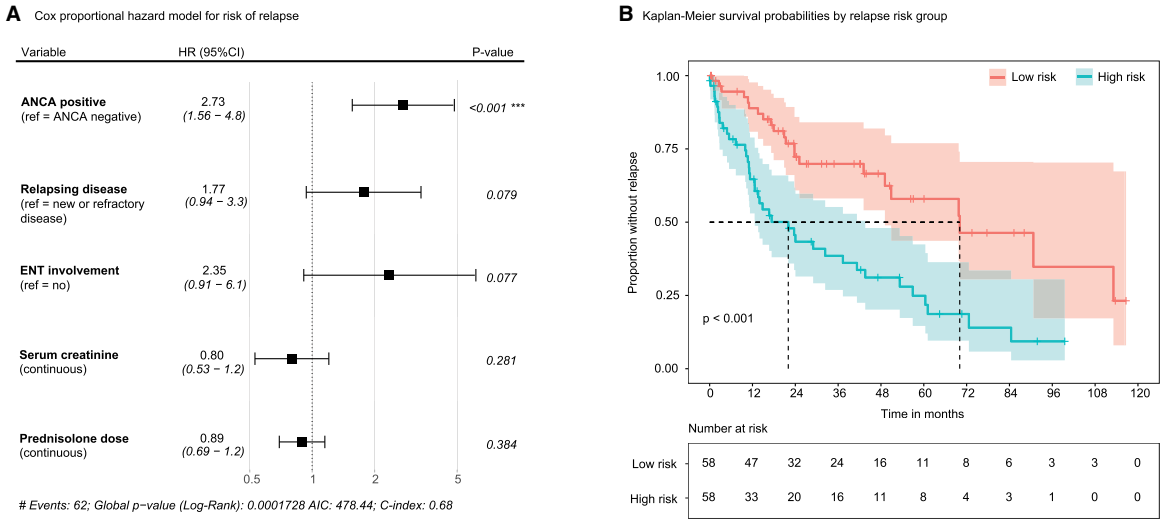
At time of last RTX, a total of 5 (out of 13) predictors were retained in the final model. The presence of structural lung disease [HR = 1.83 (1.17–2.90); $P = 0.008$], diabetes [HR = 2.72 (1.65–4.50); $P < 0.001$], the occurrence of infections during RTX treatment [HR = 2.32 (1.29–4.20); $P = 0.005$] and lower serum IgG level at the end of RTX [HR = 0.71 (0.56–0.90); $P = 0.005$] were significantly associated with infection (Fig. 3A). Age group, use of concomitant CYC (or another oral immunosuppressant), use of antibiotic prophylaxis at the end of RTX, cumulative CYC dose before first RTX, cumulative RTX dose, prednisolone dose at end of RTX, serum creatinine at end of RTX and total lymphocyte count at the end of RTX were not selected for the final model. The optimism-corrected C-index was 0.64 allowing discrimination between low and high risk of infection groups. Median time to infection was 74.8 months and 29 months for the low- and high-risk group, respectively (Fig. 3B).

Fig. 1 Relapse prediction at time of last RTX



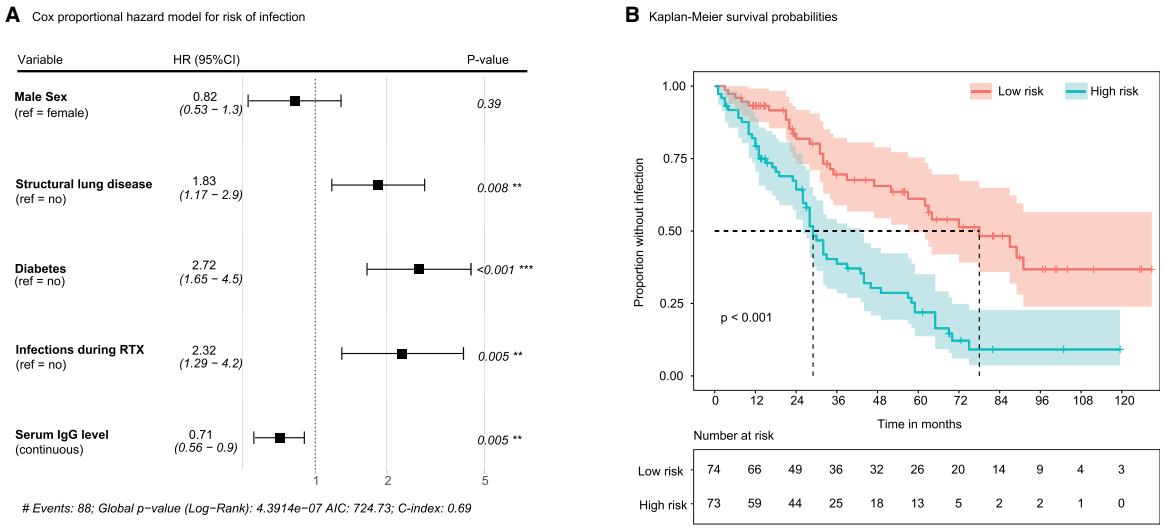
(**A**) Unshrunken multivariable hazard ratios from the Cox proportional hazard model for risk of relapse after the last RTX treatment ($N = 147$). Apparent concordance index (C-index) = 0.62 (optimism corrected C-index = 0.54). (**B**) Estimated survival probabilities by patient risk groups based on the final model using shrunken coefficients. Kaplan-Meier survival probabilities of patients in the low- (below median risk) and high-risk (above median risk) groups of relapse. *P*-value is derived from the non-parametric log-rank test for the differentiability of survival curves. *P*-values <0.05 indicates survival curves were statistically differentiable between groups.

Fig. 2 Relapse prediction 12 months post last RTX



(**A**) Unshrunken multivariable hazard ratios from the Cox proportional hazard model for updated risk of relapse 12 months after the last RTX treatment ($N = 114$). Apparent concordance index (C-index) = 0.68 (optimism corrected C-index = 0.65). (**B**) Estimated survival probabilities by patient risk groups based on the final model using shrunken coefficients. Kaplan-Meier survival probabilities of patients in the low- (below median risk) and high-risk (above median risk) groups of relapse after 12 months post last RTX treatments. *P*-value is derived from the non-parametric log-rank test for the differentiability of survival curves. *P*-values <0.05 indicates survival curves were statistically differentiable between groups.

Fig. 3 Infection prediction at time of last RTX



(**A**) Unshrunken multivariable hazard ratios from the Cox proportional hazard model for risk of infection after the last RTX treatment ($N = 146$). Apparent concordance index (C-index) = 0.68 (optimism corrected C-index= 0.64). (**B**) Estimated survival probabilities by patient risk groups based on the final model using shrunken coefficients. Kaplan-Meier survival probabilities of patients in the low- (below median risk) and high-risk (above median risk) groups of infection. *P*-value is derived from the non-parametric log-rank test for the differentiability of survival curves. *P*-values <0.05 indicates survival curves were statistically differentiable between groups.

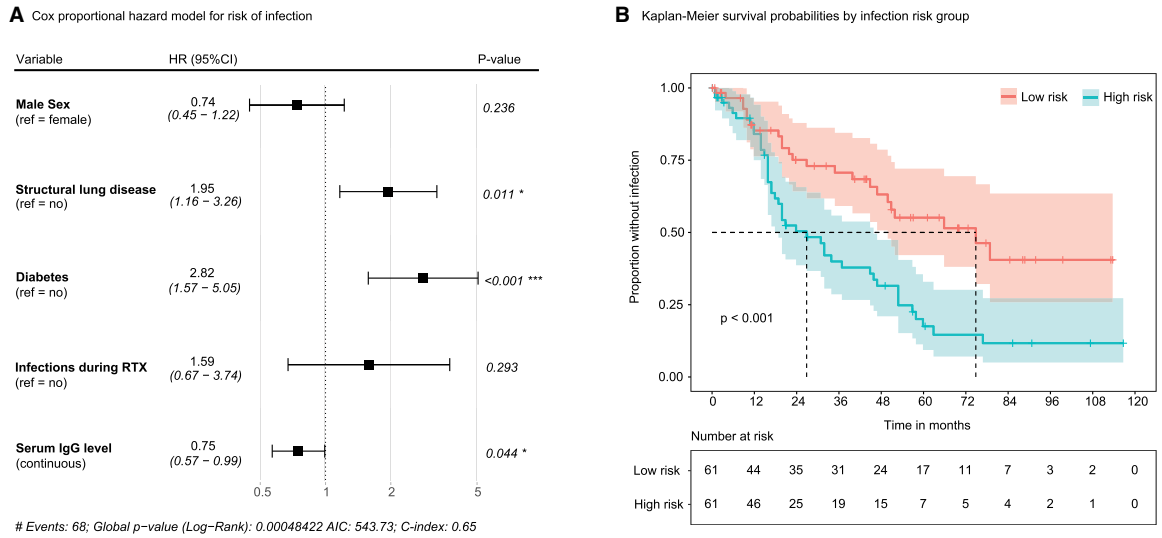
At 12 months post RTX, the predictive power of the presence of lung disease [HR = 1.95 (1.16–3.26); P = 0.011], diabetes [HR = 2.82 (1.57–5.05); P =<0.001] and lower serum IgG level [HR = 0.75 (0.57–0.99); P = 0.044] was strong but the discriminability of the final model was marginally worse than previously (optimism-corrected C-index = 0.63) (Fig. 4A). Once again, clear separation of patients from two risk groups was observed, where median time to infection was 74.8 months and 26.8 months for the low- and high-risk group, respectively (Fig. 4B). The final infection models (Supplementary Table S3, available at *Rheumatology* online) with shrunken coefficients were both well calibrated (Supplementary Figs S3 C1, C3, C5; D1, D3, D5, available at *Rheumatology* online).

Discussion

The aim of this study was to develop relapse and infection risk prediction models to help guide decision making regarding extended RTX maintenance therapy beyond a 2-year treatment course for patients with AAV. Cox proportional hazard models were fitted for each outcome using clinically relevant predictors at two key time points: first, at the time of last RTX and again 12 months after the last RTX. The relapse prediction model when assessed at the time of last RTX performed poorly in terms of its ability to discriminate risk of relapse between individual patients but could discriminate between high- and low-risk groups. The strength of the model improved when performed 12 months later with additional data, once again allowing discrimination into low- and high-risk groups. The improvement in the model was largely driven by the contribution of ANCA positive status, which was associated with a much higher risk of relapse 12 months after RTX but not immediately following RTX. While there is ongoing debate about the clinical utility of ANCA status for predicting relapse, there is growing evidence suggesting greater relevance in the context of B cell-targeted therapy with RTX compared with other less specific immunosuppressive treatments [11, 26]. Contrary to the findings of others [27], B cell return within 12 months of RTX was not associated with earlier relapse. While the relative infrequency and variability of time between measurements of returning B cells among individuals may have limited the strength of this association in our study, a recent randomized trial evaluating the usefulness of B cells and ANCA to inform treatment decisions (RTX given for re-emergence of B cells or ANCA reappearance/rise in titre *vs* fixed-interval RTX administrations) [28], also did not provide strong support for the biomarker-based regimen, highlighting the limitations of these commonly measured biomarkers.

The infection risk models were also able to clearly discriminate between low- and high-risk groups at both last RTX and 12 months after last dose; however, once again, discrimination between individual patients was not possible (C-index 0.64 and 0.63, respectively, for

Fig. 4 Infection prediction 12 months post last RTX



(**A**) Unshrunken multivariable hazard ratios from the Cox proportional hazard model for updated risk of infection 12 months after the last RTX treatment (N = 122). Apparent concordance index (C-index) = 0.71 (optimism corrected C-index = 0.63). (**B**) Estimated survival probabilities by patient risk groups. Kaplan-Meier survival probabilities of patients in the low- (below median risk) and high-risk (above median risk) groups of infection after 12 months post last RTX treatments. P-value is derived from the non-parametric log-rank test for the differentiability of survival curves. P-values <0.05 indicates survival curves were statistically differentiable between groups.

each time point). Previously reported factors driving up the infective risk were the presence of structural lung disease, diabetes and hypogammaglobulinaemia [8, 16, 29], all of which were associated with infection in this cohort and were retained in the final models at both time points. Importantly, infections during RTX were predictive of future infections when assessed immediately after RTX. In contrast to other studies [7], renal impairment and older age did not contribute to infection risk in this study.

Infections are common in patients with diabetes [14]. The hyperglycaemic environment can directly induce immune dysfunction at a cellular level, and complications such as neuropathy, gastrointestinal and urinary dysmotility predispose these patients to more frequent and/or serious infectious events. Diabetes has been shown to be an independent risk factor for infection in patients with autoimmune diseases including AAV, and systemic immunosuppression probably increases the infective risk further [8, 30]. This effect has been observed with conventional therapies and is therefore probably not specific to RTX treatment [8, 31]. Nevertheless, as the strongest predictor of infection in both models, this study highlights the importance of taking diabetes into account when assessing an individual's infective risk.

The association between structural lung disease and infections is also well recognized [15]. Patients with structural lung disease are often colonized with potentially pathogenic microorganisms that predispose to recurrent lower respiratory tract infections. Importantly, chronic infections have also been implicated as triggers as well as persistent drivers of various autoimmune diseases including AAV [32, 33]. However, this paradigm was not supported by the present study when an alternative model was fitted using structural lung disease and previous infections as candidate predictors for relapse as well as infection: structural disease was a risk factor for infection but was not associated with relapse, and no significant association was observed between previous infections and later relapse (data not shown).

Consistent with randomized controlled trials, average IgG levels of this cohort are within population norms [4, 34]. Greater infection risk has been identified in those with moderate to severe hypogammaglobulinaemia [18, 35]. The observed association between IgG levels and risk of infection in this study highlights the impact of immunoglobulin levels on infection risk in patients with AAV following RTX. Extrapolated from its use in the common variable immunodeficiency setting, antibiotic prophylaxis and immunoglobulin replacement has been used in this setting to reduce the risk of infection in this population.

When developing a risk prediction model, a rule of thumb based on the events per variable (EPV) ratio is often used to determine the sample size, where an EPV ratio of 10 or more is needed to avoid the problem of overfitting [36]. When the EPV ratio is <10, the effect of overfitting is pronounced. In the present study the EPV of all four models was >10; however, despite meeting this widely accepted criteria for EPV ratio the strength of our models is limited by the small sample size, highlighted by the wide CIs observed. Nonetheless, a notable strength of our approach was that any over-optimism in apparent performance statistics was considered and adjusted for accordingly. Beyond the methodological limitations of this study, we also acknowledge that the variables themselves may not be such strong predictors of our chosen outcomes. Although previous studies have identified factors such as PR3-ANCA (*vs* MPO-ANCA), GPA (*vs* MPO), lower serum creatinine levels, and a history of prior relapse to be associated with relapse [37–39], we know a proportion of newly diagnosed patients with PR3-ANCA and GPA do not relapse, and conversely a subset of patients with MPO-ANCA and MPA do relapse. Such heterogeneity within AAV limits the accuracy of relapse prediction and may explain why discrimination between individual patients' risk was so difficult to achieve.

Both relapse and infection models are subject to unmeasured bias common to retrospective observational datasets. The exclusion of 47 patients who were given ongoing fixed-interval RTX beyond 2 years as they were deemed to have the highest risk of relapse represents a selection bias that likely weakened the strength of the relapse models. Bias also exists for the infection outcome: it is recognized that the presence of diabetes or structural lung disease and lower lymphocyte and IgG levels are associated with high infection risk [8, 16, 29, 40]. It is likely that the presence of one or more of these risk factors would concern the treating clinician who may take measures to mitigate risk including more frequent clinic follow-up appointments, reduction in corticosteroid dose or use of prophylactic antibiotics, or the use of immunoglobulin replacement therapy. Additionally, non-serious infections treated in the community and serious infection treated in local hospitals were potentially underreported to the specialist clinic. Randomized clinical trials are the gold standard for defining the risk of drug-related adverse effects; however, the published clinical trials of maintenance RTX in AAV [4] are too small to provide reliable risk prediction models and extrapolating risk from induction trials is problematic as outcomes are confounded by differences in the treatment regimens and use of higher doses of corticosteroids when compared with maintenance regimens. A further limitation of the study is the lack of generalizability to other populations given the small sample size derived from a single institution and the comparatively low representation of patients with MPA. While this reflects the more frequent use of maintenance RTX for relapsing GPA, RTX maintenance strategies are used for MPA and thus relapse and infection risk evaluation are of great importance for this group of patients and should be addressed in future studies.

While maintenance protocols have been shaped by the evidence provided by two landmark trials [4, 34]

supporting the use of fixed-interval maintenance RTX (500 mg every 6 months for 18 months in MAINRITSAN and 1000 mg every 4 months for 20 months in RITAZAREM), evidence supporting extended RTX maintenance is lacking, and common practice is to stop therapy after 2 years. Thus, the time points chosen for assessment of relapse and infection risk in the present study (after a 2-year course and again 12 months later) represent important and clinically relevant time points. However, we acknowledge that relapse and infection risk prediction is equally important following a single induction course of RTX, as there is a subgroup of patients who remain in remission for long periods after induction therapy and do not require repeat-dose maintenance RTX. Further studies and more reliable biomarkers are needed to help identify these patients who would benefit from a more personalized and tailored treatment strategy.

Conclusion

To our knowledge these are the first published relapse risk and infection risk prediction models with RTX in AAV. While our models had insufficient power to discriminate risk between individual patients they were able to assign patients into risk groups for both relapse and infection. The ability to identify risk groups may help in decisions regarding the potential benefit of ongoing RTX treatment. However, we caution the use of these prediction models until prospective multi-centre validation studies have been performed.

Funding: This research was co-funded by the NIHR Cambridge Biomedical Research Centre and MRC unit programme MC_UU_00002/5.

Disclosure statement: R.J. has received research funding from GSK, previously undertook an academic secondment to GSK 2011–2013, and currently undertakes consultancy work for Chemocentryx. M.M. is in receipt of an MRC-GSK Experimental Medicine Initiative to Explore New Therapies (EMINENT) fellowship. D.J. has received research grants from Roche/Genentech, Chemocentryx, Genzyme/Sanofi. The other authors have declared no conflicts of interest. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Data sharing statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Jennette JC, Falk RJ. Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. Nat Rev Rheumatol 2014;10:463–73.

2 Specks U, Merkel PA, Seo P *et al.* Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013;369:417–27.

3 Jones RB, Furuta S, Tervaert JWC *et al.* Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. Ann Rheum Dis 2015;74:1178–82.

4 Guillevin L, Pagnoux C, Karras A *et al.* Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771–80.

5 Smith RM, Jones RB, Guerry M-J *et al.* Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:3760–9.

6 Sanders J-SF, Huitma MG, Kallenberg CGM, Stegeman CA. Prediction of relapses in PR3-ANCA-associated vasculitis by assessing responses of ANCA titres to treatment. Rheumatology 2006;45:724–9.

7 Harper L, Savage CO. ANCA-associated renal vasculitis at the end of the twentieth century—a disease of older patients. Rheumatology 2005;44:495–501.

8 Yang L, Xie H, Liu Z *et al.* Risk factors for infectious complications of ANCA-associated vasculitis: a cohort study. BMC Nephrol 2018;19:138.

9 Walsh M, Flossmann O, Berden A *et al.* Risk factors for relapse of antineutrophil cytoplasmic antibody–associated vasculitis. Arthritis Rheum 2012;64:542–8.

10 Hilhorst M, van Paassen P, Tervaert JWC for the Limburg Renal Registry. Proteinase 3-ANCA vasculitis versus myeloperoxidase-ANCA vasculitis. J Am Soc Nephrol 2015;26:2314–27.

11 McClure ME, Wason J, Gopaluni S *et al.* Evaluation of PR3-ANCA status after rituximab for ANCA-associated vasculitis. J Clin Rheumatol 2019;25(5):217–23.

12 Laudien M, Gadola SD, Podschun R *et al.* Nasal carriage of Staphylococcus aureus and endonasal activity in Wegener's granulomatosis as compared to rheumatoid arthritis and chronic rhinosinusitis with nasal polyps. Clin Exp Rheumatol 2010;28:51–5.

13 McGovern D, Williams SP, Parsons K *et al.* Long-term outcomes in elderly patients with ANCA-associated vasculitis. Rheumatology 2019;59(5):1076–83.

14 Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: a review of pathogenesis. Indian J Endocrinol Metab 2012;16(Suppl 1):S27–36.

15 Whitters D, Stockley R. Immunity and bacterial colonisation in bronchiectasis. Thorax 2012;67:1006–13.

16 Roberts DM, Jones RB, Smith RM *et al.* Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun 2015;57:60–5.

17 Marco H, Smith RM, Jones RB *et al.* The effect of rituximab therapy on immunoglobulin levels in patients

with multisystem autoimmune disease. BMC Musculoskelet Disord 2014;15:178.

18 Cortazar FB, Pendergraft WF, Wenger J *et al.* Effect of continuous B cell depletion with rituximab on pathogenic autoantibodies and total IgG levels in antineutrophil cytoplasmic antibody–associated vasculitis. Arthritis Rheumatol 2017;69:1045–53.

19 Tieu J, Gopaluni S, McClure M, Smith R, Jayne D. JD. Rituximab associated hypogammaglobulinemia in autoimmune disease: long term outcomes. Rheumatology 2019;58(Suppl 2):kez063.080.

20 Lionaki S, Blyth ER, Hogan SL *et al.* Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis Rheum 2012;64:3452–62.

21 de Groot K, Gross WL, Herlyn K, Reinhold-Keller E. Development and validation of a disease extent index for Wegener's granulomatosis. Clin Nephrol 2001;55(1): 31–8.

22 Chen M, Yu F, Zhang Y, Zhao M-H. Antineutrophil cytoplasmic autoantibody-associated vasculitis in older patients. Medicine (Baltimore) 2008;87:203–9.

23 Harrell FE Jr. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. Cham, Switzerland: Springer, 2015.

24 Harrell FE Jr. Regression modeling strategies. R Package version 2016;5. https://cran.r-project.org/web/packages/rms/rms.pdf

25 Kassambara A, Kosinski M, Biecek P. Survminer: drawing survival curves using 'ggplot2'. R Package version 03, 2017. https://mi2-warsaw.github.io/publication/kassambara2017survminer/.

26 Fussner LA, Hummel AM, Schroeder DR *et al.* Factors determining the clinical utility of serial measurements of antineutrophil cytoplasmic antibodies targeting proteinase 3. Arthritis Rheumatol 2016;68:1700–10.

27 Alberici F, Smith RM, Jones RB *et al.* Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis. Rheumatology (Oxford) 2015;54:1153–60.

28 Charles P, Terrier B, Perrodeau É *et al.* Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis 2018;77(8):1143–9.

29 Roberts DM, Jones RB, Smith RM *et al.* Immunoglobulin G replacement for the treatment of infective complications of rituximab-associated hypogammaglobulinemia in autoimmune disease: a case series. J Autoimmun 2015;57:24–9.

30 Heusele M, Clerson P, Guery B *et al.* Risk factors for severe bacterial infections in patients with systemic autoimmune diseases receiving rituximab. Clin Rheumatol 2014;33:799–805

31 Trivin C, Tran A, Moulin B *et al.* Infectious complications of a rituximab-based immunosuppressive regimen in patients with glomerular disease. Clin Kidney J 2017; 10(4):461–9. https://academic.oup.com/ckj/article-abstract/10/4/461/2527583.

32 Flint J, Morgan MD, Savage COS. Pathogenesis of ANCA-associated vasculitis. Rheum Dis Clin North Am 2010;36:463–77.

33 Borgmann S. Infectious trigger of Anca-associated vasculitides and other autoimmune diseases. J Bacteriol Parasitol 2012;3(8):e112.

34 Smith R, David J, Peter M. A randomized controlled trial of rituximab versus azathioprine after induction of remission with rituximab for patients with ANCA-associated vasculitis and relapsing disease [abstract]. 2019 ACR/ARP Annual Meeting. Arthritis Rheumatol 2019;71(Suppl. 10). https://acrabstracts.org/abstract/a-randomized-controlled-trial-of-rituximab-versus-azathioprine-after-induction-of-remission-with-rituximab-for-patients-with-anca-associated-vasculitis-and-relapsing-disease/.

35 Shah S, Jaggi K, Greenberg K, Geetha D. Immunoglobulin levels and infection risk with rituximab induction for anti-neutrophil cytoplasmic antibody-associated vasculitis. Clin Kidney J 2017;10:470–4.

36 Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates. J Clin Epidemiol 1995;48(12):1503–10.

37 Booth AD, Almond MK, Burns A *et al.* Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. Am J Kidney Dis 2003;41:776–84.

38 Westman KW, Bygren PG, Olsson H *et al.* Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. J Am Soc Nephrol 1998;9: 842–52.

39 Sanders JSF, Stassen PM, Van Rossum AP, Kallenberg CGM, Stegeman CA. Risk factors for relapse in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis: tools for treatment decisions? Clin Exp Rheumatol 2004;22:94–101.

40 Goupil R, Brachemi S, Nadeau-Fredette A-C *et al.* Lymphopenia and treatment-related infectious complications in ANCA-associated vasculitis. Clin J Am Soc Nephrol 2013;8:416–23.

Appendix 5 RITAZAREM data preparation

Individual trial forms reviewed to ensure all relevant variables were identified

Individual forms were cleaned and reformatted to allow merging of data to “long form”

```
// import visit dates //

import delimited "***\RITAZAREM\forms for dataset\visitdates.csv", varnames(1) clear

reshape long m_, i(studyid) j(visit)

gen month = "screening" if visit == 0
replace month = "M_0" if visit == 1
replace month = "M_1_5" if visit == 2
replace month = "M_3" if visit == 3
replace month = "M_4" if visit == 4

gen visitdate = m_
drop m_

save "***\RITAZAREM\forms for dataset\STATA files for merge\5_visitdate_long.dta"

//import clinical labs //

import delimited "***\RITAZAREM\forms for dataset\7. ClinicalLabs.csv", varnames(1) clear

gen visit0_clesrdatex = date(visit0_clesrdate, "DMY")
format visit0_clesrdatex %tdD_m_Y
drop visit0_clesrdate
rename visit0_clesrdatex visit0_clesrdate

gen visit0_clcrpdatex = date(visit0_clcrpdate, "DMY")
format visit0_clcrpdatex %tdD_m_Y
drop visit0_clcrpdate
rename visit0_clcrpdatex visit0_clcrpdate

gen visit0_clantipr3datex = date(visit0_clantipr3date, "DMY")
format visit0_clantipr3datex %tdD_m_Y
drop visit0_clantipr3date
rename visit0_clantipr3datex visit0_clantipr3date

gen visit0_clantimpodatex = date(visit0_clantimpodate, "DMY")
format visit0_clantimpodatex %tdD_m_Y
drop visit0_clantimpodate
rename visit0_clantimpodatex visit0_clantimpodate

gen visit1_clesrdatex = date(visit1_clesrdate, "DMY")
format visit1_clesrdatex %tdD_m_Y
drop visit1_clesrdate
```

```
rename visit1_clesrdatex visit1_clesrdate

gen visit1_clcrpdatex = date(visit1_clcrpdate, "DMY")
format visit1_clcrpdatex %tdD_m_Y
drop visit1_clcrpdate
rename visit1_clcrpdatex visit1_clcrpdate

gen visit1_clantipr3datex = date(visit1_clantipr3date, "DMY")
format visit1_clantipr3datex %tdD_m_Y
drop visit1_clantipr3date
rename visit1_clantipr3datex visit1_clantipr3date

gen visit1_clantimpodatex = date(visit1_clantimpodate, "DMY")
format visit1_clantimpodatex %tdD_m_Y
drop visit1_clantimpodate
rename visit1_clantimpodatex visit1_clantimpodate

gen visit2_clesrdatex = date(visit2_clesrdate, "DMY")
format visit2_clesrdatex %tdD_m_Y
drop visit2_clesrdate
rename visit2_clesrdatex visit2_clesrdate

gen visit2_clcrpdatex = date(visit2_clcrpdate, "DMY")
format visit2_clcrpdatex %tdD_m_Y
drop visit2_clcrpdate
rename visit2_clcrpdatex visit2_clcrpdate

gen visit2_clantipr3datex = date(visit2_clantipr3date, "DMY")
format visit2_clantipr3datex %tdD_m_Y
drop visit2_clantipr3date
rename visit2_clantipr3datex visit2_clantipr3date

gen visit2_clantimpodatex = date(visit2_clantimpodate, "DMY")
format visit2_clantimpodatex %tdD_m_Y
drop visit2_clantimpodate
rename visit2_clantimpodatex visit2_clantimpodate

gen visit3_clesrdatex = date(visit3_clesrdate, "DMY")
format visit3_clesrdatex %tdD_m_Y
drop visit3_clesrdate
rename visit3_clesrdatex visit3_clesrdate

gen visit3_clcrpdatex = date(visit3_clcrpdate, "DMY")
format visit3_clcrpdatex %tdD_m_Y
drop visit3_clcrpdate
rename visit3_clcrpdatex visit3_clcrpdate

gen visit3_clantipr3datex = date(visit3_clantipr3date, "DMY")
format visit3_clantipr3datex %tdD_m_Y
drop visit3_clantipr3date
rename visit3_clantipr3datex visit3_clantipr3date
```

```
gen visit3_clantimpodatex = date(visit3_clantimpodate, "DMY")
format visit3_clantimpodatex %tdD_m_Y
drop visit3_clantimpodate
rename visit3_clantimpodatex visit3_clantimpodate

gen visit4_clesrdatex = date(visit4_clesrdate, "DMY")
format visit4_clesrdatex %tdD_m_Y
drop visit4_clesrdate
rename visit4_clesrdatex visit4_clesrdate

gen visit4_clcrpdatex = date(visit4_clcrpdate, "DMY")
format visit4_clcrpdatex %tdD_m_Y
drop visit4_clcrpdate
rename visit4_clcrpdatex visit4_clcrpdate

gen visit4_clantipr3datex = date(visit4_clantipr3date, "DMY")
format visit4_clantipr3datex %tdD_m_Y
drop visit4_clantipr3date
rename visit4_clantipr3datex visit4_clantipr3date

gen visit4_clantimpodatex = date(visit4_clantimpodate, "DMY")
format visit4_clantimpodatex %tdD_m_Y
drop visit4_clantimpodate
rename visit4_clantimpodatex visit4_clantimpodate

gen visitBL_clesryn = visit0_clesryn if visit0_clesryn !=""
replace visitBL_clesryn = visit1_clesryn if visit1_clesrdate !=. & visit1_clesrdate >
visit0_clesrdate
replace visitBL_clesryn = visit1_clesryn if visit0_clesrdate ==.

gen visitBL_clesrsigns = visit0_clesrsigns if visit0_clesrsigns !=""
replace visitBL_clesrsigns = visit1_clesrsigns if visit1_clesrdate !=. & visit1_clesrdate >
visit0_clesrdate
replace visitBL_clesrsigns = visit1_clesrsigns if visit0_clesrdate ==.

gen visitBL_clesr = visit0_clesr if visit0_clesr !=""
replace visitBL_clesr = visit1_clesr if visit1_clesrdate !=. & visit1_clesrdate > visit0_clesrdate
replace visitBL_clesr = visit1_clesr if visit0_clesrdate ==.

gen visitBL_clesrdate = visit0_clesrdate if visit0_clesrdate !=.
replace visitBL_clesrdate = visit1_clesrdate if visit1_clesrdate !=. & visit1_clesrdate >
visit0_clesrdate
replace visitBL_clesrdate = visit1_clesrdate if visit0_clesrdate ==.
format visitBL_clesrdate %tdD_m_Y

gen visitBL_clcrpyn = visit0_clcrpyn if visit0_clcrpyn !=""
replace visitBL_clcrpyn = visit1_clcrpyn if visit1_clcrpdate !=. & visit1_clcrpdate >
visit0_clcrpdate
replace visitBL_clcrpyn = visit1_clcrpyn if visit0_clcrpdate ==.
```

```
gen visitBL_clcrpuom = visit0_clcrpuom if visit0_clcrpuom !=""
replace visitBL_clcrpuom = visit1_clcrpuom if visit1_clcrpdate !=. & visit1_clcrpdate >
visit0_clcrpdate
replace visitBL_clcrpuom = visit1_clcrpuom if visit0_clcrpdate ==.

gen visitBL_clcrpsigns = visit0_clcrpsigns if visit0_clcrpsigns !=""
replace visitBL_clcrpsigns = visit1_clcrpsigns if visit1_clcrpdate !=. & visit1_clcrpdate >
visit0_clcrpdate
replace visitBL_clcrpsigns = visit1_clcrpsigns if visit0_clcrpdate ==.

gen visitBL_clcrp = visit0_clcrp if visit0_clcrp !=""
replace visitBL_clcrp = visit1_clcrp if visit1_clcrpdate !=. & visit1_clcrpdate > visit0_clcrpdate
replace visitBL_clcrp = visit1_clcrp if visit0_clcrpdate ==.

gen visitBL_clcrpdate = visit0_clcrpdate if visit0_clcrpdate !=.
replace visitBL_clcrpdate = visit1_clcrpdate if visit1_clcrpdate !=. & visit1_clcrpdate >
visit0_clcrpdate
replace visitBL_clcrpdate = visit1_clcrpdate if visit0_clcrpdate ==.
format visitBL_clcrpdate %tdD_m_Y

gen visitBL_clantipr3 = visit0_clantipr3 if visit0_clantipr3 !=""
replace visitBL_clantipr3 = visit1_clantipr3 if visit1_clantipr3date !=. & visit1_clantipr3date >
visit0_clantipr3date
replace visitBL_clantipr3 = visit1_clantipr3 if visit0_clantipr3date ==.

gen visitBL_clantipr3date = visit0_clantipr3date if visit0_clantipr3date !=.
replace visitBL_clantipr3date = visit1_clantipr3date if visit1_clantipr3date !=. &
visit1_clantipr3date > visit0_clantipr3date
replace visitBL_clantipr3date = visit1_clantipr3date if visit0_clantipr3date ==.
format visitBL_clantipr3date %tdD_m_Y

gen visitBL_clantimpo = visit0_clantimpo if visit0_clantimpo !=""
replace visitBL_clantimpo = visit1_clantimpo if visit1_clantimpodate !=. &
visit1_clantimpodate > visit0_clantimpodate
replace visitBL_clantimpo = visit1_clantimpo if visit0_clantimpodate ==.

gen visitBL_clantimpodate = visit0_clantimpodate if visit0_clantimpodate !=.
replace visitBL_clantimpodate = visit1_clantimpodate if visit1_clantimpodate !=. &
visit1_clantimpodate > visit0_clantimpodate
replace visitBL_clantimpodate = visit1_clantimpodate if visit0_clantimpodate ==.
format visitBL_clantimpodate %tdD_m_Y

drop visit0_clesryn visit0_clesrsigns visit0_clesr visit0_clcrpyn visit0_clcrpuom visit0_clcrpsigns
visit0_clcrp visit0_clcrpdate visit0_clantipr3 visit0_clantipr3date visit0_clantimpo
visit0_clantimpodate visit1_dob_dr visit1_clesryn visit1_clesrsigns visit1_clesr visit1_clesrdate
visit1_clcrpyn visit1_clcrpuom visit1_clcrpsigns visit1_clcrp visit1_clcrpdate visit1_clantipr3
visit1_clantipr3date visit1_clantimpo visit1_clantimpodate

rename visitBL_clesryn visit1_clesryn
rename visitBL_clesrsigns visit1_clesrsigns
rename visitBL_clesr visit1_clesr
```

```
rename visitBL_clesrdate visit1_clesrdate
rename visitBL_clcrpyn visit1_clcrpyn
rename visitBL_clcrpuom visit1_clcrpuom
rename visitBL_clcrpsigns visit1_clcrpsigns
rename visitBL_clcrp visit1_clcrp
rename visitBL_clcrpdate visit1_clcrpdate
rename visitBL_clantipr3 visit1_clantipr3
rename visitBL_clantipr3date visit1_clantipr3date
rename visitBL_clantimpo visit1_clantimpo
rename visitBL_clantimpodate visit1_clantimpodate

save "***\RITAZAREM\forms for dataset\STATA files for merge\9_clinlabs.dta"

// import BVAS //

import delimited "***\RITAZAREM\forms for dataset\4. BVAS.csv", varnames(1) clear

drop subjectinitials_dr dob_dr studyid_dr sitename_dr


// SF-36 visit 1 //

import delimited "***\RITAZAREM\forms for dataset\14. SF36_M0.csv", varnames(1) clear
bysort studyid : gen index =_n
* need to merge SF-36 by question due to the way it is structured in the excel spreadsheet=>
split off each question and reshape and/or merge in as appropriate *

* QUESTION 1 *
bysort studyid : gen index =_n
drop sf36_1yearago sf36_activequest sf36_activlimit sf36_probworkquest sf36_probworktime
sf36_emoprobquest sf36_emoprobtime sf36_socialactivty sf36_bodilypain sf36_workinterfere
sf36_feelingquest sf36_feelingtime sf36_probssocial sf36_torfquest sf36_trueorfalse
reshape wide sf36_general, i(studyid) j(index)
drop sf36_general2 sf36_general3 sf36_general4 sf36_general5 sf36_general6 sf36_general7
sf36_general8 sf36_general9 sf36_general10
gen QOL_sf36_date = date(sf36_evaldate, "DMY")
format QOL_sf36_date %tdD_m_Y
drop sf36_evaldate
gen SF36_01 = sf36_general1
drop sf36_general1
save "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q1.dta"

* QUESTION 2 *
import delimited "***\RITAZAREM\forms for dataset\14. SF36_M0.csv", varnames(1) clear
bysort studyid : gen index =_n

drop sf36_general sf36_activequest sf36_activlimit sf36_probworkquest sf36_probworktime
sf36_emoprobquest sf36_emoprobtime sf36_socialactivty sf36_bodilypain sf36_workinterfere
sf36_feelingquest sf36_feelingtime sf36_probssocial sf36_torfquest sf36_trueorfalse
reshape wide sf36_1yearago, i(studyid) j(index)
```

```
drop  sf36_1yearago2 sf36_1yearago3 sf36_1yearago4 sf36_1yearago5 sf36_1yearago6
sf36_1yearago7 sf36_1yearago8 sf36_1yearago9 sf36_1yearago10
gen QOL_sf36_date = date(sf36_evaldate, "DMY")
format QOL_sf36_date %tdD_m_Y
drop sf36_evaldate
gen SF36_02 = sf36_1yearago1
drop sf36_1yearago1
save "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q2.dta"


* QUESTION 3 *
import delimited "***\RITAZAREM\forms for dataset\14. SF36_M0.csv", varnames(1) clear
bysort studyid : gen index =_n
drop sf36_1yearago sf36_general sf36_probworkquest sf36_probworktime
sf36_emoprobquest sf36_emoprobtime sf36_socialactivty sf36_bodilypain sf36_workinterfere
sf36_feelingquest sf36_feelingtime sf36_probssocial sf36_torfquest sf36_trueorfalse
reshape wide sf36_activequest sf36_activlimit, i(studyid) j(index)
rename sf36_activlimit1 SF36_03a
rename sf36_activlimit2 SF36_03b
rename sf36_activlimit3 SF36_03c
rename sf36_activlimit4 SF36_03d
rename sf36_activlimit5 SF36_03e
rename sf36_activlimit6 SF36_03f
rename sf36_activlimit7 SF36_03g
rename sf36_activlimit8 SF36_03h
rename sf36_activlimit9 SF36_03i
rename sf36_activlimit10 SF36_03j
drop sf36_activequest1 sf36_activequest2 sf36_activequest3 sf36_activequest4
sf36_activequest5 sf36_activequest6 sf36_activequest7 sf36_activequest8 sf36_activequest9
sf36_activequest10
gen QOL_sf36_date = date(sf36_evaldate, "DMY")
format QOL_sf36_date %tdD_m_Y
drop sf36_evaldate
save "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q3.dta"

* QUESTION 4 *
import delimited "***\RITAZAREM\forms for dataset\14. SF36_M0.csv", varnames(1) clear
bysort studyid : gen index =_n
drop sf36_general sf36_1yearago sf36_activequest sf36_activlimit sf36_emoprobquest
sf36_emoprobtime sf36_socialactivty sf36_bodilypain sf36_workinterfere sf36_feelingquest
sf36_feelingtime sf36_probssocial sf36_torfquest sf36_trueorfalse
reshape wide sf36_probworkquest sf36_probworktime, i(studyid) j(index)
drop sf36_probworkquest5 sf36_probworktime5 sf36_probworkquest6 sf36_probworktime6
sf36_probworkquest7 sf36_probworktime7 sf36_probworkquest8 sf36_probworktime8
sf36_probworkquest9 sf36_probworktime9 sf36_probworkquest10 sf36_probworktime10
rename sf36_probworktime1 SF36_04a
rename sf36_probworktime2 SF36_04b
rename sf36_probworktime3 SF36_04c
rename sf36_probworktime4 SF36_04d
```

```
drop sf36_probworkquest1 sf36_probworkquest2 sf36_probworkquest3
sf36_probworkquest4
gen QOL_sf36_date = date(sf36_evaldate, "DMY")
format QOL_sf36_date %tdD_m_Y
drop sf36_evaldate
save "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q4.dta"

* QUESTION 5 *

import delimited "***\RITAZAREM\forms for dataset\14. SF36_M0.csv", varnames(1) clear
bysort studyid : gen index =_n
drop sf36_general sf36_1yearago sf36_activequest sf36_activlimit sf36_probworkquest
sf36_probworktime sf36_socialactivty sf36_bodilypain sf36_workinterfere sf36_feelingquest
sf36_feelingtime sf36_probssocial sf36_torfquest sf36_trueorfalse
reshape wide sf36_emoprobquest sf36_emoprobtime, i(studyid) j(index)
drop sf36_emoprobquest4 sf36_emoprobtime4 sf36_emoprobquest5 sf36_emoprobtime5
sf36_emoprobquest6 sf36_emoprobtime6 sf36_emoprobquest7 sf36_emoprobtime7
sf36_emoprobquest8 sf36_emoprobtime8 sf36_emoprobquest9 sf36_emoprobtime9
sf36_emoprobquest10 sf36_emoprobtime10
rename sf36_emoprobtime1 SF36_05a
rename sf36_emoprobtime2 SF36_05b
rename sf36_emoprobtime3 SF36_05c
drop sf36_emoprobquest1 sf36_emoprobquest2 sf36_emoprobquest3
gen QOL_sf36_date = date(sf36_evaldate, "DMY")
format QOL_sf36_date %tdD_m_Y
drop sf36_evaldate
save "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q5.dta"

* QUESTION 6 *
import delimited "***\RITAZAREM\forms for dataset\14. SF36_M0.csv", varnames(1) clear
bysort studyid : gen index =_n
drop sf36_general sf36_1yearago sf36_activequest sf36_activlimit sf36_probworkquest
sf36_probworktime sf36_emoprobquest sf36_emoprobtime  sf36_bodilypain
sf36_workinterfere sf36_feelingquest sf36_feelingtime sf36_probssocial sf36_torfquest
sf36_trueorfalse
reshape wide sf36_socialactivty, i(studyid) j(index)
drop  sf36_socialactivty2 sf36_socialactivty3 sf36_socialactivty4 sf36_socialactivty5
sf36_socialactivty6 sf36_socialactivty7 sf36_socialactivty8 sf36_socialactivty9
sf36_socialactivty10
rename sf36_socialactivty1 SF36_06
gen QOL_sf36_date = date(sf36_evaldate, "DMY")
format QOL_sf36_date %tdD_m_Y
drop sf36_evaldate
save "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q6.dta"

* QUESTION 7 *
import delimited "***\RITAZAREM\forms for dataset\14. SF36_M0.csv", varnames(1) clear
bysort studyid : gen index =_n
drop  sf36_general sf36_1yearago sf36_activequest sf36_activlimit sf36_probworkquest
sf36_probworktime sf36_emoprobquest sf36_emoprobtime sf36_socialactivty
```

```
sf36_workinterfere sf36_feelingquest sf36_feelingtime sf36_probssocial sf36_torfquest
sf36_trueorfalse
reshape wide sf36_bodilypain, i(studyid) j(index)
drop sf36_bodilypain2 sf36_bodilypain3 sf36_bodilypain4 sf36_bodilypain5 sf36_bodilypain6
sf36_bodilypain7 sf36_bodilypain8 sf36_bodilypain9 sf36_bodilypain10
rename sf36_bodilypain1 SF36_07
gen QOL_sf36_date = date(sf36_evaldate, "DMY")
format QOL_sf36_date %tdD_m_Y
drop sf36_evaldate
save "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q7.dta"

* QUESTION 8 *
import delimited "***\RITAZAREM\forms for dataset\14. SF36_M0.csv", varnames(1) clear
bysort studyid : gen index =_n
drop  sf36_general sf36_1yearago sf36_activequest sf36_activlimit sf36_probworkquest
sf36_probworktime sf36_emoprobquest sf36_emoprobtime sf36_socialactivty
sf36_bodilypain sf36_feelingquest sf36_feelingtime sf36_probssocial sf36_torfquest
sf36_trueorfalse
reshape wide sf36_workinterfere, i(studyid) j(index)
drop sf36_workinterfere2 sf36_workinterfere3 sf36_workinterfere4 sf36_workinterfere5
sf36_workinterfere6 sf36_workinterfere7 sf36_workinterfere8 sf36_workinterfere9
sf36_workinterfere10
rename sf36_workinterfere SF36_08
gen QOL_sf36_date = date(sf36_evaldate, "DMY")
format QOL_sf36_date %tdD_m_Y
drop sf36_evaldate
save "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q8.dta"

* QUESTION 9 *
import delimited "***\RITAZAREM\forms for dataset\14. SF36_M0.csv", varnames(1) clear
bysort studyid : gen index =_n
drop  sf36_general sf36_1yearago sf36_activequest sf36_activlimit sf36_probworkquest
sf36_probworktime sf36_emoprobquest sf36_emoprobtime sf36_socialactivty
sf36_bodilypain sf36_workinterfere sf36_probssocial sf36_torfquest sf36_trueorfalse
reshape wide sf36_feelingquest sf36_feelingtime, i(studyid) j(index)
rename sf36_feelingtime1 SF36_09a
rename sf36_feelingtime2 SF36_09b
rename sf36_feelingtime3 SF36_09c
rename sf36_feelingtime4 SF36_09d
rename sf36_feelingtime5 SF36_09e
rename sf36_feelingtime6 SF36_09f
rename sf36_feelingtime7 SF36_09g
rename sf36_feelingtime8 SF36_09h
rename sf36_feelingtime9 SF36_09i
drop sf36_feelingquest1 sf36_feelingquest2 sf36_feelingquest3 sf36_feelingquest4
sf36_feelingquest5 sf36_feelingquest6 sf36_feelingquest7 sf36_feelingquest8
sf36_feelingquest9 sf36_feelingquest10 sf36_feelingtime10
gen QOL_sf36_date = date(sf36_evaldate, "DMY")
format QOL_sf36_date %tdD_m_Y
drop sf36_evaldate
```

```
save "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q9.dta"

* QUESTION 10 *
import delimited "***\RITAZAREM\forms for dataset\14. SF36_M0.csv", varnames(1) clear
bysort studyid : gen index =_n
drop  sf36_general sf36_1yearago sf36_activequest sf36_activlimit sf36_probworkquest
sf36_probworktime sf36_emoprobquest sf36_emoprobtime sf36_socialactivty
sf36_bodilypain sf36_workinterfere sf36_feelingquest sf36_feelingtime  sf36_torfquest
sf36_trueorfalse
reshape wide sf36_probssocial, i(studyid) j(index)
drop sf36_probssocial2 sf36_probssocial3 sf36_probssocial4 sf36_probssocial5
sf36_probssocial6 sf36_probssocial7 sf36_probssocial8 sf36_probssocial9 sf36_probssocial10
rename sf36_probssocial1 SF36_10
gen QOL_sf36_date = date(sf36_evaldate, "DMY")
format QOL_sf36_date %tdD_m_Y
drop sf36_evaldate
save "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q10.dta"

* QUESTION 11 *
import delimited "***\RITAZAREM\forms for dataset\14. SF36_M0.csv", varnames(1) clear
bysort studyid : gen index =_n
drop  sf36_general sf36_1yearago sf36_activequest sf36_activlimit sf36_probworkquest
sf36_probworktime sf36_emoprobquest sf36_emoprobtime sf36_socialactivty
sf36_bodilypain sf36_workinterfere sf36_feelingquest sf36_feelingtime sf36_probssocial
reshape wide sf36_torfquest sf36_trueorfalse, i(studyid) j(index)
rename sf36_trueorfalse1 SF36_11a
rename sf36_trueorfalse2 SF36_11b
rename sf36_trueorfalse3 SF36_11c
rename sf36_trueorfalse4 SF36_11d
drop sf36_torfquest1 sf36_torfquest2 sf36_torfquest3 sf36_torfquest4 sf36_torfquest5
sf36_trueorfalse5 sf36_torfquest6 sf36_trueorfalse6 sf36_torfquest7 sf36_trueorfalse7
sf36_torfquest8 sf36_trueorfalse8 sf36_torfquest9 sf36_trueorfalse9 sf36_torfquest10
sf36_trueorfalse10
gen QOL_sf36_date = date(sf36_evaldate, "DMY")
format QOL_sf36_date %tdD_m_Y
drop sf36_evaldate
save "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q11.dta"

* MERGE *
* q1 + q2 *
use "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q1.dta", clear
mmerge studyid QOL_sf36_date using "***RITAZAREM\forms for dataset\STATA files for
merge\SF-36 month 0\q2.dta", type (1:1) unmatched(both)
tabulate _merge
drop _merge
* +q3 *
mmerge studyid QOL_sf36_date using "***\RITAZAREM\forms for dataset\STATA files for
merge\SF-36 month 0\q3.dta", type (1:1) unmatched(both)
tabulate _merge
drop _merge
* +q4 *
```

```
mmerge studyid QOL_sf36_date using "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q4.dta", type (1:1) unmatched(both)
tabulate _merge
drop _merge
* +q5 *
mmerge studyid QOL_sf36_date using "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q5.dta", type (1:1) unmatched(both)
tabulate _merge
drop _merge
* + q6 *
mmerge studyid QOL_sf36_date using "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q6.dta", type (1:1) unmatched(both)
tabulate _merge
drop _merge
* + q7 *
mmerge studyid QOL_sf36_date using "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q7.dta", type (1:1) unmatched(both)
tabulate _merge
drop _merge
* + q8 *
mmerge studyid QOL_sf36_date using "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q8.dta", type (1:1) unmatched(both)
tabulate _merge
drop _merge
* + q9 *
mmerge studyid QOL_sf36_date using "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q9.dta", type (1:1) unmatched(both)
tabulate _merge
drop _merge
* + q10 *
mmerge studyid QOL_sf36_date using "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q10.dta", type (1:1) unmatched(both)
tabulate _merge
drop _merge
* + q11 *
mmerge studyid QOL_sf36_date using "***\RITAZAREM\forms for dataset\STATA files for merge\SF-36 month 0\q11.dta", type (1:1) unmatched(both)
tabulate _merge
drop _merge
save "*** \RITAZAREM\forms for dataset\STATA files for merge\10_SF36_month4.dta"

// RUN SF-36 ADO //
* relabel all the variables as numbers *
label define q1 1 "Excellent" 2 "Very Good" 3 "Good" 4 "Fair" 5 "Poor"
gen SF36_01x = .
replace SF36_01x = 1 if SF36_01 == "Excellent"
replace SF36_01x = 2 if SF36_01 == "Very Good"
replace SF36_01x = 3 if SF36_01 == "Good"
replace SF36_01x = 4 if SF36_01 == "Fair"
replace SF36_01x = 5 if SF36_01 == "Poor"
```

```
tabulate SF36_01 SF36_01x
drop SF36_01
rename SF36_01x SF36_01
label values SF36_01 q1
label define q2 1 "Much better now than 1 year ago" 2 "Somewhat better now than 1 year ago" 3 "About the same as 1 year ago" 4 "Somewhat worse now than 1 year ago" 5 "Much worse now than 1 year ago"
gen SF36_02x = .
replace SF36_02x = 1 if SF36_02 == "Much better now than 1 year ago"
replace SF36_02x = 2 if SF36_02 == "Somewhat better now than 1 year ago"
replace SF36_02x = 3 if SF36_02 == "About the same as 1 year ago"
replace SF36_02x = 4 if SF36_02 == "Somewhat worse now than 1 year ago"
replace SF36_02x = 5 if SF36_02 == "Much worse now than 1 year ago"
tabulate SF36_02 SF36_02x
drop SF36_02
rename SF36_02x SF36_02
label values SF36_02 q2
label define q3 1 "Yes, limited a lot" 2 "Yes, limited a little" 3 "No, Not limited at all"
gen SF36_03ax =.
replace SF36_03ax = 1 if SF36_03a == "Yes, limited a lot"
replace SF36_03ax = 2 if SF36_03a == "Yes, limited a little"
replace SF36_03ax = 3 if SF36_03a == "No, Not limited at all"
tabulate SF36_03a SF36_03ax
drop SF36_03a
rename SF36_03ax SF36_03a
label values SF36_03a q3
gen SF36_03bx =.
replace SF36_03bx = 1 if SF36_03b == "Yes, limited a lot"
replace SF36_03bx = 2 if SF36_03b == "Yes, limited a little"
replace SF36_03bx = 3 if SF36_03b == "No, Not limited at all"
tabulate SF36_03b SF36_03bx
drop SF36_03b
rename SF36_03bx SF36_03b
label values SF36_03b q3
gen SF36_03cx =.
replace SF36_03cx = 1 if SF36_03c == "Yes, limited a lot"
replace SF36_03cx = 2 if SF36_03c == "Yes, limited a little"
replace SF36_03cx = 3 if SF36_03c == "No, Not limited at all"
tabulate SF36_03c SF36_03cx
drop SF36_03c
rename SF36_03cx SF36_03c
label values SF36_03c q3
gen SF36_03dx =.
replace SF36_03dx = 1 if SF36_03d == "Yes, limited a lot"
replace SF36_03dx = 2 if SF36_03d == "Yes, limited a little"
replace SF36_03dx = 3 if SF36_03d == "No, Not limited at all"
tabulate SF36_03d SF36_03dx
drop SF36_03d
rename SF36_03dx SF36_03d
label values SF36_03d q3
```

```
gen SF36_03ex =.
replace SF36_03ex = 1 if SF36_03e == "Yes, limited a lot"
replace SF36_03ex = 2 if SF36_03e == "Yes, limited a little"
replace SF36_03ex = 3 if SF36_03e == "No, Not limited at all"
tabulate SF36_03e SF36_03ex
drop SF36_03e
rename SF36_03ex SF36_03e
label values SF36_03e q3
gen SF36_03fx =.
replace SF36_03fx = 1 if SF36_03f == "Yes, limited a lot"
replace SF36_03fx = 2 if SF36_03f == "Yes, limited a little"
replace SF36_03fx = 3 if SF36_03f == "No, Not limited at all"
tabulate SF36_03f SF36_03fx
drop SF36_03f
rename SF36_03fx SF36_03f
label values SF36_03f q3
gen SF36_03gx =.
replace SF36_03gx = 1 if SF36_03g == "Yes, limited a lot"
replace SF36_03gx = 2 if SF36_03g == "Yes, limited a little"
replace SF36_03gx = 3 if SF36_03g == "No, Not limited at all"
tabulate SF36_03g SF36_03gx
drop SF36_03g
rename SF36_03gx SF36_03g
label values SF36_03g q3
gen SF36_03hx =.
replace SF36_03hx = 1 if SF36_03h == "Yes, limited a lot"
replace SF36_03hx = 2 if SF36_03h == "Yes, limited a little"
replace SF36_03hx = 3 if SF36_03h == "No, Not limited at all"
tabulate SF36_03h SF36_03hx
drop SF36_03h
rename SF36_03hx SF36_03h
label values SF36_03h q3
gen SF36_03ix =.
replace SF36_03ix = 1 if SF36_03i == "Yes, limited a lot"
replace SF36_03ix = 2 if SF36_03i == "Yes, limited a little"
replace SF36_03ix = 3 if SF36_03i == "No, Not limited at all"
tabulate SF36_03i SF36_03ix
drop SF36_03i
rename SF36_03ix SF36_03i
label values SF36_03i q3
gen SF36_03jx =.
replace SF36_03jx = 1 if SF36_03j == "Yes, limited a lot"
replace SF36_03jx = 2 if SF36_03j == "Yes, limited a little"
replace SF36_03jx = 3 if SF36_03j == "No, Not limited at all"
tabulate SF36_03j SF36_03jx
drop SF36_03j
rename SF36_03jx SF36_03j
label values SF36_03j q3
label define yesno 1 "Yes" 2 "No"
gen SF36_04ax = .
replace SF36_04ax = 1 if SF36_04a == "Yes"
```

```
replace SF36_04ax = 2 if SF36_04a == "No"
tabulate SF36_04a SF36_04ax
drop SF36_04a
rename SF36_04ax SF36_04a
label values SF36_04a yesno
gen SF36_04bx = .
replace SF36_04bx = 1 if SF36_04b == "Yes"
replace SF36_04bx = 2 if SF36_04b == "No"
tabulate SF36_04b SF36_04bx
drop SF36_04b
rename SF36_04bx SF36_04b
label values SF36_04b yesno
gen SF36_04cx = .
replace SF36_04cx = 1 if SF36_04c == "Yes"
replace SF36_04cx = 2 if SF36_04c == "No"
tabulate SF36_04c SF36_04cx
drop SF36_04c
rename SF36_04cx SF36_04c
label values SF36_04c yesno
gen SF36_04dx = .
replace SF36_04dx = 1 if SF36_04d == "Yes"
replace SF36_04dx = 2 if SF36_04d == "No"
tabulate SF36_04d SF36_04dx
drop SF36_04d
rename SF36_04dx SF36_04d
label values SF36_04d yesno
gen SF36_05ax = .
replace SF36_05ax = 1 if SF36_05a == "Yes"
replace SF36_05ax = 2 if SF36_05a == "No"
tabulate SF36_05a SF36_05ax
drop SF36_05a
rename SF36_05ax SF36_05a
label values SF36_05a yesno
gen SF36_05bx = .
replace SF36_05bx = 1 if SF36_05b == "Yes"
replace SF36_05bx = 2 if SF36_05b == "No"
tabulate SF36_05b SF36_05bx
drop SF36_05b
rename SF36_05bx SF36_05b
label values SF36_05b yesno
gen SF36_05cx = .
replace SF36_05cx = 1 if SF36_05c == "Yes"
replace SF36_05cx = 2 if SF36_05c == "No"
tabulate SF36_05c SF36_05cx
drop SF36_05c
rename SF36_05cx SF36_05c
label values SF36_05c yesno
label define q6 1 "Not at all" 2 "Slightly" 3 "Moderately" 4 "Quite a bit" 5 "Extremely"
gen SF36_06x = .
replace SF36_06x = 1 if SF36_06 == "Not at all"
replace SF36_06x = 2 if SF36_06 == "Slightly"
```

```
replace SF36_06x = 3 if SF36_06 == "Moderately"
replace SF36_06x = 4 if SF36_06 == "Quite a bit"
replace SF36_06x = 5 if SF36_06 == "Extremely"
tabulate SF36_06 SF36_06x
drop SF36_06
rename SF36_06x SF36_06
label values SF36_06 q6
label define q7 1 "None" 2 "Very mild" 3 "Mild" 4 "Moderate" 5 "Severe" 6 "Very severe"
gen SF36_07x = .
replace SF36_07x = 1 if SF36_07 == "None"
replace SF36_07x = 2 if SF36_07 == "Very mild"
replace SF36_07x = 3 if SF36_07 == "Mild"
replace SF36_07x = 4 if SF36_07 == "Moderate"
replace SF36_07x = 5 if SF36_07 == "Severe"
replace SF36_07x = 6 if SF36_07 == "Very severe"
tabulate SF36_07 SF36_07x
drop SF36_07
rename SF36_07x SF36_07
label values SF36_07 q7
gen SF36_08x = .
replace SF36_08x = 1 if SF36_08 == "Not at all"
replace SF36_08x = 2 if SF36_08 == "Slightly"
replace SF36_08x = 3 if SF36_08 == "Moderately"
replace SF36_08x = 4 if SF36_08 == "Quite a bit"
replace SF36_08x = 5 if SF36_08 == "Extremely"
tabulate SF36_08 SF36_08x
drop SF36_08
rename SF36_08x SF36_08
label values SF36_08 q6
label define q9 1 "All of the time" 2 "Most of the time" 3 "A good bit of the time" 4 "Some of
the time" 5 "A little of the time" 6 "None of the time"
gen SF36_09ax = .
replace SF36_09ax = 1 if SF36_09a == "All of the time"
replace SF36_09ax = 2 if SF36_09a == "Most of the time"
replace SF36_09ax = 3 if SF36_09a == "A good bit of the time"
replace SF36_09ax = 4 if SF36_09a == "Some of the time"
replace SF36_09ax = 5 if SF36_09a == "A little of the time"
replace SF36_09ax = 6 if SF36_09a == "None of the time"
tabulate SF36_09a SF36_09ax
drop SF36_09a
rename SF36_09ax SF36_09a
label values SF36_09a q9
gen SF36_09bx = .
replace SF36_09bx = 1 if SF36_09b == "All of the time"
replace SF36_09bx = 2 if SF36_09b == "Most of the time"
replace SF36_09bx = 3 if SF36_09b == "A good bit of the time"
replace SF36_09bx = 4 if SF36_09b == "Some of the time"
replace SF36_09bx = 5 if SF36_09b == "A little of the time"
replace SF36_09bx = 6 if SF36_09b == "None of the time"
tabulate SF36_09b SF36_09bx
```

```
drop SF36_09b
rename SF36_09bx SF36_09b
label values SF36_09b q9
gen SF36_09cx = .
replace SF36_09cx = 1 if SF36_09c == "All of the time"
replace SF36_09cx = 2 if SF36_09c == "Most of the time"
replace SF36_09cx = 3 if SF36_09c == "A good bit of the time"
replace SF36_09cx = 4 if SF36_09c == "Some of the time"
replace SF36_09cx = 5 if SF36_09c == "A little of the time"
replace SF36_09cx = 6 if SF36_09c == "None of the time"
tabulate SF36_09c SF36_09cx
drop SF36_09c
rename SF36_09cx SF36_09c
label values SF36_09c q9
gen SF36_09dx = .
replace SF36_09dx = 1 if SF36_09d == "All of the time"
replace SF36_09dx = 2 if SF36_09d == "Most of the time"
replace SF36_09dx = 3 if SF36_09d == "A good bit of the time"
replace SF36_09dx = 4 if SF36_09d == "Some of the time"
replace SF36_09dx = 5 if SF36_09d == "A little of the time"
replace SF36_09dx = 6 if SF36_09d == "None of the time"
tabulate SF36_09d SF36_09dx
drop SF36_09d
rename SF36_09dx SF36_09d
label values SF36_09d q9
gen SF36_09ex = .
replace SF36_09ex = 1 if SF36_09e == "All of the time"
replace SF36_09ex = 2 if SF36_09e == "Most of the time"
replace SF36_09ex = 3 if SF36_09e == "A good bit of the time"
replace SF36_09ex = 4 if SF36_09e == "Some of the time"
replace SF36_09ex = 5 if SF36_09e == "A little of the time"
replace SF36_09ex = 6 if SF36_09e == "None of the time"
tabulate SF36_09e SF36_09ex
drop SF36_09e
rename SF36_09ex SF36_09e
label values SF36_09e q9
gen SF36_09fx = .
replace SF36_09fx = 1 if SF36_09f == "All of the time"
replace SF36_09fx = 2 if SF36_09f == "Most of the time"
replace SF36_09fx = 3 if SF36_09f == "A good bit of the time"
replace SF36_09fx = 4 if SF36_09f == "Some of the time"
replace SF36_09fx = 5 if SF36_09f == "A little of the time"
replace SF36_09fx = 6 if SF36_09f == "None of the time"
tabulate SF36_09f SF36_09fx
drop SF36_09f
rename SF36_09fx SF36_09f
label values SF36_09f q9
gen SF36_09gx = .
replace SF36_09gx = 1 if SF36_09g == "All of the time"
replace SF36_09gx = 2 if SF36_09g == "Most of the time"
replace SF36_09gx = 3 if SF36_09g == "A good bit of the time"
```

```
replace SF36_09gx = 4 if SF36_09g == "Some of the time"
replace SF36_09gx = 5 if SF36_09g == "A little of the time"
replace SF36_09gx = 6 if SF36_09g == "None of the time"
tabulate SF36_09g SF36_09gx
drop SF36_09g
rename SF36_09gx SF36_09g
label values SF36_09g q9
gen SF36_09hx = .
replace SF36_09hx = 1 if SF36_09h == "All of the time"
replace SF36_09hx = 2 if SF36_09h == "Most of the time"
replace SF36_09hx = 3 if SF36_09h == "A good bit of the time"
replace SF36_09hx = 4 if SF36_09h == "Some of the time"
replace SF36_09hx = 5 if SF36_09h == "A little of the time"
replace SF36_09hx = 6 if SF36_09h == "None of the time"
tabulate SF36_09h SF36_09hx
drop SF36_09h
rename SF36_09hx SF36_09h
label values SF36_09h q9
gen SF36_09ix = .
replace SF36_09ix = 1 if SF36_09i == "All of the time"
replace SF36_09ix = 2 if SF36_09i == "Most of the time"
replace SF36_09ix = 3 if SF36_09i == "A good bit of the time"
replace SF36_09ix = 4 if SF36_09i == "Some of the time"
replace SF36_09ix = 5 if SF36_09i == "A little of the time"
replace SF36_09ix = 6 if SF36_09i == "None of the time"
tabulate SF36_09i SF36_09ix
drop SF36_09i
rename SF36_09ix SF36_09i
label values SF36_09i q9
label define q10 1 "All of the time" 2 "Most of the time" 3 "Some of the time" 4 "A little of the
time" 5 "None of the time"
gen SF36_10x = .
replace SF36_10x = 1 if SF36_10 == "All of the time"
replace SF36_10x = 2 if SF36_10 == "Most of the time"
replace SF36_10x = 3 if SF36_10 == "Some of the time"
replace SF36_10x = 4 if SF36_10 == "A little of the time"
replace SF36_10x = 5 if SF36_10 == "None of the time"
tabulate SF36_10 SF36_10x
drop SF36_10
rename SF36_10x SF36_10
label values SF36_10 q10
label define q11 1 "Definitely true" 2 "Mostly true" 3 "Don't know" 4 "Mostly false" 5
"Definitely false"
gen SF36_11ax = .
replace SF36_11ax = 1 if SF36_11a == "Definitely true"
replace SF36_11ax = 2 if SF36_11a == "Mostly true"
replace SF36_11ax = 3 if SF36_11a == "Don't know"
replace SF36_11ax = 4 if SF36_11a == "Mostly false"
replace SF36_11ax = 5 if SF36_11a == "Definitely false"
tabulate SF36_11a SF36_11ax
drop SF36_11a
```

```
rename SF36_11ax SF36_11a
label values SF36_11a q11
gen SF36_11bx = .
replace SF36_11bx = 1 if SF36_11b == "Definitely true"
replace SF36_11bx = 2 if SF36_11b == "Mostly true"
replace SF36_11bx = 3 if SF36_11b == "Don't know"
replace SF36_11bx = 4 if SF36_11b == "Mostly false"
replace SF36_11bx = 5 if SF36_11b == "Definitely false"
tabulate SF36_11b SF36_11bx
drop SF36_11b
rename SF36_11bx SF36_11b
label values SF36_11b q11
gen SF36_11cx = .
replace SF36_11cx = 1 if SF36_11c == "Definitely true"
replace SF36_11cx = 2 if SF36_11c == "Mostly true"
replace SF36_11cx = 3 if SF36_11c == "Don't know"
replace SF36_11cx = 4 if SF36_11c == "Mostly false"
replace SF36_11cx = 5 if SF36_11c == "Definitely false"
tabulate SF36_11c SF36_11cx
drop SF36_11c
rename SF36_11cx SF36_11c
label values SF36_11c q11
gen SF36_11dx = .
replace SF36_11dx = 1 if SF36_11d == "Definitely true"
replace SF36_11dx = 2 if SF36_11d == "Mostly true"
replace SF36_11dx = 3 if SF36_11d == "Don't know"
replace SF36_11dx = 4 if SF36_11d == "Mostly false"
replace SF36_11dx = 5 if SF36_11d == "Definitely false"
tabulate SF36_11d SF36_11dx
drop SF36_11d
rename SF36_11dx SF36_11d
label values SF36_11d q11
sf36, check var val natver(US)
=> SF-36 domain scores and summary scores generated
save "***\RITAZAREM\forms for dataset\STATA files for merge\10_SF36_month0_results.dta"

// SF-36 4 month //
import delimited "***\RITAZAREM\forms for dataset\14. SF36_M4.csv", varnames(1) clear
* month 0 process repeated for month 4 data … *

 // EQ5D //
import delimited "***\RITAZAREM\forms for dataset\13. EQ5D_visit4.csv", varnames(1) clear
gen eqmobx = .
replace eqmobx = 1 if eqmob == "I have no problems walking about"
replace eqmobx = 2 if eqmob == "I have some problems walking about"
replace eqmobx = 3 if eqmob == "I am confined to bed"
tabulate eqmob eqmobx
drop eqmob
rename eqmobx eqmob
label define eqmob 1 "I have no problems walking about" 2 "I have some problems walking
about" 3 "I am confined to bed"
```

```
label values eqmob eqmob
 gen eqcarex = .
replace eqcarex = 1 if eqcare == "I have no problems with self-care"
replace eqcarex = 2 if eqcare == "I have some problems with self-care"
replace eqcarex = 3 if eqcare == "I am unable to wash or dress myself"
tabulate eqcare eqcarex
drop eqcare
rename eqcarex eqcare
label define eqcare 1 "I have no problems with self-care" 2 "I have some problems with self-
care" 3 "I am unable to wash or dress myself"
label values eqcare eqcare
 gen equactx = .
replace equactx = 1 if equact == "I have no problems with performing my usual activities"
replace equactx = 2 if equact == "I have some problems with performing my usual activities"
replace equactx = 3 if equact == "I am unable to perform my usual activities"
tabulate equact equactx
drop equact
rename equactx equact
label define equact 1 "I have no problems with performing my usual activities" 2 "I have some
problems with perfoming my usual activities" 3 "I am unable to perform my usual activities"
label values equact equact
gen eqpainx = .
replace eqpainx = 1 if eqpain == "I have no pain or discomfort"
replace eqpainx = 2 if eqpain == "I have moderate pain or discomfort"
replace eqpainx = 3 if eqpain == "I have extreme pain or discomfort"
tabulate eqpain eqpainx
drop eqpain
rename eqpainx eqpain
label define eqpain 1 "I have no pain or discomfort" 2 "I have moderate pain or discomfort" 3
"I have extreme pain or discomfort"
label values eqpain eqpain
gen eqanxx = .
replace eqanxx = 1 if eqanx == "I am not anxious or depressed"
replace eqanxx = 2 if eqanx == "I am moderately anxious or depressed"
replace eqanxx = 3 if eqanx == "I am extremely anxious or depressed"
tabulate eqanx eqanxx
drop eqanx
rename eqanxx eqanx
label define eqanx 1 "I am not anxious or depressed" 2 "I am moderately anxious or
depressed" 3 "I am extremely anxious or depressed"
label values eqanx eqanx
gen eq_scale = real(eq_vas) if eq_vas !="NA"
drop eq_vas
gen eq5d_date = date(eq_date, "DMY")
format eq5d_date %tdD_m_Y
drop eq_date
eq5d eqmob eqcare equact eqpain eqanx, country(US)
rename eqmob eqmob_1
rename eqcare eqcare_1
rename equact equact_1
rename eqpain eqpain_1
```

```
rename eqanx eqanx_1
rename eq_scale eq_scale_1
rename eq5D_date_visit1 eq5d_date_1
rename _index eqindex_1
rename eqmob eqmob_4
rename eqcare eqcare_4
rename equact equact_4
rename eqpain eqpain_4
rename eqanx eqanx_4
rename eq_scale eq_scale_4
rename eq5d_date eq5d_date_4
rename _index eqindex_4
// MERGE MORE //
use "***\RITAZAREM\forms for dataset\STATA files for merge\stable variables.dta", clear
drop _merge
mmerge studyid using "***\RITAZAREM\forms for dataset\STATA files for
merge\5_death.dta", simple
drop _merge
mmerge studyid using "***\RITAZAREM\forms for dataset\STATA files for
merge\6_BVAS_wide.dta", simple
drop _merge
mmerge studyid using "***\Box\RITAZAREM\forms for dataset\STATA files for
merge\7_CDAvisit1.dta", simple
drop _merge
mmerge studyid using "***\Box\RITAZAREM\forms for dataset\STATA files for
merge\8_CDAvisit4.dta", simple
drop _merge
mmerge studyid using "***\Box\RITAZAREM\forms for dataset\STATA files for
merge\9_clinlabs.dta", simple
drop _merge
mmerge studyid using "***\Box\RITAZAREM\forms for dataset\STATA files for
merge\10_SF36_month0_results.dta", simple
drop _merge
rename QOL_sf36_date sf36_date_1
rename SF36_01 SF36_01_1
rename SF36_02 SF36_02_1
rename SF36_03a SF36_03a_1
rename SF36_03b SF36_03b_1
rename SF36_03c SF36_03c_1
rename SF36_03d SF36_03d_1
rename SF36_03e SF36_03e_1
rename SF36_03f SF36_03f_1
rename SF36_03g SF36_03g_1
rename SF36_03h SF36_03h_1
rename SF36_03i SF36_03i_1
rename SF36_03j SF36_03j_1
rename SF36_04a SF36_04a_1
rename SF36_04b SF36_04b_1
rename SF36_04c SF36_04c_1
rename SF36_04d SF36_04d_1
rename SF36_05a SF36_05a_1
```

```
rename SF36_05b SF36_05b_1
rename SF36_05c SF36_05c_1
rename SF36_06 SF36_06_1
rename SF36_07 SF36_07_1
rename SF36_08 SF36_08_1
rename SF36_09a SF36_09a_1
rename SF36_09b SF36_09b_1
rename SF36_09c SF36_09c_1
rename SF36_09d SF36_09d_1
rename SF36_09e SF36_09e_1
rename SF36_09f SF36_09f_1
rename SF36_09g SF36_09g_1
rename SF36_09h SF36_09h_1
rename SF36_09i SF36_09i_1
rename SF36_10 SF36_10_1
rename SF36_11a SF36_11a_1
rename SF36_11b SF36_11b_1
rename SF36_11c SF36_11c_1
rename SF36_11d SF36_11d_1
rename tx_01 tx_01_1
rename tx_02 tx_02_1
rename tx_03a tx_03a_1
rename tx_03b tx_03b_1
rename tx_03c tx_03c_1
rename tx_03d tx_03d_1
rename tx_03e tx_03e_1
rename tx_03f tx_03f_1
rename tx_03g tx_03g_1
rename tx_03h tx_03h_1
rename tx_03i tx_03i_1
rename tx_03j tx_03j_1
rename tx_04a tx_04a_1
rename tx_04b tx_04b_1
rename tx_04c tx_04c_1
rename tx_04d tx_04d_1
rename tx_05a tx_05a_1
rename tx_05b tx_05b_1
rename tx_05c tx_05c_1
rename tx_06 tx_06_1
rename tx_07 tx_07_1
rename tx_08 tx_08_1
rename tx_09a tx_09a_1
rename tx_09b tx_09b_1
rename tx_09c tx_09c_1
rename tx_09d tx_09d_1
rename tx_09e tx_09e_1
rename tx_09f tx_09f_1
rename tx_09g tx_09g_1
rename tx_09h tx_09h_1
rename tx_09i tx_09i_1
rename tx_10 tx_10_1
```

```
rename tx_11a tx_11a_1
rename tx_11b tx_11b_1
rename tx_11c tx_11c_1
rename tx_11d tx_11d_1
rename PF PF_1
rename RP RP_1
rename RE RE_1
rename MH MH_1
rename VT VT_1
rename BP BP_1
rename GH GH_1
rename SF SF_1
rename HT HT_1
rename PF_trans PF_trans_1
rename GH_trans GH_trans_1
rename VT_trans VT_trans_1
rename MH_trans MH_trans_1
rename RP_trans RP_trans_1
rename RE_trans RE_trans_1
rename SF_trans SF_trans_1
rename BP_trans BP_trans_1
rename raw_PHYS raw_PHYS_1
rename raw_MENT raw_MENT_1
rename std_PHYS std_PHYS_1
rename std_MENT std_MENT_1
mmerge studyid using "***\RITAZAREM\forms for dataset\STATA files for
merge\10_SF36_month4.dta", simple
* rename process repeated with _4
drop _merge
mmerge studyid using "***\RITAZAREM\forms for dataset\STATA files for
merge\11_EQ5D_visit1.dta", simple
drop _merge
mmerge studyid using "***\RITAZAREM\forms for dataset\STATA files for
merge\11_EQ5Dvisit4.dta", simple
drop _merge

// PROMIS- fatigue //
import delimited "***\RITAZAREM\forms for dataset\15. PROMIS.csv"
rename studyid PIN
rename promfatigued_0 HI7_0
rename promfatigued_1 HI7_1
rename promfatigued_3 HI7_3
rename promfatigued_4 HI7_4
rename profatigstart_0 AN3_0
rename profatigstart_1 AN3_1
rename profatigstart_3 AN3_3
rename profatigstart_4 AN3_4
rename promfatrundown_0 FATEXP41_0
rename promfatrundown_1 FATEXP41_1
rename promfatrundown_3 FATEXP41_3
rename promfatrundown_4 FATEXP41_4
```

```
rename promfataverage_0 FATEXP40_0
rename promfataverage_1 FATEXP40_1
rename promfataverage_3 FATEXP40_3
rename promfataverage_4 FATEXP40_4
drop promisevaldate_0 promis_month v33 promisevaldate_3 promisevaldate_4 v48
promisevaldate_1 v18
preserve
reshape long HI7_ AN3_ FATEXP41_ FATEXP40_, i(PIN) j(Assmnt)
label define fatigue 1 "Not at all" 2 "A little bit" 3 "Somewhat" 4 "Quite a bit" 5 "Very much"
rename HI7_ HI7
rename AN3_ AN3
rename FATEXP41_ FATEXP41
rename FATEXP40_ FATEXP40
gen HI7x = 999
replace HI7x = 1 if HI7 == "Not at all"
replace HI7x = 2 if HI7 == "A little bit"
replace HI7x = 3 if HI7 == "Somewhat"
replace HI7x = 4 if HI7 == "Quite a bit"
replace HI7x = 5 if HI7 == "Very much"
tabulate HI7 HI7x
drop HI7
rename HI7x HI7
label values HI7 fatigue
gen AN3x = 999
replace AN3x = 1 if AN3 == "Not at all"
replace AN3x = 2 if AN3 == "A little bit"
replace AN3x = 3 if AN3 == "Somewhat"
replace AN3x = 4 if AN3 == "Quite a bit"
replace AN3x = 5 if AN3 == "Very much"
tabulate AN3 AN3x
drop AN3
rename AN3x AN3
label values AN3 fatigue
gen FATEXP41x = 999
replace FATEXP41x = 1 if FATEXP41 == "Not at all"
replace FATEXP41x = 2 if FATEXP41 == "A little bit"
replace FATEXP41x = 3 if FATEXP41 == "Somewhat"
replace FATEXP41x = 4 if FATEXP41 == "Quite a bit"
replace FATEXP41x = 5 if FATEXP41 == "Very much"
tabulate FATEXP41 FATEXP41x
drop FATEXP41
rename FATEXP41x FATEXP41
label values FATEXP41 fatigue
gen FATEXP40x = 999
replace FATEXP40x = 1 if FATEXP40 == "Not at all"
replace FATEXP40x = 2 if FATEXP40 == "A little bit"
replace FATEXP40x = 3 if FATEXP40 == "Somewhat"
replace FATEXP40x = 4 if FATEXP40 == "Quite a bit"
replace FATEXP40x = 5 if FATEXP40 == "Very much"
```

```
tabulate FATEXP40 FATEXP40x
drop FATEXP40
rename FATEXP40x FATEXP40
label values FATEXP40 fatigue
label drop fatigue
export delimited using "***\RITAZAREM\forms for dataset\RITAZAREM_4m_fatigue.csv",
replace
label define fatigue 1 "Not at all" 2 "A little bit" 3 "Somewhat" 4 "Quite a bit" 5 "Very much"

// PAIN interference
import delimited "***\RITAZAREM\forms for dataset\15. PROMIS.csv"
rename studyid PIN
rename prompainactiv_0 PAININ9_0
rename prompainactiv_1 PAININ9_1
rename prompainactiv_3 PAININ9_3
rename prompainactiv_4 PAININ9_4
rename prompainwork_0 PAININ22_0
rename prompainwork_1 PAININ22_1
rename prompainwork_3 PAININ22_3
rename prompainwork_4 PAININ22_4
rename prompainsocial_0 PAININ31_0
rename prompainsocial_1 PAININ31_1
rename prompainsocial_3 PAININ31_3
rename prompainsocial_4 PAININ31_4
rename prompainchores_0 PAININ34_0
rename prompainchores_1 PAININ34_1
rename prompainchores_3 PAININ34_3
rename prompainchores_4 PAININ34_4
reshape long PAININ9_ PAININ22_ PAININ31_ PAININ34_, i(PIN) j(Assmnt)
label define pain 1 "Not at all" 2 "A little bit" 3 "Somewhat" 4 "Quite a bit" 5 "Very much"
rename PAININ9_ PAININ9
rename PAININ22_ PAININ22
rename PAININ31_ PAININ31
rename PAININ34_ PAININ34
gen PAININ9x = 999
replace PAININ9x = 1 if PAININ9 == "Not at all"
replace PAININ9x = 2 if PAININ9 == "A little bit"
replace PAININ9x = 3 if PAININ9 == "Somewhat"
replace PAININ9x = 4 if PAININ9 == "Quite a bit"
replace PAININ9x = 5 if PAININ9 == "Very much"
tabulate PAININ9 PAININ9x
drop PAININ9
rename PAININ9x PAININ9
gen PAININ22x = 999
replace PAININ22x = 1 if PAININ22 == "Not at all"
replace PAININ22x = 2 if PAININ22 == "A little bit"
replace PAININ22x = 3 if PAININ22 == "Somewhat"
replace PAININ22x = 4 if PAININ22 == "Quite a bit"
replace PAININ22x = 5 if PAININ22 == "Very much"
tabulate PAININ22 PAININ22x
drop PAININ22
```

```
rename PAININ22x PAININ22
gen PAININ31x = 999
replace PAININ31x = 1 if PAININ31 == "Not at all"
replace PAININ31x = 2 if PAININ31 == "a little bit"
replace PAININ31x = 3 if PAININ31 == "Somewhat"
replace PAININ31x = 4 if PAININ31 == "Quite a bit"
replace PAININ31x = 5 if PAININ31 == "Very much"
tabulate PAININ31 PAININ31x
drop PAININ31
rename PAININ31x PAININ31
gen PAININ34x = 999
replace PAININ34x = 1 if PAININ34 == "Not at all"
replace PAININ34x = 2 if PAININ34 == "A little bit"
replace PAININ34x = 3 if PAININ34 == "Somewhat"
replace PAININ34x = 4 if PAININ34 == "Quite a bit"
replace PAININ34x = 5 if PAININ34 == "Very much"
tabulate PAININ34 PAININ34x
drop PAININ34
rename PAININ34x PAININ34
export delimited using "***\RITAZAREM\forms for dataset\RITAZAREM_4m_PROMIS.csv",
replace
label values PAININ9 pain
label values PAININ22 pain
label values PAININ31 pain
label values PAININ34 pain
// physical ability //
import delimited "***\RITAZAREM\forms for dataset\15. PROMIS.csv", clear
* manual drop of unnecessary variables
rename studyid PIN
rename promphysvacuum_0 PFA11_0
rename promphysvacuum_1 PFA11_1
rename promphysvacuum_3 PFA11_3
rename promphysvacuum_4 PFA11_4
rename promphysstairs_0 PFA21_0
rename promphysstairs_1 PFA21_1
rename promphysstairs_3 PFA21_3
rename promphysstairs_4 PFA21_4
rename promphys15mins_0 PFA23_0
rename promphys15mins_1 PFA23_1
rename promphys15mins_3 PFA23_3
rename promphys15mins_4 PFA23_4
rename promphysshop_0 PFA53_0
rename promphysshop_1 PFA53_1
rename promphysshop_3 PFA53_3
rename promphysshop_4 PFA53_4
reshape long PFA11_ PFA21_ PFA23_ PFA53_, i(PIN) j(Assmnt)
label define physical 5 "Without any difficulty" 4 "With a little difficulty" 3 "With some
difficulty" 2 "With much difficulty" 1 "Unable to do it"
rename PFA11_ PFA11
rename PFA21_ PFA21
rename PFA23_ PFA23
```

```
rename PFA53_ PFA53
gen PFA11x = 999
replace PFA11x = 1 if PFA11 == "Unable to do it"
replace PFA11x = 2 if PFA11 == "With much difficulty"
replace PFA11x = 3 if PFA11 == "With some difficulty"
replace PFA11x = 4 if PFA11 == "With little difficulty"
replace PFA11x = 5 if PFA11 == "Without any difficulty"
tabulate PFA11 PFA11x
drop PFA11
rename PFA11x PFA11
gen PFA21x = 999
replace PFA21x = 1 if PFA21 == "Unable to do it"
replace PFA21x = 2 if PFA21 == "With much difficulty"
replace PFA21x = 3 if PFA21 == "With some difficulty"
replace PFA21x = 4 if PFA21 == "With a little difficulty"
replace PFA21x = 5 if PFA21 == "Without any difficulty"
tabulate PFA21 PFA21x
drop PFA21
rename PFA21x PFA21
gen PFA23x = 999
replace PFA23x = 1 if PFA23 == "Unable to do it"
replace PFA23x = 2 if PFA23 == "With much difficulty"
replace PFA23x = 3 if PFA23 == "With some difficulty"
replace PFA23x = 4 if PFA23 == "With a little difficulty"
replace PFA23x = 5 if PFA23 == "Without any difficulty"
tabulate PFA23 PFA23x
drop PFA23
rename PFA23x PFA23
gen PFA53x = 999
replace PFA53x = 1 if PFA53 == "Unable to do it"
replace PFA53x = 2 if PFA53 == "With much difficulty"
replace PFA53x = 3 if PFA53 == "With some difficulty"
replace PFA53x = 4 if PFA53 == "With a little difficulty"
replace PFA53x = 5 if PFA53 == "Without any difficulty"
tabulate PFA53 PFA53x
drop PFA53
rename PFA53x PFA53
export
label values PFA11 physical
label values PFA21 physical
label values PFA23 physical
label values PFA53 physical

// dates and PGA //
* re-import file
keep studyid promisevaldate_0 promispga_0 promisevaldate_1 promispga_1
promisevaldate_3 promispga_3 promisevaldate_4 promispga_4
reshape long promispga_ promisevaldate_, i(studyid) j(month)
rename promisevaldate_ promdate
rename promispga_ promispga
```

```
gen promdatex = date(promdate, "DMY")
format promdatex %tdD_m_Y
drop promdate
rename promdatex promdate
save "***\RITAZAREM\forms for dataset\STATA files for merge\15_PROMIS_stem.dta"

// merge PROMIS datasets //
import delimited "***\RITAZAREM\forms for dataset\PROMIS results\fatigue_formerge.csv",
clear
save "***\RITAZAREM\forms for dataset\STATA files for
merge\15_PROMIS_fatigue_merge.dta"
import delimited "***\RITAZAREM\forms for dataset\PROMIS results\pain_formerge.csv",
clear
drop inst
save "***\RITAZAREM\forms for dataset\STATA files for merge\15_PROMIS_stem_pain.dta"
import delimited "***\RITAZAREM\forms for dataset\PROMIS results\phys_formerge.csv",
clear
drop inst
save "***\RITAZAREM\forms for dataset\STATA files for
merge\15_PROMIS_phys_formerge.dta"
use "***\RITAZAREM\forms for dataset\STATA files for merge\15_PROMIS_stem.dta"
mmerge studyid month using "***\RITAZAREM\forms for dataset\STATA files for
merge\15_PROMIS_fatigue_merge.dta"
save "***\RITAZAREM\forms for dataset\STATA files for
merge\15_PROMIS_stem_fatigue.dta"
use "***\RITAZAREM\forms for dataset\STATA files for merge\15_PROMIS_stem_fatigue.dta"
drop inst _merge
mmerge studyid month using "***\RITAZAREM\forms for dataset\STATA files for
merge\15_PROMIS_stem_pain.dta"
use "***\RITAZAREM\forms for dataset\STATA files for
merge\15_PROMIS_stem_fatigue_pain.dta", clear
drop _merge
mmerge studyid month using "***\RITAZAREM\forms for dataset\STATA files for
merge\15_PROMIS_phys_formerge.dta"
save "***\RITAZAREM\forms for dataset\STATA files for merge\15_PROMIS_processed.dta"

*** MERGING PROCESS ***

// start with demographics form //
import delimited "*** \RITAZAREM\forms for dataset\1. demographics.csv"
// convert dob from string to date //
gen dobx = date(dob, "DMY")
format dobx %tdD_m_Y
 // save section //
 save "***\RITAZAREM\forms for dataset\STATA files for merge\1_demographics.dta"
 // baseline information //
import delimited "***\RITAZAREM\forms for dataset\2. BLMedHistory.csv", varnames(1) clear
drop subjectinitials_dr dob_dr studyid_dr sitename_dr
gen datedx = date(mhdatediagno, "DMY")
format datedx %tdD_m_Y
/* replace mhimmunofloyes="" if mhimmunofloyes == "NA" */
```

```
save "***\RITAZAREM\forms for dataset\STATA files for merge\2_Baseline.dta"
// baseline information 2 //
import delimited "***\RITAZAREM\forms for dataset\3. BLMedHistory2.csv", varnames(1)
clear
drop subjectinitials_dr dob_dr studyid_dr sitename_dr
save "***\RITAZAREM\forms for dataset\STATA files for merge\3_baseline.dta"
// import enrollment //
import delimited "***\RITAZAREM\forms for dataset\9. enrollment.csv", varnames(1) clear
gen date_enrolment = date(enroldate, "DMY")
format date_enrolment %tdD_m_Y
save "***\RITAZAREM\forms for dataset\STATA files for merge\4_enrolment.dta"
// merge baseline data //
/* ssc install mmerge */
use "***\RITAZAREM\forms for dataset\STATA files for merge\1_demographics.dta"
mmerge studyid using "***\RITAZAREM\forms for dataset\STATA files for
merge\2_Baseline.dta", simple
mmerge studyid using "***\RITAZAREM\forms for dataset\STATA files for
merge\3_baseline.dta", simple
mmerge studyid using "***\RITAZAREM\forms for dataset\STATA files for
merge\4_enrolment.dta", simple
save "***\RITAZAREM\forms for dataset\STATA files for merge\stable variables.dta"
/*expand 4*/
// import death //
import delimited "***\RITAZAREM\forms for dataset\8. death.csv", varnames(1) clear
gen death_date = date(deathdate, "DMY")
format death_date %tdD_m_Y
drop deathdate
save "***\RITAZAREM\forms for dataset\STATA files for merge\5_death.dta"
//  merge death data in //
mmerge studyid using "***\RITAZAREM\forms for dataset\STATA files for
merge\5_death.dta"
* total of 9 deaths
// withdrawal form //
import delimited "***\RITAZAREM\forms for dataset\12. WithdrawalTrial.csv", varnames(1)
clear
drop wdothspec_trial
save "***\RITAZAREM\forms for dataset\STATA files for merge\12_withdrawal.dta"
// merge withdrawal form in //
use "***\RITAZAREM\forms for dataset\STATA files for merge\stable variables 20200501.dta",
clear
mmerge studyid using "***\RITAZAREM\forms for dataset\STATA files for
merge\12_withdrawal.dta"
* 25 in using and master=> correct, only 25 patients in withdrawal => studyid and dates of
withdrawal checked
gen withdrawal_date = date(wddate_trial, "DMY")
format withdrawal_date %tdD_m_Y
drop wddate_trial
// BVAS //

// import BVAS //
```

```
import delimited "***\RITAZAREM\forms for dataset\4. BVAS.csv", varnames(1) clear
drop subjectinitials_dr dob_dr studyid_dr sitename_dr
rename visit1_bvas11majornew bvas11majornew_0
rename visit2_bvas11majornew bvas11majornew_1
rename visit3_bvas11majornew bvas11majornew_3
rename visit4_bvas11majornew bvas11majornew_4
rename visit1_bvas11minornew bvas11minornew_0
rename visit2_bvas11minornew bvas11minornew_1
rename visit3_bvas11minornew bvas11minornew_3
rename visit4_bvas11minornew bvas11minornew_4
rename visit1_bvas11majorpers bvas11majorpers_0
rename visit2_bvas11majorpers bvas11majorpers_1
rename visit3_bvas11majorpers bvas11majorpers_3
rename visit4_bvas11majorpers bvas11majorpers_4
rename visit1_bvas11minorpers bvas11minorpers_0
rename visit2_bvas11minorpers bvas11minorpers_1
rename visit3_bvas11minorpers bvas11minorpers_3
rename visit4_bvas11minorpers bvas11minorpers_4
rename visit1_bvas_majtotal bvasmajtotal_0
rename visit2_bvas_majtotal bvasmajtotal_1
rename visit3_bvas_majtotal bvasmajtotal_3
rename visit4_bvas_majtotal bvasmajtotal_4
rename visit1_bvas_minortotal bvasminortotal_0
rename visit2_bvas_minortotal bvasminortotal_1
rename visit3_bvas_minortotal bvasminortotal_3
rename visit4_bvas_minortotal bvasminortotal_4
rename visit1_bvasscore bvasscore_0
rename visit2_bvasscore bvasscore_1
rename visit3_bvasscore bvasscore_3
rename visit4_bvasscore bvasscore_4
rename visit1_bvas12a bvas12a_0
rename visit2_bvas12a bvas12a_1
rename visit3_bvas12a bvas12a_3
rename visit4_bvas12a bvas12a_4
rename visit1_bvas12b bvas12b_0
rename visit2_bvas12b bvas12b_1
rename visit3_bvas12b bvas12b_3
rename visit4_bvas12b bvas12b_4
rename visit1_bvas12c bvas12c_0
rename visit2_bvas12c bvas12c_1
rename visit3_bvas12c bvas12c_3
rename visit4_bvas12c bvas12c_4
rename visit1_bvas12d bvas12d_0
rename visit2_bvas12d bvas12d_1
rename visit3_bvas12d bvas12d_3
rename visit4_bvas12d bvas12d_4
rename visit1_bvaspga bvaspga_0
rename visit2_bvaspga bvaspga_1
rename visit3_bvaspga bvaspga_3
rename visit4_bvaspga bvaspga_4
```

```
* change BVAS items froms strings to numbers where it's a number *
* rename BVAS/CDA and reshape to long *
reshape long bvas11majornew_ bvas11minornew_ bvas11majorpers_ bvas11minorpers_
bvasmajtotal_ bvasminortotal_ bvasscore_ bvas12a_ bvas12b_ bvas12c_ bvas12d_ bvaspga_,
i(studyid) j(month)
rename bvas12a_ bvas12a
rename bvas12b_ bvas12b
rename bvas12c_ bvas12c
rename bvas12d_ bvas12d
rename bvas11majornew_ bvas11majornew
rename bvas11minornew_ bvas11minornew
rename bvas11minorpers_ bvas11minorpers
rename bvas11majorpers_ bvas11majorpers
rename bvasmajtotal_ bvasmajtotal
rename bvasminortotal_ bvasminortotal
rename bvasscore_ bvasscore
rename bvaspga_ bvaspga
// CDA \\
use "***\RITAZAREM\forms for dataset\STATA files for merge\7_CDAvisit1.dta", clear
rename visit1_cda_a cdaa_0
rename visit1_cda_b cdab_0
rename visit1_cda_c cdac_0
rename visit1_cda_d cdad_0
rename visit1_cda_e cdae_0
rename visit1_cda_f cdaf_0
rename visit1_cda_g cdag_0
rename visit1_cda_h cdah_0
rename visit1_cda_i cdai_0
rename visit1_cda_j cdaj_0
rename visit1_cda_k cdak_0
rename visit1_cdascore cdascore_0
rename visit1_cdascore_cat cdascorecat_0
rename visit1_cdascore_grp cdascoregrp_0
save "***\RITAZAREM\forms for dataset\STATA files for merge\7_CDAvisit1.dta"
use "***\RITAZAREM\forms for dataset\STATA files for merge\8_CDAvisit4.dta", clear
rename visit4_cda_a_4 cdaa_4
rename visit4_cda_b_4 cdab_4
rename visit4_cda_c_4 cdac_4
rename visit4_cda_d_4 cdad_4
rename visit4_cda_e_4 cdae_4
rename visit4_cda_f_4 cdaf_4
rename visit4_cda_g_4 cdag_4
rename visit4_cda_h_4 cdah_4
rename visit4_cda_i_4 cdai_4
rename visit4_cda_j_4 cdaj_4
rename visit4_cda_k_4 cdak_4
rename visit4_cdascore_4 cdascore_4
rename visit4_cdascore_cat_4 cdascorecat_4
rename visit4_cdascore_grp_4 cdascoregrp_4

save "***\RITAZAREM\forms for dataset\STATA files for merge\8_CDAvisit4.dta", replace
```

```
use "***\RITAZAREM\forms for dataset\STATA files for merge\7_CDAvisit1.dta", clear
mmerge studyid using "***\RITAZAREM\forms for dataset\STATA files for
merge\8_CDAvisit4.dta"
reshape long cdaa_ cdab_ cdac_ cdad_ cdae_ cdaf_ cdag_ cdah_ cdai_ cdaj_ cdak_ cdascore_
cdascorecat_ cdascoregrp_, i(studyid) j(month)
drop _merge
rename cdaa_ cdaa
rename cdab_ cdab
rename cdac_ cdac
rename cdad_ cdad
rename cdae_ cdae
rename cdaf_ cdaf
rename cdag_ cdag
rename cdah_ cdah
rename cdai_ cdai
rename cdaj_ cdaj
rename cdak_ cdak
rename cdascore_ cdascore
rename cdascorecat_ cdascorecat
rename cdascoregrp_ cdascoregrp
save "***\RITAZAREM\forms for dataset\STATA files for merge\7_CDA_long.dta"
// SF36 \\
use "***\RITAZAREM\forms for dataset\STATA files for merge\10_SF36_month0_results.dta",
clear
gen month = 1
save "***\RITAZAREM\forms for dataset\STATA files for
merge\10_SF36_month0_results.dta", replace
use "***\RITAZAREM\forms for dataset\STATA files for merge\10_SF36_month4.dta", clear
gen month = 4
save "***\RITAZAREM\forms for dataset\STATA files for merge\10_SF36_month4.dta",
replace
use "***\RITAZAREM\forms for dataset\STATA files for merge\10_SF36_month0_results.dta"
mmerge studyid month using "***\RITAZAREM\forms for dataset\STATA files for
merge\10_SF36_month4.dta"
save "***\RITAZAREM\forms for dataset\STATA files for merge\10_SF36_long.dta"
// EQ5D //
use "***\RITAZAREM\forms for dataset\STATA files for merge\11_EQ5D_visit1.dta", clear
mmerge studyid using "***\RITAZAREM\forms for dataset\STATA files for
merge\11_EQ5Dvisit4.dta"
reshape long eqmob_ eqcare_ equact_ eqpain_ eqanx_ eq5d_date_ eq_scale_ eqindex_,
i(studyid) j(month)
drop _merge
// follow-up form //
import delimited "*** \RITAZAREM\forms for dataset\10.
FollowUpForm_cleanv2_20200430.csv", clear
save "***\RITAZAREM\forms for dataset\STATA files for merge\10_followup.dta"
destring preddose_3, generate(preddose_3x) ignore("NA")
browse studyid preddose_3 preddose_3x
tabulate preddose_3 preddose_3x
* check *
drop preddose_3
```

```
rename preddose_3x preddose_3
destring preddose_4, generate(preddose_4x) ignore("NA")
browse studyid preddose_4 preddose_4x
tabulate preddose_4 preddose_4x
* check *
drop preddose_4
rename preddose_4x preddose_4
reshape long onpred_ preddose_ GCprotdev_ rituximabfollowup_ cumdoserituximab_
methpredfollowup_ cummethpreddose_ aza_ mtx_ mmf_ pjproph_ DMARDdosechange_
dosechangedate_ clinicalintolerancedosechange_ clinicallababnormality_ other_ death_
relapse_ infection_ numinfections_ sae_ malignancy_, i(studyid) j(month)

// MERGE wide and long //
use "***\RITAZAREM\forms for dataset\STATA files for merge\stable variables 20200501.dta",
clear
gen month_0 = 1
gen month_1 = 1
gen month_3 = 1
gen month_4 = 1
reshape long month_, i(studyid) j(month)
drop month_
mmerge studyid month using "***\RITAZAREM\forms for dataset\STATA files for
merge\6_BVAS_long.dta"
mmerge studyid month using "***\RITAZAREM\forms for dataset\STATA files for
merge\7_CDA_long.dta"
* error in SF-36 data=> month 1 is actually month 0/baseline *
use "***\RITAZAREM\forms for dataset\STATA files for merge\10_SF36_long.dta", clear
gen monthx = .
replace monthx = 0 if month == 1
replace monthx = 4 if month == 4
drop month
rename monthx month
save "***\RITAZAREM\forms for dataset\STATA files for merge\10_SF36_long.dta", replace
use "***\RITAZAREM\forms for dataset\STATA files for merge\merge
progress_20200505.dta", clear
mmerge studyid month using "***\RITAZAREM\forms for dataset\STATA files for
merge\10_SF36_long.dta"
* same month error as SF36 *
use "***\RITAZAREM\forms for dataset\STATA files for merge\11_EQ5D_long.dta", clear
gen monthx = .
replace monthx = 0 if month == 1
replace monthx = 4 if month == 4
drop month
rename monthx month
save "*** \RITAZAREM\forms for dataset\STATA files for merge\11_EQ5D_long.dta", replace
use "***\RITAZAREM\forms for dataset\STATA files for merge\merge
progress_20200505.dta", clear
mmerge studyid month using "***\RITAZAREM\forms for dataset\STATA files for
merge\11_EQ5D_long.dta"
mmerge studyid month using "***\RITAZAREM\forms for dataset\STATA files for
merge\15_PROMIS_processed.dta"
```

```
mmerge studyid month using "***\RITAZAREM\forms for dataset\STATA files for merge\10_followup_long.dta"
mmerge studyid month using "***\RITAZAREM\forms for dataset\STATA files for merge\9_clinlabs_long.dta"
mmerge studyid month using "***\RITAZAREM\forms for dataset\STATA files for merge\5_visitdate_long.dta"
```

Appendix 6 Manuscript: Perspectives of glucocorticoid use in patients with rheumatoid arthritis

ACR Open Rheumatology
Vol. 3, No. 4, April 2021, pp 231–238
DOI 10.1002/acr2.11234

American College of Rheumatology
Empowering Rheumatology Professionals

Perspectives of Glucocorticoid Use in Patients with Rheumatoid Arthritis

Gabriella Venter,[1] Joanna Tieu,[1] Rachel Black,[2] Susan Lester,[1] Nieves Leonardo,[3] Samuel L. Whittle,[1] Elizabeth Hoon,[4] Claire Barrett,[5] Debra Rowett,[6] Rachelle Buchbinder,[7] and Catherine L. Hill[2]

Objective. Prednisolone is an effective oral glucocorticoid for managing symptoms of rheumatoid arthritis (RA) but has predictable and common adverse effects. We explored patient perspectives of prednisolone use in RA.

Methods. Patients with RA registered with the Australian Rheumatology Association Database (ARAD) who had completed an ARAD questionnaire in the preceding 12 months were invited to participate in an online survey. Responses were linked to already collected respondent demographics, medication use, and patient-reported outcome measures. The Beliefs about Medicine Questionnaire (BMQ) measured patient beliefs on medication necessity and concerns. Free-text responses outlining reasons for stopping or declining prednisolone underwent thematic analysis using NVivo 12.

Results. The survey response rate was 79.6% (804/1010), including 251 (31.2%) reporting current prednisolone use and 432 (53.7%) reporting previous use. Compared with previous users, current users were older ($P = 0.0002$) and had worse self-reported pain, disease activity, health-related quality of life, and function (all $P < 0.001$). Current users had higher BMQ scores for prednisolone-specific necessity (3.6 versus 1.7; $P < 0.001$) and concerns (2.7 versus 2.3; $P < 0.001$). In previous prednisolone users (n = 432), the most frequent themes identified in free-text responses for cessation were adequate disease control (30.3%), adverse effects (25.2%), and predetermined short courses (21.3%). Of respondents citing adverse effects for cessation (n = 131), weight gain (27.5%), osteoporosis (14.7%), and neuropsychiatric issues (13.8%) were most frequent.

Conclusions. In our cohort, patients with RA taking prednisolone believed it was necessary yet remained concerned about its use. Adequate disease control and adverse effects were important considerations for patients using prednisolone.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease associated with significant morbidity and disability. Prednisolone is an effective and fast-acting glucocorticoid agent with both anti-inflammatory and disease-modifying properties in RA (1,2). It is the most common oral glucocorticoid prescribed in Australia, with equivalent potency to oral prednisone. Prednisolone has played an important role in the management of RA since the 1950s and is still a commonly prescribed treatment (3), with 50% of patients with incident RA receiving glucocorticoids in the primary care setting (3) and persistent use reported in up to one-third of patients with RA (4,5). It is, however, associated with many adverse effects, especially in the settings of high-dose therapy and long-term use (6). For this reason, current guidelines recommend limiting

The Australian Rheumatology Association Database is supported by unrestricted educational grants administered through the Australian Rheumatology Association currently from Pfizer Australia and previously from AbbVie Pty Ltd, Eli Lilly Australia Pty Ltd, Sanofi Australia, Celgene Australian & NZ, Bristol Myers Squibb Australia Pty Ltd, Amgen Australia Pty Ltd, Aventis, AstraZeneca, and Roche. The Australian Rheumatology Association Database was previously supported by an Australian National Health and Medical Research Council Enabling Grant (384330). Infrastructure support is from Cabrini Health, Monash University, Royal North Shore Hospital, and the Australian Rheumatology Association.

[1]Gabriella Venter, MBBS, Joanna Tieu, MBBS, FRACP, Susan Lester, BSc, Samuel L. Whittle, MBBS, FRACP, MEpi: The Queen Elizabeth Hospital, Woodville, South Australia, Australia, and University of Adelaide, Adelaide, South Australia, Australia; [2]Rachel Black, MBBS, PhD, Catherine L. Hill, MBBS, MD, MSc: The Queen Elizabeth Hospital, Woodville, South Australia, Australia, and University of Adelaide and Royal Adelaide Hospital, Adelaide, South Australia; [3]Nieves Leonardo, MBBS: The Queen Elizabeth Hospital, Woodville, South Australia, Australia; [4]Elizabeth Hoon, PhD: University of Adelaide, Adelaide, South Australia, Australia; [5]Claire Barrett, MBBS: Redcliffe Hospital, Redcliffe, Queensland, Australia; [6]Debra Rowett, BPharm: University of South Australia, Adelaide, South Australia, Australia; [7]Rachelle Buchbinder, MBBS, PhD: Monash University, Melbourne, Victoria, Australia, and Cabrini Institute, Malvern, Victoria, Australia.

Drs. Venter and Tieu contributed equally to this work.

No potential conflicts of interest relevant to this article were reported.

Address correspondence to Catherine L. Hill, MBBS, MD, MSc, Rheumatology Unit, The Queen Elizabeth Hospital, 28 Woodville Road, Woodville South 5011, South Australia, Australia. Email: Catherine.Hill@sa.gov.au.

Submitted for publication April 27, 2020; accepted in revised form August 20, 2020.

prednisolone use in RA to the initial treatment after diagnosis, during flares of disease activity, and as a bridging therapy while waiting for disease-modifying antirheumatic drugs (DMARDs) to take effect (7,8).

Despite a long history of use in this condition, information about the patient experience of prednisolone therapy in RA is lacking. There has been increasing interest in patient perspectives of glucocorticoid use (9–14), with the recognition that patient perspectives and beliefs are important to clinical management and correlate with treatment adherence and satisfaction (15,16). However, the current available literature focuses largely on adverse effects, with less attention on other aspects of the patient perspective.

Our study aimed to explore patient perspectives about prednisolone use for patients with RA registered in a national inflammatory arthritis database.

METHODS

The Australian Rheumatology Association Database (ARAD) is a prospective registry of patients with inflammatory arthritis, as detailed in previous publications (17–19). Patient-reported outcome measures are collected on a 6- to 12-month basis; at the time of this study, 69% of ARAD participants were opting to complete their usual questionnaires online. Patients with RA registered with ARAD who had completed an online ARAD questionnaire in the previous 12 months were invited to participate in an online survey using Survey Monkey (20). A link to the survey was sent by email to 1010 participants, with a reminder sent 2 weeks later to those who had not yet responded. The survey link was closed 4 weeks after the initial email was sent.

Data collected from annual ARAD questionnaires, including demographic information, medication use, and Assessment of Quality of Life and Health Assessment Questionnaire (HAQ) scores, were extracted from the ARAD database.

The survey collected information on prednisolone use as well as patient attitudes and beliefs about medicines, including prednisolone. Participants were asked to select one of the following four options in response to the question "Are you on prednisolone?": *1*) "I was not offered prednisolone by my doctor," *2*) "I was offered prednisolone but I declined," *3*) "I used to take prednisolone but it was stopped," and *4*) "I am currently taking prednisolone." Self-reported prevalence of current or prior prednisolone use was calculated on the basis of these responses. Respondents reporting prednisolone refusal or cessation were also asked to provide free-text responses outlining their reasons for stopping or declining this medication. Free-text responses were not collected from those not offered prednisolone or with current use.

Respondents with current or prior prednisolone use also completed the Beliefs about Medicines Questionnaire (BMQ) (21). The BMQ consists of two parts, each comprised of two subsections; one assesses beliefs about the general overuse (eg, "doctors use too many medications") and harms (eg, "medicines do more harm than good") of medicines, and the second assesses specific beliefs about the necessity of prednisolone for controlling disease (eg, "without my prednisolone I would be very ill") and concerns about its use (eg, "my prednisolone disrupts my life"). Respondents indicated their level of agreement with each item in the questionnaire on a five-point Likert scale (1 = strongly disagree to 5 = strongly agree). Average scores for each of the four BMQ subsections were calculated separately to reflect the overall beliefs of two different groups (those with current prednisolone use and those with prior use) (16). The BMQ was developed and validated using responses from patients with nonrheumatic chronic disease (21). Criterion and discriminant validity were established in these patient groups, and its use has been broadened to other settings, including patients with RA (15,22).

Statistical analysis was performed using Stata version 15.1 (23). Differences in demographics, medication use, and self-reported disease scores between all prednisolone use groups, as well as between current and prior prednisolone users, were examined using the Pearson χ^2 test and the Kruskal-Wallis rank test. Average BMQ scores for current and prior prednisolone users were compared using t-tests.

Free-text responses outlining reasons for stopping or declining prednisolone were analyzed to identify common themes for prednisolone refusal and cessation. Thematic analysis (24), taking a semantic approach, was conducted by two researchers (GV and JT) until consensus about the themes was achieved. Responses were then coded to these themes using NVivo 12, and the proportion of respondents identifying with each theme was quantified (25). As adverse effects were a predominant theme within reasons for stopping prednisolone, free-text responses referencing adverse effects were additionally analyzed to identify subthemes, and a second round of coding was performed to further explore this area. Word clouds were produced using NVivo 12 to support the generation of themes and subthemes. This analysis method included the application of a stop list of common words to be omitted, removal of spelling errors, and data processing to minimize duplication of words or phrases with equivalent meaning (Supplementary Figure 1). This process was applied iteratively by one researcher (GV) and checked by the second (JT) after the themes were agreed as above.

Ethics approval for ARAD has been obtained from Cabrini Institute (12-23-04-01) and Central Adelaide Local Health Network (HREC/17/TQEH/139). This ARAD substudy was approved by the ARAD Steering Committee before commencing the study.

RESULTS

The survey response rate was 79.6%, with 804/1010 responses received. Of the 683 respondents reporting prednisolone ever-use, 659 (96.5%) completed the BMQ.

Respondents were mostly female (75.1%), with a median age of 61 years and a median disease duration of 17 years.

Table 1. Demographics of respondents by category of prednisolone use

Variable	I Was Not Offered Prednisolone	I Was Offered Prednisolone but Declined	I Used to Take Prednisolone but It Was Stopped	I Am Currently Taking Prednisolone	Total	*P* Value (Joint)	*P* Value (Current Versus Previous)
N (%)	103 (12.8)	18 (2.2)	432 (53.7)	251 (31.2)	804		
Sex, n (%)						0.014	0.23
Female	66 (64.1)	13 (72.2)	341 (78.9)	184 (73.3)	604 (75.1)		
Age, mean (SD), yr	61 (11)	57 (10)	58 (11)	61 (11)	59 (12)	0.003	0.001
Years since Dx, mean (SD)	17 (10)	16 (11)	17 (10)	22 (12)	18 (11)	<0.001	< 0.001
Education, n (%)						0.63	0.14
Primary	1 (1.0)	0 (0)	1 (0.2)	1 (0.4)	3 (0.4)		
Some Secondary	14 (13.6)	2 (11.1)	57 (13.2)	43 (17.1)	116 (14.4)		
Completed Secondary	27 (26.2)	4 (22.2)	103 (23.8)	68 (27.1)	202 (25.1)		
Postsecondary	61 (59.2)	12 (66.7)	271 (62.7)	139 (55.4)	483 (60.1)		
HAQ, mean (SD)	0.5 (0.6)	0.9 (0.6)	0.7 (0.7)	1.1 (0.8)	0.8 (0.7)	<0.001	<0.001
Pain in last week, mean (SD)	34 (26)	46 (24)	35 (26)	47 (25)	39 (26)	<0.001	<0.001
Arthritis condition, mean (SD)	28 (24)	39 (21)	31 (26)	43 (24)	34 (26)	<0.001	<0.001
AqoL Score, mean (SD)	0.66 (0.21)	0.55 (0.23)	0.64 (0.23)	0.51 (0.24)	0.60 (0.24)	<0.001	<0.001
Methotrexate use (current)	65 (63.1)	11 (61.1)	272 (63.0)	157 (62.5)	505 (62.8)	0.11	0.90
Biological DMARD use (current)	61 (59.2)	12 (66.7)	290 (67.1)	157 (62.5)	520 (64.7)	0.39	0.23
Other DMARD use (current)	39 (37.9)	8 (44.4)	144 (33.3)	104 (41.4)	295 (36.7)	0.17	0.034
NSAID use (current)	40 (38.8)	11 (61.1)	174 (40.3)	105 (41.8)	330 (41.0)	0.34	0.69

AQol, Australian Quality of Life Questionnaire; DMARD, disease-modifying antirheumatic drug; Dx, diagnosis; HAQ, Health Assessment Questionnaire; NSAID, nonsteroid anti-inflammatory drug.

The majority (60%) had post secondary education. Compared with those who did not respond, survey respondents were older (median age 61 years versus 58 years; $P = 0.0002$) and more likely to be taking biologic agents (65% versus 53%; $P = 0.002$). No other significant differences in demographics, disease activity, or medication use were identified between responders and non-responders (data not shown).

Of the 804 respondents, 251 (31.2%) reported current prednisolone use, and 432 (53.7%) reported previous use. The remaining 121 (15.0%) reported that they had never taken prednisolone, with 103/121 (85.1%) reporting that they had not been offered prednisolone and 18/121 (14.8%) reporting that they had refused prednisolone when offered.

Table 1 compares respondents according to category of prednisolone use. There was no difference in sex or education level between current and previous prednisolone users; however, current users were older and had a longer disease duration. Current users also reported higher levels of pain, poorer disease control, greater disability, and poorer health-related quality of life. There were no significant differences between current and previous prednisolone users with respect to methotrexate, biologic agents, or nonsteroidal anti-inflammatory drug use, but current users were more likely to be taking other DMARDs compared with those with previous use (41.4% versus 33.3%; $P = 0.034$).

Prednisolone-specific and general BMQ scores for 659/683 (96.5%) respondents with current or prior prednisolone use are shown in Table 2. Current users had a significantly higher prednisolone-specific necessity score (3.6 versus 1.7; $P < 0.001$) and marginally higher, but statistically significant, prednisolone-specific concerns score (2.7 versus 2.3; $P < 0.001$) when compared with previous users. There was no significant difference in general BMQ scores between these two groups for medication overuse or harms.

Of the 18 respondents who declined prednisolone, two-thirds (n = 12) expressed concerns about potential adverse effects. Examples include "I had read negative comments about prednisolone" and ''did not want to be on steroids, am already overweight."

For self-reported previous prednisolone users (N = 432), the main reasons for stopping included adequate disease control (n = 131; 30.3%), adverse effects (n = 109; 25.2%), and prescribed short courses (n = 92; 21.3%) (Figure 1B). Prednisolone cessation was attributed to the commencement of biologic agents in 78 (18.1%) respondents. Example quotes from free-text responses by theme are displayed in Figure 1A. These themes were reflected in the word cloud in Figure 1C, as follows: adequate disease control ("need," "required," "control," and "better"), adverse effects ("side effects," "weight gain," and "weight"), predetermined short-term use ("short course," "flare," and "time"), medical advice ("doctor," "prescribed," and "weaned"), and biological DMARD treatment.

Pregnancy and breastfeeding were cited by 11 respondents, with most (7/11) indicating that it was used in the pregnancy and breastfeeding periods, whereas the remainder indicated that they stopped in these periods.

Overlapping themes for stopping prednisolone were identified in some responses (Supplementary Figure 2). Of the 131 responses describing adequate disease control, the commencement of a biologic agent was also noted in 35 (26.7%) respondents, and a predetermined short course was specified by 14 (10.6%) respondents. Of the participants citing a predetermined short course for prednisolone cessation, 14/92 (15.2%) also reported adverse effects as a reason for prednisolone cessation.

The theme of adverse effects was commonly expressed by previous users (109/432; 25.2%) and by those who had declined prednisolone (12/18; 66.7%). The most common adverse effects reported by previous users were weight gain (n = 30; 27.5%), osteoporosis (n = 16; 14.7%), and neuropsychiatric complaints (n = 15; 13.8%) (Figure 2B). Example quotes from free-text responses by subtheme are displayed in Figure 2A. These subthemes are represented in the word cloud in Figure 2C, as follows: weight gain ("weight gain," "weight," "gained," and "appetite"), osteoporosis ("bone," "bones," "density," and "osteoporosis"), and neuropsychiatric effects ("high," "anxiety," and "sleep"). Other adverse effects described included Cushingoid features (n = 10; 9.2%), impaired glucose tolerance (n = 9; 8.3%), malaise (n = 8; 7.3%), and hypertension (n = 5; 4.6%). The specific adverse effects experienced were not specified for 24/109 (22.0%) responses.

DISCUSSION

This study examined patient perspectives on prednisolone use in a cohort of patients with RA participating in a national inflammatory arthritis database. Although adequate disease control was the most commonly cited reason for stopping prednisolone, adverse effects were also a key consideration for both

Table 2. Beliefs about Medicines Questionnaire in those with previous and current prednisolone use

BMQ	Prednisolone Use		Difference	*P* Value
	Previous (n = 417)	Current (n = 242)		
Prednisolone-specific concerns	2.3 (2.2 to 2.4)	2.7 (2.6 to 2.8)	0.4 (0.2 to 0.5)	<0.001
Prednisolone-specific necessity	1.7 (1.6 to 1.7)	3.6 (3.5 to 3.7)	2.0 (1.8 to2.1)	<0.001
General overuse	2.6 (2.6 to 2.7)	2.6 (2.5 to 2.7)	0.0 (−0.2 to 0.1)	0.85
General harms	2.1 (2.1 to 2.2)	2.2 (2.1 to 2.3)	0.1 (0.0 to 0.2)	0.31

Data are given as mean (95% confidence interval); scores use a five-point Likert scale (1 = strongly disagree to 5 = strongly agree).

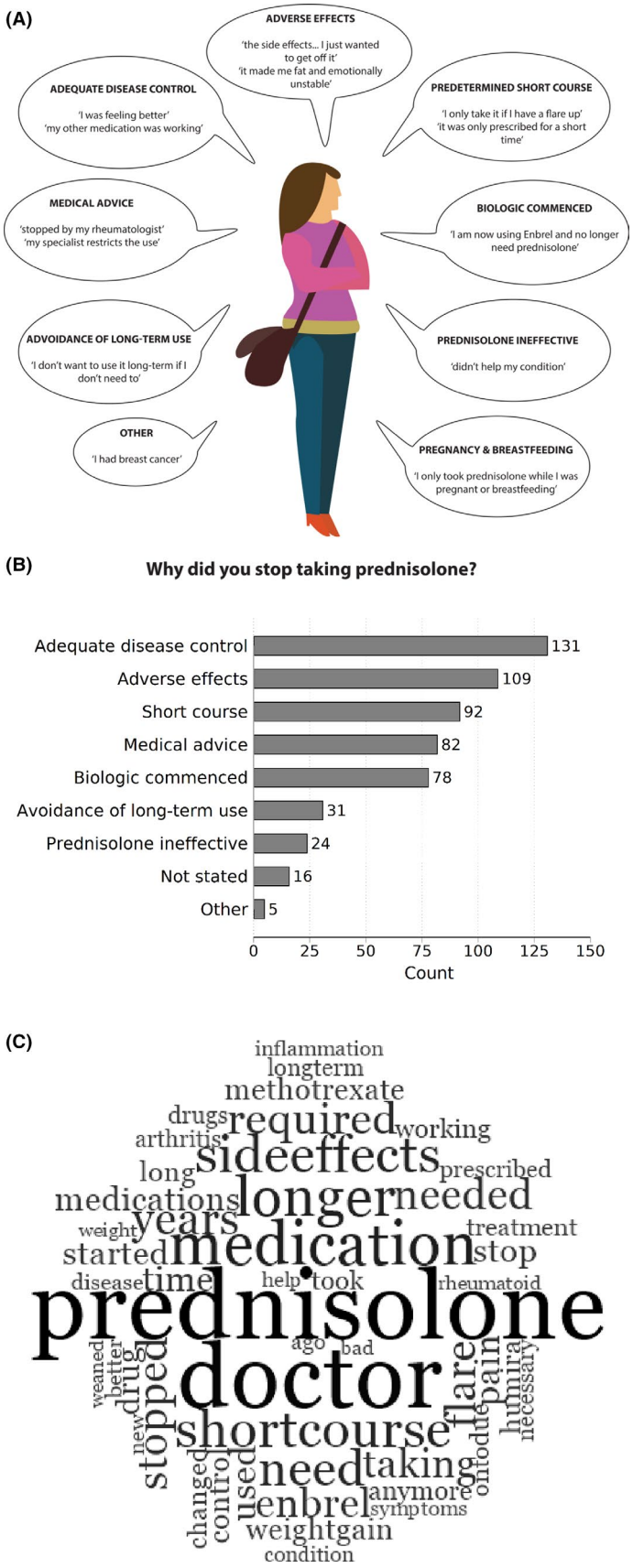


Figure 1. Reasons for stopping prednisolone: example quotes from free-text responses by theme (*A*), bar chart representing the quantity of respondents identifying with each theme (*B*), and word cloud generated from processed free-text responses (*C*).

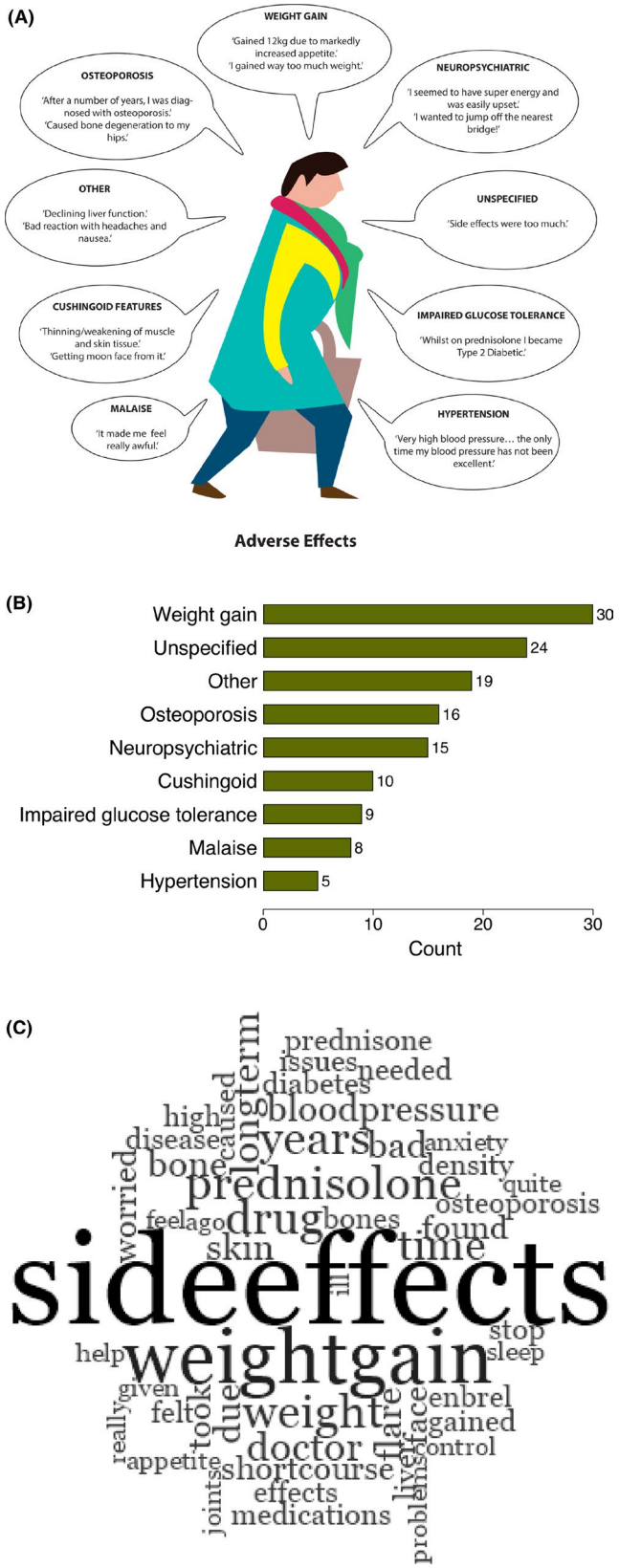


Figure 2. Adverse effects of previous prednisolone use: example quotes from free-text responses by subtheme (*A*), bar chart representing the quantity of respondents identifying with each subtheme (*B*), and word cloud generated from processed free-text responses.

stopping and declining prednisolone. Among those with previous prednisolone use, weight gain, osteoporosis, and neuropsychiatric issues were the most commonly cited adverse effects. Prescribing practices were also an influencing factor, with prednisolone cessation commonly attributed to adequate disease control, prescribed short courses, and commencement of other agents.

The prevalence of prednisolone ever-use in our study was high, with 85% reporting current or prior use. In a multinational cross-sectional study, substantial variation was observed in lifetime ever-use of glucocorticoids (26-88%) (26). Despite this, the prevalence of current prednisolone use in this cohort was slightly lower than that in previous studies (5,27). The use of oral glucocorticoids in RA has decreased over time, with patients less likely to commence prednisolone and more likely to cease it (27,28). Given that our cohort had a median disease duration of 17 years, this may partly account for the higher prevalence of prednisolone ever-use in this study.

Current users had higher levels of self-reported pain, disease activity, functional status, and health-related quality of life when compared with previous users. This is consistent with a previous study evaluating a broader group of 3699 patients from the same national inflammatory arthritis registry, which found that higher HAQ and arthritis activity scores in RA were associated with increased glucocorticoid use (27). Another study also found that patients with RA willing to accept glucocorticoid treatment had poorer disease control and function than those who were not (10). As described in other populations using glucocorticoids (29–32), it is possible that prednisolone may be contributing to disability in this group. However, given that the most common reason for prednisolone cessation in this study was adequate disease control, those requiring prednisolone may also have disease activity that is inherently more difficult to control.

Current prednisolone users were more likely to report that prednisolone was necessary to manage their condition than those with previous use. This may be related to the poorer self-reported disease control in those with current use, as previous studies have described an association between increasing disability and stronger beliefs on medication necessity in patients with RA (16). Further research is required to explore the role of patient beliefs about medication necessity on medication preferences and persistence with the medication. Interestingly, despite reporting greater prednisolone necessity, current prednisolone users remained concerned about its use.

Morrison et al, who also evaluated attitudes of patients with RA about oral glucocorticoids, reported that 46/90 (51%) patients refusing to participate in a trial did so because of concerns about glucocorticoid use (10). Moreover, the study also found that patients were able to list several adverse effects associated with glucocorticoids despite being largely unaware of their role or efficacy in RA management (10). In the 18 respondents to this survey who had declined prednisolone, concerns about potential

adverse effects were the most-reported reason for declining prednisolone (66.7%).

Of the 109 patients who described ceasing prednisolone because of adverse effects, the most frequently identified issues included weight gain, osteoporosis, and neuropsychiatric complaints. To a lesser extent, patients also expressed concern about metabolic effects. This is consistent with the findings of previous studies (9–12,33–35), which have demonstrated that patients place particular importance on adverse effects with greater psychosocial impacts (9,12,35). Clinicians more commonly focus concern on medically serious issues, such as hypertension and impaired glucose tolerance (11,13,34), which were less frequently cited in this cohort. Surprisingly, skin fragility was also less commonly reported compared with other studies. As the analyzed free-text responses asked respondents to provide reasons for stopping prednisolone treatment, dermatological issues may have been experienced without being a primary reason for prednisolone cessation. Similarly, adverse effects commonly identified by clinicians, such as hypertension, are often treatable and may also have occurred without resulting in cessation. The occurrence of adverse effects as a key consideration for both stopping and declining prednisolone highlights the importance of certain adverse effects as factors for patients in treatment decisions around prednisolone when balancing against any positive effects. The social and emotional impacts of treatment have a significant effect on quality of life and adherence (15,16), which may be underestimated by clinicians and thus are important to address. Moreover, patients may not be aware of the seriousness of other adverse effects, and education on these issues may be required. Further research is needed to explore differences in patient and clinician views on prednisolone use in more detail.

There are several limitations to our study, including the inherent limitations of a survey-based approach. The cross-sectional nature of our study prevents us from commenting on causality. Given that our population consisted mostly of older, more highly educated individuals enrolled in a registry and participating regularly in self-reported surveys, our cohort may not accurately reflect the wider RA population. As we were evaluating lifetime use of prednisolone, which may not necessarily have been recent, there is also the potential for recall bias. The wording of questions limited our study to evaluating prednisolone use specifically, and, although prednisolone is the most commonly prescribed glucocorticoid for RA in Australia, other forms of glucocorticoids were not evaluated. Moreover, we did not collect information about patterns of use, dosing, or duration of prednisolone therapy. As free-text data aimed to examine reasons for declining and ceasing prednisolone, free-text data were not collected from patients not offered prednisolone or with current use. Strengths of the study included the excellent response rate, resulting in a large sample of 804 participants. Although most (85%) patients enrolled in ARAD have been prescribed a biologic agent for treatment, previous data have indicated that these patients are nationally representative on the basis of residential postcode, demographic, and clinical characteristics, supporting the generalizability of our findings (19). Furthermore, the current literature evaluating patient perceptions of glucocorticoid use focuses mostly on adverse effects, whereas we were able to expand current knowledge by investigating other aspects of patient experiences and exploring considerations important to patients in decision-making about prednisolone use and discontinuation as well as beliefs about medications.

In conclusion, patients with RA taking prednisolone strongly believed it was a necessary treatment yet remained concerned about its use. The results of this study have highlighted that although cessation occurs with adequate disease control, adverse effects (namely, weight gain, osteoporosis, and neuropsychiatric effects) were a particularly important reason for stopping prednisolone in our cohort of patients with RA. Clinicians should remain mindful of these common reasons for prednisolone cessation in shared decision-making on treatment with patients. The small number of respondents who refused prednisolone without prior experience frequently cited concern about adverse effects, and further research to understand reasons for these beliefs should be explored.

ACKNOWLEDGEMENTS

We thank the participants and staff of ARAD for their invaluable contributions. We also thank Rachel Maria Venter for her assistance in producing Figures 1A and 2A.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Professor Catherine Hill had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design Lester, Leonardo, Hill.
Acquisition of data Lester, Barrett, Rowett, Buchbinder, Hill.
Analysis and interpretation of data Venter, Tieu, Black, Whittle, Hoon, Hill.

REFERENCES

1. Kirwan JR, The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. N Engl J Med 1995;333:142–6.
2. Van Everdingen AA, Jacobs JW, Siewertsz van Reesema DR, Bijlsma JW. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med 2002;136:1–12.
3. Black RJ, Joseph RM, Brown B, Movahedi M, Lunt M, Dixon WG. Half of UK patients with rheumatoid arthritis are prescribed oral glucocorticoid therapy in primary care: a retrospective drug utilisation study. Arthritis Res Ther 2015;17:375.
4. Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. Rheumatology (Oxford) 2011;50:1982–90.
5. Caplan L, Wolfe F, Russell AS, Michaud K. Corticosteroid use in rheumatoid arthritis: prevalence, predictors, correlates, and outcomes. J Rheumatol 2007;34:696–705.

6. Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum 2006; 55:420–6.
7. Palmowski Y, Buttgereit T, Dejaco C, Bijlsma JW, Matteson EL, Voshaar M, et al. "Official view" on glucocorticoids in rheumatoid arthritis: a systematic review of international guidelines and consensus statements. Arthritis Care Res (Hoboken) 2017;69: 1134–41.
8. Combe B, Landewe R, Daien CI, Hua C, Aletaha D, Alvaro-Gracia JM, et al. 2016 update of the EULAR recommendations for the management of early arthritis. Ann Rheum Dis 2017;76:948–59.
9. Black RJ, Goodman SM, Lester S, Mackie SL, Hill CL. A survey of glucocorticoid adverse effects and benefits in rheumatic diseases: the patient perspective. J Clin Rheumatol 2017;23:416–20.
10. Morrison E, Crosbie D, Capell HA. Attitude of rheumatoid arthritis patients to treatment with oral corticosteroids. Rheumatology (Oxford) 2003;42:1247–50.
11. Nassar K, Janani S, Roux C, Rachidi W, Etaouil N, Mkinsi O. Long-term systemic glucocorticoid therapy: patients' representations, prescribers' perceptions, and treatment adherence. Joint Bone Spine 2014;81:64–8.
12. Robson JC, Dawson J, Cronholm PF, Ashdown S, Easley E, Kellom KS, et al. Patient perceptions of glucocorticoids in anti-neutrophil cytoplasmic antibody-associated vasculitis. Rheumatol Int 2018;38:675–82.
13. Van der Goes MC, Jacobs JW, Boers M, Andrews T, Blom-Bakkers MA, Buttgereit F, et al. Patient and rheumatologist perspectives on glucocorticoids: an exercise to improve the implementation of the European League Against Rheumatism (EULAR) recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 2010;69:1015–21.
14. Zerah L, Arena C, Morin A-S, Blanchon T, Cabane J, Fardet L. Patients' beliefs about long-term glucocorticoid therapy and their association to treatment adherence. Rev Med Interne 2012;33:300–4.
15. McCulley C, Katz P, Trupin L, Yelin EH, Barton JL. Association of medication beliefs, self-efficacy, and adherence in a diverse cohort of adults with rheumatoid arthritis. J Rheumatol 2018;45:1636–42.
16. Neame R, Hammond A. Beliefs about medications: a questionnaire survey of people with rheumatoid arthritis. Rheumatology (Oxford) 2005;44:762–7.
17. Buchbinder R, March L, Lassere M, Briggs AM, Portek I, Reid C, et al. Effect of treatment with biological agents for arthritis in Australia: the Australian Rheumatology Association Database. Intern Med J 2007;37:591–600.
18. Leonardo N, Lester S, Graham M, Barrett C, Whittle S, Rowett D, et al. Selection and perception of methotrexate treatment information in people with rheumatoid arthritis. Int J Rheum Dis 2020;23:805–12.
19. Williams MP, Buchbinder R, March L, Lassere M. The Australian Rheumatology Association Database (ARAD). Semin Arthritis Rheum 2011;40:e2–3.
20. SurveyMonkey Inc. URL: www.surveymonkey.com.
21. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology & Health 1999;14:1–24.
22. Horne R, Albert A, Boone C. Relationship between beliefs about medicines, adherence to treatment, and disease activity in patients with rheumatoid arthritis under subcutaneous anti-TNFα therapy. Patient Prefer Adherence 2018;12:1099–111.
23. Stata statistical software: release 15.0. College Station (TX): StataCorp; 2017.
24. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology 2006;3:77–101.
25. O'Cathain A, Thomas KJ. "Any other comments?" Open questions on questionnaires - a bane or a bonus to research? BMC Med Res Methodol 2004;4:25.
26. Sokka T, Kautiainen H, Toloza S, Makinen H, Verstappen SM, Hetland ML, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Ann Rheum Dis 2007;66:1491–6.
27. Black RJ, Lester S, Buchbinder R, Barrett C, Lassere M, March L, et al. Factors associated with oral glucocorticoid use in patients with rheumatoid arthritis: a drug use study from a prospective national biologics registry. Arthritis Res Ther 2017;19:253.
28. Makol A, Davis JM, Crowson CS, Therneau TM, Gabriel SE, Matteson EL. Time trends in glucocorticoid use in rheumatoid arthritis: results from a population-based inception cohort, 1980–1994 versus 1995–2007. Arthritis Care Res (Hoboken) 2014;66:1482–8.
29. Apostolopoulos D, Kandane-Rathnayake R, Raghunath S, Hoi A, Nikpour M, Morand EF. Independent association of glucocorticoids with damage accrual in SLE. Lupus Sci Med 2016;3:e000157.
30. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Hoglund P, et al. Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials. Rheumatology (Oxford) 2015;54:471–81.
31. Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. Arthritis Rheum 2000;43:1801–8.
32. Ruiz-Arruza I, Ugarte A, Cabezas-Rodriguez I, Medina J-A, Moran M-A, Ruiz-Irastorza G. Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. Rheumatology (Oxford) 2014;53:1470–6.
33. Morin C, Fardet L. Systemic glucocorticoid therapy: risk factors for reported adverse events and beliefs about the drug: a cross-sectional online survey of 820 patients. Clin Rheumatol 2015;34:2119–26.
34. Fardet L, Blanchon T, Perdoncini-Roux A, Kettaneh A, Tiev K, Turbelin C, et al. Internal medicine physicians' perception of frequency and impact of corticosteroid-induced adverse events. Rev Med Interne 2009;30:113–8.
35. Costello R, Patel R, Humphreys J, McBeth J, Dixon WG. Patient perceptions of glucocorticoid side effects: a cross-sectional survey of users in an online health community. BMJ Open 2017;7:e014603.

Appendix 7 Manuscript: Improving benefit-harm assessment of glucocorticoid therapy incorporating the patient perspective: The OMERACT glucocorticoid core domain set

Seminars in Arthritis and Rheumatism 51 (2021) 1139–1145

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Improving benefit-harm assessment of glucocorticoid therapy incorporating the patient perspective: The OMERACT glucocorticoid core domain set

Joanna Tieu[a], Jonathan TL Cheah[b], Rachel J Black[c], Robin Christensen[d], Nilasha Ghosh[e], Pamela Richards[f], Joanna Robson[g], Beverley Shea[h], Lee S Simon[i], Jasvinder A Singhi[j], Peter Tugwell[k], Maarten Boers[l], Marco A Alba Garibay[m], Corrado Campochiaro[n], Simon Decary[o], Maarten de Witt[p], Anthony P Fernandez[q], Helen I Keen[r], Lauren King[s], Andrea Hinojosa-Azaola[t], Cathie Hofstetter[u], Inna Gaydukova[v], Michael D George[w], Latika Gupta[x], Suellen Lyne[y], Ashima Makol[z], Chetan Mukhtyar[aa], Win Min Oo[bb], Michelle Petri[A], Huai Leng Pisaniello[B], Sebastian E Sattui[C], Oscar Russell[D], Vitor Teixeira[E], Karine Toupin-April[F], Courage Uhunmwangho[G], Margaret Whitstock[H], Kevin Yip[I], Sarah L Mackie[J], Susan M Goodman[K], Catherine L Hill[L,*]

[a] *Rheumatology Research Group, Basil Hetzel Institute, Adelaide, Australia, Adelaide Medical School, University of Adelaide, Rheumatology Unit, The Queen Elizabeth Hospital, Adelaide, Australia, Rheumatology Unit, Lyell McEwin Hospital, Adelaide, Australia, Adelaide, Australia*
[b] *Division of Rheumatology, University of Massachusetts Medical School, Worcester, Massachusetts, USA, Division of Rheumatology, UMass Memorial Health Care, Worcester, MA, USA*
[c] *Rheumatology Research Group, Basil Hetzel Institute, Adelaide, Australia, Adelaide Medical School, University of Adelaide, Adelaide, Australia, Rheumatology Unit, The Queen Elizabeth Hospital, Adelaide, Australia, Rheumatology Unit, Royal Adelaide Hospital, Adelaide, Australia*
[d] *Musculoskeletal Statistics Unit at The Parker Institute, Bispebjerg, Denmark, Frederiksberg Hospital, Copenhagen & Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark*
[e] *Division of Rheumatology, Hospital for Special Surgery, New York, USA*
[f] *Patient research partner*
[g] *Rheumatology Research, Centre for Health and Clinical Research, University of the West of England, Bristol, UK, Rheumatology Department, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK*
[h] *Bruyère Research Institute, Senior Methodologist, Ottawa Hospital Research Institute, Ottawa, Canada, Adjunct Professor, Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Canada*
[i] *SDG, LLC, Cambridge, MA, USA*
[j] *Medicine Service, VA Medical Center, 700 19th St S, Birmingham, AL 35233 USA, Department of Medicine at the School of Medicine, University of Alabama at Birmingham (UAB), 1720 Second Ave. South, Birmingham, AL 35294-0022, USA, Department of Epidemiology at the UAB School of Public Health, 1665 University Blvd., Ryals Public Health Building, Room 220, Birmingham, AL, 35294-0022, USA*
[k] *Division of Rheumatology, Department of Medicine, University of Ottawa, School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Abbreviation:*
[l] *Department of Epidemiology & Data Science, Amsterdam Rheumatology and Immunology Center, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands, Marco A Alba Garibay, Vasculitis Research Unit, Department of Autoimmune Diseases, Hospital Clínic, University of Barcelona, IRB-CELLEX, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Barcelona, Spain*
[m] *Vasculitis Research Unit, Department of Autoimmune Diseases, Hospital Clínic, University of Barcelona, IRB-CELLEX, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Barcelona, Spain*
[n] *Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele, Vita-Salute San Raffaele University, Milan, Italy*
[o] *Patient-Oriented Rehabilitation Lab (SPOR-REHAB), University of Sherbrooke, Faculty of Medicine and Health Sciences, School of Rehabilitation, Research Centre of the CHUS, CIUSSS de l'Estrie-CHUS, Canada*
[p] *Patient research partner*
[q] *Department of Dermatology & Department of Pathology Cleveland Clinic, Cleveland, OH, USA*
[r] *School of Medicine, University of Western Australia, Perth, Australia, Rheumatology Department, Fiona Stanley Hospital, Perth, Australia*
[s] *Department of Medicine, University of Toronto, Canada*
[t] *Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*
[u] *Patient research partner*
[v] *North-Western State medical University named after II Mechnikov, Saint-Petersburg, Russia*
[w] *University of Pennsylvania, Division of Rheumatology, Philadelphia, PA, USA*
[x] *Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow India*

* Corresponding author at: Rheumatology Unit, The Queen Elizabeth Hospital, 35 Woodville Road, Woodville South 5011, South Australia, Australia.
E-mail address: catherine.hill@sa.gov.au (C.L. Hill).

https://doi.org/10.1016/j.semarthrit.2021.06.010
0049-0172/

[Y] Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, College of Medicine and Public Health, Flinders University, Adelaide, South Australia
[z] Division of Rheumatology, Mayo Clinic, Rochester, MN, USA
[aa] Rheumatologist, Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich, UK
[bb] Rheumatology department, Royal North Shore Hospital, Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, Australia, University of Medicine, Mandalay, Mandalay, Myanmar
[A] Division of Rheumatology, Johns Hopkins University School of Medicine, USA
[B] Discipline of Medicine, Faculty of Health and Medical Sciences, The University of Adelaide, South Australia, Australia, Rheumatology Research Group, Basil Hetzel Institute for Translational Health Research, The Queen Elizabeth Hospital, Woodville South, South Australia, Australia
[C] Division of Rheumatology, Hospital for Special Surgery, New York, USA
[D] Adelaide Medical School, The University of Adelaide, Adelaide, South Australia
[E] Serviço de Reumatologia, Hospital de Faro, Centro Hospitalar Universitário do Algarve, Portugal
[F] School of Rehabilitation Sciences, Faculty of Health Sciences, University of Ottawa, Department of Pediatrics, Faculty of Medicine, University of Ottawa, Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada
[G] Department of Medicine, University of Jos, Nigeria
[H] Patient research partner
[I] Division of Rheumatology, Hospital for Special Surgery, New York, USA
[J] Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[K] Division of Rheumatology, Hospital for Special Surgery, New York, USA, Weill Cornell Medical College, New York, USA
[L] Rheumatology Unit, The Queen Elizabeth Hospital, Adelaide, Australia, Rheumatology Research Group, Basil Hetzel Institute, Adelaide, Australia, Adelaide Medical School, University of Adelaide, Adelaide, Australia

ARTICLE INFO

Keywords:
OMERACT
Glucocorticoid
Adverse effects
Patient perspective
Prednisolone/prednisone/steroid

ABSTRACT

Objective: Our primary objective was to develop an Outcome Measures in Rheumatology (OMERACT) core domain set to capture the impact of glucocorticoids (GC), both positive and negative, on patients with Rheumatic conditions.
Methods: The OMERACT Filter 2.1 was used to guide core domain selection. Systematic literature reviews, qualitative studies and quantitative surveys were conducted by the OMERACT GC Impact working group to identify candidate domains for a core domain set. A summary of prior work and Delphi exercise were presented at the OMERACT 2020 virtual GC workshop. A proposed GC Impact core domain set derived from this work was presented for discussion in facilitated breakout groups. Participants voted on the proposed GC Impact core domain set.
Results: 113 people, including 23 patient research partners, participated in two virtual workshops conducted at different times on the same day. The proposed mandatory domains to be evaluated in clinical trials involving GCs were: infection, bone fragility, hypertension, diabetes, weight, fatigue, mood disturbance and death. In addition, collection of disease specific outcomes was included in the core domain set as "mandatory in specific circumstances". The proposed core domain set was endorsed by 100% (23/23) of the patient research partners and 92% (83/90) of the remaining participants, including clinicians, researchers and industry stakeholders.
Conclusion: A GC Impact core domain set was endorsed at the OMERACT 2020 virtual workshop. The OMERACT GC Impact working group will now progress to identify, develop and validate measurement tools to best address these domains in clinical trials.

Background

Glucocorticoids (GCs) have been widely used for the treatment of patients with inflammatory disorders since 1948 [1]. Despite the recognized benefits and well-documented GC-related adverse effects that are delineated in the Glucocorticoid Toxicity Index (GTI) [2], there has been no standardized method to measure the impact of systemic GC use from the patient perspective in rheumatic diseases.

The Outcome Measures in Rheumatology (OMERACT) GC Impact Working Group was established to develop a core set of outcomes that reflect the impact of GC treatment to be measured in future clinical trials. Central to this process has been patient engagement, following the OMERACT filter 2.1 for core domain selection, using the OMERACT handbook [3-6]. In prior OMERACT GC Impact special interest group meetings, we presented preliminary work to review existing outcome measures for GCs and identify GC-related outcomes important to patients [7, 8]. This work included an initial and an updated systematic literature review of validated GC patient reported outcome measures [9]. Additionally, qualitative studies [10, 11] and surveys [12] involving patients with a range of rheumatic conditions were carried out by the working group.

In this paper, we report on the OMERACT 2020 GC virtual workshop, where we presented the additional qualitative and quantitative work conducted since the OMERACT 2018 GC Special Interest Group meeting in 2018, the development process of the core domain set including the Delphi process, and ultimately voted on the mandatory outcomes in this core domain set.

Methods and results

Nominal groups involving patients with systemic lupus erythematosus (SLE) and idiopathic inflammatory myositis (IIM)

The original qualitative and quantitative work included patients with rheumatoid arthritis (RA), polymyalgia rheumatica/giant cell arteritis and anti-neutrophil cytoplasm antibody (ANCA)- associated vasculitis (AAV) [10–12]. Following an interim review of patient disease subgroups from the first Delphi round, the working group recognized the need to increase representation from patients with SLE and IIM, who typically receive high doses of GCs and/or require long-term GC. Patients with SLE and IIM who were current or previous GC users were invited to participate in discussion groups using Nominal Group Technique [13], a highly structured method that involves

reaching consensus by generation and sharing of ideas, clarification of ideas, and ranking of results. Groups of 5–10 participants were asked two open-ended questions about their experience of the positive benefits and adverse effects of GC use.

This study was conducted in the USA and involved 21 patients (17 with SLE, 4 with IIM), and 57% had experience taking GC for greater than 10 years. The domains identified were:

- Benefits: controls disease and symptoms, works fast, increases energy, relieves pain
- Adverse effects: bone loss, weight gain, psychological effects, damaged internal organs

RA online survey

A survey of Australian RA patients participating in a prospective biologics registry was conducted to supplement the previous studies, specifically evaluating reasons for stopping prednisolone (prednisone equivalent; most common form of oral GC in Australia) cessation [14]. This study used the Beliefs in Medicines Questionnaire (BMQ), which employs a five-point Likert scale to assess the level of agreement to statements on the necessity and concerns of prednisolone and medicines in general. A qualitative analysis of respondents' free-text comments on reasons for stopping prednisolone was performed.

Of the 1010 patients invited to participate in this online survey, 804 (80%) patients responded, of which 432 had stopped prednisolone, 251 (31%) were currently taking prednisolone, 18 (2%) declined prednisolone and 103 (13%) had not been offered prednisolone. Current prednisolone users had greater prednisolone specific necessity scores (3.6 [3.5–3.7] vs 1.7 [1.6 – 2.7], $p < 0.001$) indicating that, on average, they had stronger agreement on the necessity of prednisolone. The main reasons for stopping prednisolone were adequate disease control (131/432, 30%) and adverse effects (109/432, 25%). The most common adverse effects cited in patients who had ceased prednisolone were weight gain, osteoporosis and neuropsychiatric effects.

Delphi exercise and developing a core domain set

A Delphi exercise was carried out to identify domains important to patients, researchers and clinicians. An extended report of the Delphi process and results are available in a separate publication *[parallel publication in preparation]*. Patients from several patient organizations and registries were invited to participate to enable diversity amongst participants, inclusion of a broad range of disease groups and GC doses and durations. Most patients were from the United States (41%), United Kingdom (40%) and Australia (13%). Whilst patients with RA (21%) represented the largest disease group, patients who responded also self-reported diagnoses of other inflammatory arthritis, vasculitis and connective tissue disease. Clinicians and researchers who have contributed to GC literature or members in Rheumatology and musculoskeletal disease research groups were invited to participate. Most clinicians and researchers were from the United States (26%), Australia (26%) and United Kingdom (19%).

Delphi items were informed by the results of the systematic reviews, patient surveys and qualitative work previously reported, with 63 candidate outcomes to be prioritized to a core set [7, 8]. Three rounds of the Delphi were completed (Round 1: 295 patients/68 clinician-researchers, Round 2: 137 patient/53 clinician-researchers, Round 3: 123 patients /45 clinician researchers). Results and feedback from Delphi participants were reviewed by the OMERACT GC Impact working group after each round.

Based upon the initial three rounds of the Delphi, the outcomes which met OMERACT definitions for inclusion in the core domain set (reaching agreement of critical to measure in clinical trials by ≥70% of all stakeholder groups) were:

1. Bone fragility
2. Diabetes Mellitus
3. Eye problems and/or changes in vision
4. Infection
5. High blood pressure
6. Osteonecrosis
7. Making the condition noticeably better

Discordance between patients and clinicians/researchers in prioritizing outcomes and the need to explore novel ways of incorporating patient perspectives in determining the relative importance of GC effects have been recognized as key challenges in developing the GC core domain set in prior OMERACT meetings. The working group identified outcomes that did not meet strict OMERACT definitions for inclusion but had featured prominently in the prior work. A final survey asked respondents to consider whether these outcomes should be measured in "every", "some" or "never" in clinical trials.

The final survey was analyzed using proportional weighting based upon stakeholder group and number of participants. The following additional domains were included into the core domain set:

1. Mood disturbance
2. Fatigue
3. Sleep disturbance
4. Weight

The domain names were refined to reflect shared common terminology among patients, clinicians, and researchers. The combined group of domains were reviewed by the OMERACT GC Impact working group. To refine the core outcome set further, the working group acknowledged that the outcome "making the condition noticeably better" would already be measured in the context of a clinical trial as disease-specific outcomes. Disease-specific outcomes will vary by clinical trial and are included as "mandatory in specific circumstances" in the GC core domain set. In OMERACT GC working group discussions, it was agreed that outcomes deemed rare, typically occurring with high doses or long-term follow-up (osteonecrosis, eye problems and sleep disturbance), would be better included as optional domains. During these discussions, the working group also reflected on patients' views in the qualitative work linking weight and appearance. Appearance was therefore included in the core domain set as an optional domain. Death is included as a mandatory domain for all OMERACT core domain sets. The final core domain set is depicted in Fig. 1.

Virtual workshop

OMERACT 2020 was conducted virtually due to the COVID-19 pandemic. Participation was invited through the OMERACT patient research partners network, OMERACT working groups, the Australia and New Zealand Vasculitis group (ANZVASC) and all patient, research and clinician participants of the Delphi process.

Prior to the workshop, a lay summary and video summarizing the work was made available to participants [15]. Additional detailed written reports and a pre-recorded presentation of the qualitative and quantitative work, and core domain selection, were provided online. Registered workshop participants were able to comment or post questions related to the reading material or core domain set on the OMERACT GC discussion board.

Two identical 90-minute workshops comprised a short plenary session prior to simultaneous breakout group sessions, led by an OMERACT facilitator with the assistance of a content expert and reporter. Each group was asked to discuss the proposed core domain set (Fig. 1) and provide feedback. Finally, all participants were invited to vote on whether to endorse the mandatory domains of the core domain set.

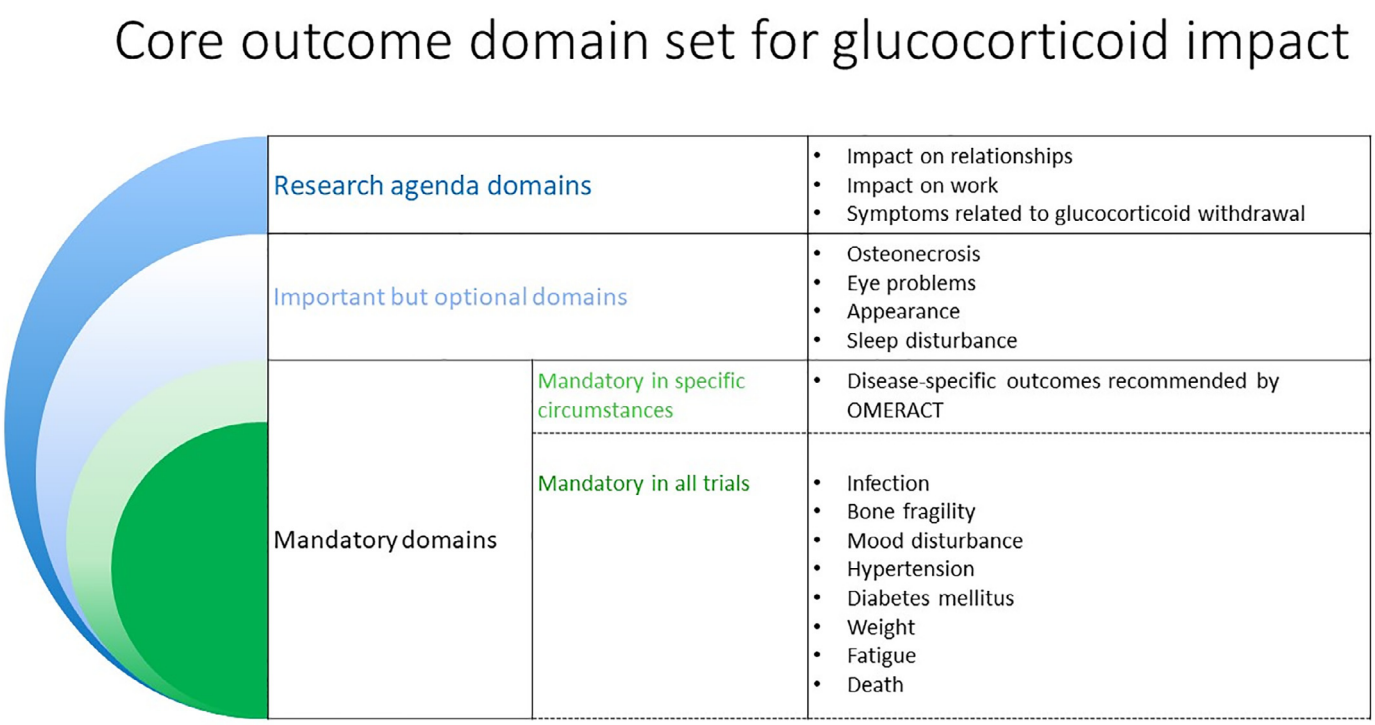


Fig. 1. OMERACT Glucocorticoid impact core domain set.

A total of 113 people participated in the two workshops, including 23 patient research partners. The proposed mandatory domains of the core domain set were endorsed, with 100% (23/23) of the patient research partners voting to ratify and 92% (83/90) of the remaining participants, including clinicians, researchers and industry stakeholders.

Overall, feedback from the breakout groups was positive. Key issues highlighted by the breakout groups could be summarised in the following themes:

a) Domain definitions

For the workshop, working definitions of each domain were provided to facilitate discussion during breakout sessions based on original descriptions from the Delphi exercise and preliminary work identifying candidate outcomes. It was clear from the workshop summaries that opinions on the breadth of domains differed. The preliminary working definitions were refined after reviewing this feedback (Table 1). Breakout groups facilitated insightful discussion on how the interpretation and measurement of each domain is influenced by several factors including: GC dose, trial design, and feasibility of measurement.

b) Attribution

Although there was general agreement on the proposed mandatory domains of the core domain set, participants recognized the overlap with other effects from other medications and rheumatic conditions.

c) Contextual factors

Breakout groups noted the dependence of the GC Impact domains on patient and disease related factors. The development of the core domain set was informed from work involving patients from different countries and living with a wide range of rheumatic conditions. However, it was acknowledged that clinical trials will focus on select patient and clinical factors, which may influence the impact of GCs.

Table 1.
Mandatory domains and working definitions.

Domain	Working definition
Diabetes Mellitus	blood glucose (sugar), high blood glucose, development of diabetes mellitus and/or worsening control
Hypertension	blood pressure, development of hypertension (high blood pressure), and worsening hypertension
Bone Fragility	bone density, report of fractures, and osteoporosis or osteopenia
Fatigue	tiredness or feeling wiped out
Infection	recurrent, atypical and serious infections
Mood disturbance	changes in mood including depression, irritability, mood swings, euphoria and anxiety
Weight	weight, appetite, and weight gain
Death	**mandatory OMERACT domain*

d) Patterns of GC use

The breakout groups discussed potential differences in how GC related effects are experienced based on the dose range, dosing pattern and duration. These are likely to impact the way each domain is measured.

Discussion

We present the endorsed OMERACT core domain set for clinical trials involving GCs, developed by a multi-national group of stakeholders, including patients, clinicians, and researchers. The core domain set received strong support by both patient and clinician/researcher/industry stakeholder groups, who endorsed the proposed domains at the OMERACT 2020 virtual workshop. This OMERACT GC core domain set enables the validation of existing instruments and the development and validation of new instruments incorporating these domains to measure the effects of GCs in clinical trials.

The domains and definitions are not prescriptive of how each will be measured. The terminology used in the core domain set have been determined according to shared terminology and to enable sufficient

flexibility to adapt to specific contextual factors, including varied trial designs, GC dose and duration, and disease related factors. Working domain definitions were informed by the prior work and we have incorporated feedback from the OMERACT 2020 GC workshop. It is anticipated that outcome measurement instruments, both clinician-assessed and patient-reported, will be sought to address the mandatory items in the core domain set. In the context of a clinical trial, GC-specific tools will be used in conjunction with the relevant disease-specific measurement instruments. Discussion at the virtual workshop reiterated the need for instruments to be adaptable to the context of different trial conditions. Moreover, the attribution of a domain to GC, disease or other medication(s) remains a challenge that will be faced in instrument selection.

The qualitative and quantitative work consistently emphasized the positive impact of GCs, particularly in treating the underlying disease and the effects on fatigue [11, 12]. These positive effects were reiterated in the results of the Delphi process. The outcome "making the condition noticeably better" met OMERACT definitions for inclusion into the core domain set. In practical terms, the impact of GCs on the underlying disease in the clinical trial setting will be varied and disease specific and was therefore included as "mandatory in specific circumstances". This means the positive benefits of GCs in each disease condition will be quantified in clinical trials using disease specific outcome measures. In future work on instrument selection, the positive and negative impacts of GCs will remain important considerations to reflect the balance that both patients and clinicians have emphasized.

The OMERACT GC workshop aimed to discuss and vote on the proposed OMERACT GC core domain set; instrument selection, including considering the GTI, forms a later stage of the OMERACT framework. A number of breakout groups raised the GTI as a potential measurement tool, which the working group acknowledged the need to consider as a measurement tool in subsequent stages. In the words of its authors, the GTI was developed as an instrument for the assessment of GC toxicity. It was developed by an expert panel of clinicians and researchers without patient input, who sought to create an instrument to assess the impact of GC-associated morbidity. Notably, the objectives and item selection process for the GTI differ from the OMERACT process in several key areas. GTI items were identified from literature review and items were selected for inclusion by nominal group technique amongst an expert panel of clinicians [2]. Moreover, the focus was on items that could be attributable to GC rather than disease, and unlikely related to GC therapy prior to trial entry. The OMERACT GC core domain set has been developed using a patient-centered approach to qualitative and quantitative studies to supplement literature reviews, incorporating both positive and negative impacts of GC into a core domain set after the Delphi process described, and did not exclude domains influenced by both disease and GC. Patients, clinicians, and researchers were invited to participate in the Delphi exercise. At this stage, the GTI has not undergone extensive validation despite its inclusion in RCTs and will be considered within the instrument selection stage of the OMERACT process for GC.

Since inception, the OMERACT GC group has recognized that the experience of inflammatory conditions and of GCs allows patients a unique perspective on the impact of GCs that overlaps but remains distinct from the perspective that clinicians have observing patients with different conditions and GC regimens. The difficulty in capturing both perspectives to achieve a representative domain set has been a challenge throughout the domain selection process including the Delphi exercise. The initial three rounds of the Delphi demonstrated that both groups prioritize pathophysiological domains commonly ascribed to GCs, and which are typically easier to define and measure in the context of a clinical trial. A bias to these domains had been considered possible in light of the methodology used to develop consensus.

The approach to the final survey including proportional weighting of responses was developed in OMERACT GC working group meetings. The proportional weighting of patient and clinician/researcher responses from the final survey recognized the imbalance in group sizes and the exclusion of domains that featured prominently in the patient-centered qualitative work used to derive the candidate domains for the Delphi. The final survey sought to identify whether there were additional domains important to both patient and clinicians/researcher groups after acknowledging the effects of GCs included from the initial three rounds. Although novel, this approach acknowledged the consistent data and results derived from the qualitative work conducted and drew from OMERACT principles and methodology, maintaining a minimum 70% threshold for consensus after weighting. Moreover, this adapted methodology enabled the inclusion of mood disturbance, fatigue, weight and sleep disturbance as domains; the approach and inclusion of these domains was positively received by patients and clinicians/researchers at the virtual workshop.

In all rounds of the Delphi exercise and final survey, patients highly ranked fatigue, which also featured prominently the prior qualitative work. Fatigue as an outcome of GC use warrants particular mention, as the patient experience of fatigue in this setting is multifaceted and complex. Discussions at the virtual workshop highlighted some important considerations for evaluating measurement tools incorporating fatigue. These included the overlap of fatigue with other GC effects such as mood and sleep disturbance, difficulties in separating fatigue attributed to GCs versus the underlying disease, and the bi-directional effect of GCs on fatigue in different contexts including GC dose, patient age, comorbidities, other medications and disease states.

The focus of OMERACT and the OMERACT GC group are outcomes in patients with Rheumatic diseases. Patient participation in the qualitative studies for candidate domain selection for the Delphi have included only patients with Rheumatic diseases. Responses from a small number of patients with other inflammatory conditions and clinicians/researchers with a focus on non-Rheumatic inflammatory disease were included in the Delphi process. Owing to the multisystem nature of Rheumatic disease, clinicians practicing outside of Rheumatic disease are often involved in the co-management of these patients. As the domain set has been developed for GC use in Rheumatic disease, however, further validation work would be required for this domain set to be used in non-Rheumatic inflammatory disease.

Although developed and endorsed by a multi-national group, the mandatory domains and endorsement at the virtual workshop were formulated and conducted in English. Further work to evaluate the relevance of these domains in non-English speakers will be important to its generalizability.

Conclusion

Using OMERACT methodology, the GC Impact working group has developed the GC Impact core domain set, which was successfully endorsed at the OMERACT 2020 virtual workshop. Future work involves the collaboration between patients, clinicians and researchers in the identification, development, validation and integration of GC-specific measurement tools in future clinical trials.

Declaration of Competing Interest

MD George reports grants from Bristol-Myers Squibb and personal fees from Dysimmune Diseases Foundation outside the submitted work.

M de Witt reports being a collaborating partner in the EU/IMI funded trial to investigate the efficacy and safety of low-dose GC in the elderly.

M Boers is principal investigator of the GLORIA trial on low-dose prednisolone or placebo in elderly RA patients, funded by the

European Union's Horizon 2020 research and innovation program under the topic ''Personalizing Health and Care'', grant agreement No 634886.

M Petri reports grants and personal fees from AstraZeneca, grants and personal fees from Eli Lilly, grants and personal fees from Exagen, grants and personal fees from GSK, grants and personal fees from Thermofisher, personal fees from Aurinia, personal fees from Abbvie, personal fees from Amgen, personal fees from Blackrock, personal fees from BMS, personal fees from Glenmark, personal fees from IQVIA, grants and personal fees from Janssen, personal fees from Merck EMD Serono, personal fees from Novartis, personal fees from Sanofi Japan, personal fees from UCB, outside the submitted work.

JA Singh has received consultant fees from Crealta/Horizon, Medisys, Fidia, Two labs Inc, Adept Field Solutions, Clinical Care options, Clearview healthcare partners, Putnam associates, Focus forward, Navigant consulting, Spherix, MedIQ, UBM LLC, Trio Health, Medscape, WebMD, and Practice Point communications; and the National Institutes of Health and the American College of Rheumatology. JA Singh owns stock options in TPT Global Tech, Vaxart pharmaceuticals and Charlotte's Web Holdings, Inc. JAS previously owned stock options in Amarin, Viking and Moderna pharmaceuticals. JA Singh is on the speaker's bureau of Simply Speaking. JA Singh is a member of the executive of Outcomes Measures in Rheumatology (OMERACT), an organization that develops outcome measures in rheumatology and receives arms-length funding from 8 companies. JA Singh serves on the FDA Arthritis Advisory Committee. JAS is the chair of the Veterans Affairs Rheumatology Field Advisory Committee. JAS is the editor and the Director of the University of Alabama at Birmingham (UAB) Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis.

R Christensen reports honoraria paid to the Parker institute from: Lecture- Research Methods (Pfizer, DK; 2017), GRADE Lecture (Celgene, DK; 2017), Ad Board Lecture: CAM (Orkla Health, DK; 2017), Project Grant: "GreenWhistle" (Mundipharma, 2019), Lecture: Diet in RMD (Novartis, DK; 2019), Consultancy Report: Network MA's (Biogen, DK; 2017), Ad Board Lecture: GRADE (Lilly, DK; 2017), Consultancy Report: GRADE (Celgene, 2018), Lecture: Network MA's (LEO; 2020), outside the submitted work; and Musculoskeletal Statistics Unit, The Parker Institute is grateful for the financial support received from public and private foundations, companies and private individuals over the years. The Parker Institute is supported by a core grant from the Oak Foundation. R Christensen is a founding member of the Technical Advisory Group of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 8 companies.

I Gaydukova reports personal fees from Abbvie, grants and personal fees from Pfizer, grants and personal fees from MSD, grants and personal fees from Novartis, personal fees from Sandoz, personal fees from Celgen, grants and personal fees from Biocad, personal fees from Teva, outside the submitted work.

A Fernandez reports personal fees and other from AbbVie, grants and personal fees from Novartis, grants and personal fees from Mallinckrodt, personal fees from BMS, personal fees from Alexion, other from Corbus, other from Pfizer, outside the submitted work.

S Goodman reports research grant support from Novartis and Horizon, and consulting fees from UCB.

J Tieu reports research grant support from Vifor Pharmaceuticals, outside the submitted work.

C Hill reports research grant support from Vifor Pharmaceuticals, outside the submitted work.

H Keen reports personal fees from Roche and Pfizer, outside the submitted work.

P Tugwell is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 8 companies.

S Mackie reports consultancy on behalf of her institution for Roche/Chugai, Sanofi, AbbVie and AstraZeneca, and received support from Roche to attend EULAR2019. SLM is supported by the Leeds Biomedical Research center.

J Robson reports speaker fees from Roche and Vifor Pharma, research support from Vifor Pharma and acted as a clinical trials investigator for Chemocentryx and Novartis, outside the submitted work.

No disclosures: A Makol, L King, A Hinojosa-Azaola, O Russell, S Lyne, K Toupin-April, S Decary, M Whitstock, L Gupta, M Alba Garibay, K Yip, C Mukhtyar, C Uhunmwangho, WM Oo, C Ruediger, L Yue, LS Simon, RJ Black, JTL Cheah, N Ghosh, C Campochiaro, B Shea, P Richards.

MD George reports grants from Bristol-Myers Squibb and personal fees from Dysimmune Diseases Foundation outside the submitted work.

M de Witt reports being a collaborating partner in the EU/IMI funded trial to investigate the efficacy and safety of low-dose GC in the elderly.

M Boers is principal investigator of the GLORIA trial on low-dose prednisolone or placebo in elderly RA patients, funded by the European Union's Horizon 2020 research and innovation program under the topic ''Personalizing Health and Care'', grant agreement No 634886.

M Petri reports grants and personal fees from AstraZeneca, grants and personal fees from Eli Lilly, grants and personal fees from Exagen, grants and personal fees from GSK, grants and personal fees from Thermofisher, personal fees from Aurinia, personal fees from Abbvie, personal fees from Amgen, personal fees from Blackrock, personal fees from BMS, personal fees from Glenmark, personal fees from IQVIA, grants and personal fees from Janssen, personal fees from Merck EMD Serono, personal fees from Novartis, personal fees from Sanofi Japan, personal fees from UCB, outside the submitted work.

JA Singh has received consultant fees from Crealta/Horizon, Medisys, Fidia, Two labs Inc, Adept Field Solutions, Clinical Care options, Clearview healthcare partners, Putnam associates, Focus forward, Navigant consulting, Spherix, MedIQ, UBM LLC, Trio Health, Medscape, WebMD, and Practice Point communications; and the National Institutes of Health and the American College of Rheumatology. JA Singh owns stock options in TPT Global Tech, Vaxart pharmaceuticals and Charlotte's Web Holdings, Inc. JAS previously owned stock options in Amarin, Viking and Moderna pharmaceuticals. JA Singh is on the speaker's bureau of Simply Speaking. JA Singh is a member of the executive of Outcomes Measures in Rheumatology (OMERACT), an organization that develops outcome measures in rheumatology and receives arms-length funding from 8 companies. JA Singh serves on the FDA Arthritis Advisory Committee. JAS is the chair of the Veterans Affairs Rheumatology Field Advisory Committee. JAS is the editor and the Director of the University of Alabama at Birmingham (UAB) Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis.

R Christensen reports honoraria paid to the Parker institute from: Lecture- Research Methods (Pfizer, DK; 2017), GRADE Lecture (Celgene, DK; 2017), Ad Board Lecture: CAM (Orkla Health, DK; 2017), Project Grant: "GreenWhistle" (Mundipharma, 2019), Lecture: Diet in RMD (Novartis, DK; 2019), Consultancy Report: Network MA's (Biogen, DK; 2017), Ad Board Lecture: GRADE (Lilly, DK; 2017), Consultancy Report: GRADE (Celgene, 2018), Lecture: Network MA's (LEO; 2020), outside the submitted work; and Musculoskeletal Statistics Unit, The Parker Institute is grateful for the financial support received from public and private foundations, companies and private individuals over the years. The Parker Institute is supported by a core grant from the Oak Foundation. R Christensen is a founding member of the Technical Advisory Group of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 8 companies.

I Gaydukova reports personal fees from Abbvie, grants and personal fees from Pfizer, grants and personal fees from MSD, grants and personal fees from Novartis, personal fees from Sandoz, personal fees from Celgen, grants and personal fees from Biocad, personal fees from Teva, outside the submitted work.

A Fernandez reports personal fees and other from AbbVie, grants and personal fees from Novartis, grants and personal fees from Mallinckrodt, personal fees from BMS, personal fees from Alexion, other from Corbus, other from Pfizer, outside the submitted work.

S Goodman reports research grant support from Novartis and Horizon, and consulting fees from UCB.

J Tieu reports research grant support from Vifor Pharmaceuticals, outside the submitted work.

C Hill reports research grant support from Vifor Pharmaceuticals, outside the submitted work.

H Keen reports personal fees from Roche and Pfizer, outside the submitted work.

P Tugwell is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 8 companies.

S Mackie reports consultancy on behalf of her institution for Roche/Chugai, Sanofi, AbbVie and AstraZeneca, and received support from Roche to attend EULAR2019. SLM is supported by the Leeds Biomedical Research center.

J Robson reports speaker fees from Roche and Vifor Pharma, research support from Vifor Pharma and acted as a clinical trials investigator for Chemocentryx and Novartis, outside the submitted work.

No disclosures: A Makol, L King, A Hinojosa-Azaola, O Russell, S Lyne, K Toupin-April, S Decary, M Whitstock, L Gupta, M Alba Garibay, K Yip, C Mukhtyar, C Uhunmwangho, WM Oo, C Ruediger, L Yue, LS Simon, RJ Black, JTL Cheah, N Ghosh, C Campochiaro, B Shea, P Richards.

Acknowledgments

Patient consumer organisations and participants of the qualitative interviews, quantitative surveys, and Delphi exercise. We acknowledge all participants of the workshop: Gerd Jenny Aanerud, Ade Adebajo, Marco A Alba, Alhanouf Alsaleem, Rieke Alten, Rieke Alten, Zoi Anastasa, Vinicius Antao, Brent Appleton, Laurent Arnaud, Devender Bairwa, Susan Bartlett, Wilson Bautista Molano, Geoffrey Baxter, Dorcas Beaton, Karima Becetti, Clifton Bingham, Rachel Black, Boris A. Blanco-Cáceres, Maarten Boers, Annelies Boonen, Shona Brewster, Edith Brown, Flo Callahan, Corrado Campochiaro, Kelli Carlson, David Carrott, Peter Chaplin, Lara Chapman, Jonathan Cheah, Jiehan Chong, Lucinda Chornyak, Robin Christensen, Jenny Christensson, Brittany Clark, Deb Constien, Cindy Copenhaver, Mary Cowern, Maurizio cutolo, Jose A.P. da Silva, Maria Antonietta D'Agostino, Anna C Das, Bhaskar Dasgupta, Ingrid de groot, Maarten de Wit, Haner Direskeneli, Will Dixon, Saikumar Dunga, Geetha Duvuru, Vicki Evans, Elizabeth Farchette, Anthony Fernandez, Michael Fiene, Diyu Fisher, Caroline Flurey, Shelley Fritz, Michael George, Nilasha Ghosh, Tiffany Gill, Elena Gkrouzman, Niti Goel, carol golden, Susan Goodman, Aishwarya Gopal, Rebecca Grainger, David Grossberg, Shawna Grosskleg, Latika Gupta, Raouf Hajji, Serena Halls, Glen Hazlewood, Halbert Hernández Negrín, Catherine Hill, Andrea Hinojosa-Azaola, Marc Hochberg, Catherine Hofstetter, Alberta Hoi, Diana Hollander, Elizabeth Hoon, Ben Horgan, Jen Horonjeff, Zdenka Hruskova, Onyeka Illoh, Francesca Ingegnoli, Laura Jamieson, David Jayne, Robert Kaner, Chengappa Kavadichanda, Helen Keen, Lauren King, Tina King, Marios Kouloumas, Andreas Kronbichler, Brian LaMoreaux, Alex Lee, Sue Lester, David Liew, Christine Lindsay, Suellen Lyne, Sarah Mackie, Ashima Makol, Lyn March, Alexander Martin, Jason Melehani, Peter Merkel, Caroline Meyrick, Eric Morand, Chetan Mukhtyar, Kawtar Nassar, Victoria Navarro Compán, José Bernardo Negrón, Lorna Neill, Sabrina Mai Nielsen, Pavel Novikov, Shannan O'Hara-Levi, Rodica Olteanu, May Padamyar Oo, Win Min Oo, Shelby Oppermann, Claire Owen, Esther Bastos Palitot, Elektra Papadopoulos, Polina Pchelnikova, Michelle Petri, Huai Leng Pisaniello, Irene Pitsillidou, Cristina Ponte, Bryan Poole, Yevgeniy Popov, Susanna Proudman, Kaitlin Quinn, Amy Reynolds, Pamela Richards, Anne Robins, Vasco Romão, Carlee Ruediger, Oscar Russell, Jessica Ryan, Ken Saag, Hinda Sack, Anthony Sammel, Tânia Santiago, Sebastian Sattui, Aman Sharma, Beverley Shea, Lee Simon, Jasvinder Singh, Rani Sinnathurai, Cathy Sparks, Susan Sparks, Marilyn St Quintin, Amy Stanley, Maria Simona Stoenoiu, Simon Stones, Vibeke Strand, Maria Suarez-Almazor, Stephanie Taylor, Suzy Taylor, Sara Tedeschi, Vitor Teixeira, Catarina Tenazinha, Joanna Tieu, Karine Toupin April, Courage Uhunmwangho, Vannia Valinotti, Marieke Voshaar, Margaret Whitstock, Thasia Woodworth, Max Yates, Kevin Yip, Linda Yue.

References

[1] Hench PS, Kendall EC, et al. The effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone; compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc Staff Meet Mayo Clin 1949;24 (8):181–97.

[2] Miloslavsky EM, Naden RP, Bijlsma JWJ, Brogan PA, Brown ES, Brunetta P, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis 2017;76(3):543–6.

[3] Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol 2014;67(7):745–53.

[4] Maxwell LJ, Beaton DE, Shea BJ, Wells GA, Boers M, Grosskleg S, et al. Core Domain Set Selection According to OMERACT Filter 2.1: the OMERACT Methodology. J Rheumatol 2019;46(8):1014–20.

[5] Boers M, Beaton DE, Shea BJ, Maxwell LJ, Bartlett SJ, Bingham CO, et al. OMERACT Filter 2.1: elaboration of the Conceptual Framework for Outcome Measurement in Health Intervention Studies. J Rheumatol 2019 jrheum.181096.

[6] OMERACT. OMERACT handbook. 2019. p. https://omeracthandbook.org.

[7] Black RJ, Robson JC, Goodman SM, Hoon E, Lai LYH, Simon LS, et al. A Patient-reported Outcome Measure for Effect of Glucocorticoid Therapy in Adults with Inflammatory Diseases Is Needed: report from the OMERACT 2016 Special Interest Group. J Rheumatol 2017;44(11):1754–8.

[8] Cheah JTL, Black RJ, Robson JC, Navarro-Millán IY, Young SR, Richards P, et al. Toward a Core Domain Set for Glucocorticoid Impact in Inflammatory Rheumatic Diseases: the OMERACT 2018 Glucocorticoid Impact Working Group. J Rheumatol 2019 jrheum.181082.

[9] Cheah JTL, Robson JC, Black RJ, Goodman SM, Lester S, Mackie SL, et al. The patient's perspective of the adverse effects of glucocorticoid use: a systematic review of quantitative and qualitative studies. From an OMERACT working group. Semin Arthritis Rheum 2020;50(5):996–1005.

[10] Hoon E, Ruediger C, Gill TK, Black RJ, Hill CL. A qualitative study of patient perspectives related to glucocorticoid therapy in polymyalgia rheumatica and giant cell arteritis. Open Access Rheumatol 2019;11:189–98.

[11] Robson JC, Dawson J, Cronholm PF, Ashdown S, Easley E, Kellom KS, et al. Patient perceptions of glucocorticoids in anti-neutrophil cytoplasmic antibody-associated vasculitis. Rheumatol Int 2018;38(4):675–82.

[12] Black RJ, Goodman SM, Ruediger C, Lester S, Mackie SL, Hill CL. A Survey of Glucocorticoid Adverse Effects and Benefits in Rheumatic Diseases: the Patient Perspective. J Clin Rheumatol 2017;23(8):416–20.

[13] Humphrey-Murto S, Crew R, Shea B, Bartlett SJ, March L, Tugwell P, et al. Consensus Building in OMERACT: recommendations for Use of the Delphi for Core Outcome Set Development. J Rheumatol 2019;46(8):1041–6.

[14] Venter GTJ, Black R, Lester S, Leonardo N, Whittle SL, Hoon E, et al. Perspectives of glucocorticoid use in patients with rheumatoid arthritis. ACR Open Rheumatol 2021.

[15] OMERACT working group: glucocorticoids. 2020. Available from: https://omeract.org/working-groups/glucocorticoids/.

Appendix 8 South Australian Epidemiology of ANCA-associated vasculitis proposal

Study title: Epidemiology of anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis (AAV) in South Australia

Investigator: Dr Joanna Tieu

PhD student, University of Adelaide [Primary supervisor: Prof Catherine Hill]

Rheumatologist, The Queen Elizabeth Hospital

Rheumatologist, Lyell McEwin Hospital

Principal Investigator: Professor Catherine Hill

Director, Rheumatology Unit, The Queen Elizabeth Hospital

Staff Specialist, Royal Adelaide Hospital

Clinical Professor, University of Adelaide

Associate investigators: Dr Pravin Hissaria

Immunologist, Royal Adelaide Hospital

Immunopathologist, SA Pathology

Ms Susan Lester

Chief Medical Scientist, Rheumatology research group,

Basil Hetzel Institute

Table of Contents

Abbreviations

AAV	anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis
AIHW	Australian Institute of Health and Welfare
ANCA	anti-neutrophil cytoplasm antibody
DOMINO	Data Over Multiple INdividual Occurrences
DSS	Department of Social Services
EGPA	eosinophilic granulomatosis with polyangiitis
GPA	granulomatosis with polyangiitis
HREC	human research ethics committee
MPA	microscopic polyangiitis
MPO	myeloperoxidase
NT	Northern Territory
PBS	pharmaceutical benefits scheme
PSLK	project specific linkage key
PR3	proteinase 3
SA	SA
SURE	secure unified research environment

1. Introduction

Anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis (AAV) is a multi-system autoimmune condition resulting in severe organ and life-threatening manifestations. Through this project, we aim to better understand the impact of AAV in the South Australian (SA) population.

Key studies of patients with AAV have predominantly taken place in multinational randomised controlled trials, centred in Europe and North America. Population studies have identified that these patients differ to those in observational cohorts. The incidence and prevalence of AAV in Australia is unclear with estimates based on single-centre studies. Moreover, the impact of AAV to patients in Australia is unclear.

Using population-based data linkage, this study will examine real-world data on the burden of AAV to patients suffering from this condition in SA and provide estimates on its impact. This data linkage project will study the following themes:

(1) Prevalence of AAV
(2) Incidence of AAV
(3) Mortality of patients with AAV
(4) Comorbidities and hospitalisation patterns of patients with AAV
(5) Health care and social service utilization of patients with AAV before and after the diagnosis

2. Background

AAV encompasses three disease phenotypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA).

Untreated, AAV is highly fatal, and considerable improvements mean that induction of remission occurs in most patients with AAV (1-3). With current treatment strategies, infection, refractory disease and cardiovascular disease are the key contributors to mortality in the first year following diagnosis (4). Moreover, the risk of relapse is substantial with approximately 50% relapsing within 5 years (5). Morbidity accrues through disease related damage and adverse effects of therapies used to manage these relapses.

With advances in treatment approaches, it has become increasingly important to improve estimates on the incidence and prevalence of rare diseases such as AAV, the burden of AAV that currently exists to patients and the health care system. Moreover, assuming static incidence rates, with improvements in treatment strategies in AAV, the cumulative prevalence of AAV could be increasing. An assessment of the clinical and financial needs of this group of people is required.

Estimates on the incidence and prevalence of AAV vary. Ethnic or genetic differences, environmental effects and latitude differences are postulated to contribute to these differences (6-10). Similar to international studies, Australasian studies of the epidemiology of AAV have used single source cohorts (11-13), with reported prevalence of up to 189 per million and incidence of 13 per million when MPA and GPA are combined.

The use of capture-recapture methodology in health care has been extrapolated from ecological studies providing estimates of closed animal populations. Using this process, animals are captured and tagged or marked and released at two time points- the ‘capture’ and ‘recapture’. The numbers captured at both time points are used to estimate the total population of animals in the area.

Extrapolating this to the health care setting, we can estimate population incidence and prevalence of a particular illness by using multiple sources with overlapping but incomplete identification of patients. This has been used successfully in a number of studies including in the medical literature to provide estimates of incidence and prevalence of notifiable infectious diseases and inflammatory bowel disease in addition to vasculitis (14-18).

Greater accuracy of incidence and prevalence estimates allow patients and clinicians to better inform projections for healthcare expenditure for specific diseases. The impact of AAV extends beyond disease activity, including disease related damage, comorbid conditions, adverse effects of medications used to treat AAV and the impact to overall patient function, social and work participation. The prodrome often associated with AAV can be attributed to more common explanations of these manifestations; the health care utilisation patterns prior to diagnosis in the Australian setting is unknown.

Using a population-based approach, we are able to investigate some of the real-world burdens faced by patients diagnosed with AAV in SA.

3. Objectives

Primary objectives

1. Estimate the prevalence of AAV in the SA population
2. Estimate the annual incidence of AAV in the SA population

Secondary objectives

1. Evaluate the health care burden to patients with AAV and incurred health care costs, with comparisons to age, sex and cohort matched controls by:
    a. Determining mortality rate and causes of death in patients with AAV
    b. Identifying the comorbidities of patients with AAV
    c. Evaluating the patterns and reasons for hospital admissions in patients after diagnosis of AAV
    d. Determining health care utilisation costs related to AAV and comorbidities
    e. Determining the broader impact of AAV to patients through use of social services after diagnosis

4. Study design

4.1 Data sources

We plan to use the SA NT DataLink framework to perform data linkage and enable a capture-recapture analysis to identify patients with AAV in SA and estimate the incidence and prevalence of AAV in SA.

Using three data sources, we will identify patients diagnosed with AAV in SA:

1. SA public hospital separation summaries,
2. SA Pathology ANCA enzyme linked immunosorbent assay (ELISA) results, and
3. SA Pathology tissue histopathology

Data linkage will allow for diagnostic verification and provide data to achieve the key objectives of this study. Information will be linked for individuals' co-morbidities, cause of death and health care utilisation, allowing an assessment of the burden of AAV to these patients and estimate its cost in SA.

The following data time periods will be used to achieve the objectives outlined in above3 Objectives:

- 01/07/2000 – current: cohort identification and validation, comorbidity identification, mortality and hospitalisation analyses. Comparisons made to control group.
- 01/01/1990 – current: additional analysis of trends in ANCA testing against attribution to mortality and hospitalisation
- 01/07/1990 – current: 10 year look-back period for health care and social services utilization prior to diagnosis and following diagnosis. Comparisons made to control group.

4.2 Study procedures

4.2.1. Patient identification

We will be using data sources to identify patients with AAV in SA from first linkage of SA public hospital separations. Using the SA NT datalink, three data sources will be used to identify patients with possible AAV: SA public hospital separations, ANCA results (SA Pathology, ClinPath, Adelaide Pathology Partners) and histopathology consistent with AAV (SA Pathology, ClinPath, Adelaide Pathology Partners).

SA public hospital separation summaries that include an ICD 10 code for AAV, GPA, MPA and EGPA will be identified. From pathology data, individuals with an ANCA enzyme linked immunosorbent assay (ELISA) result above the upper limit of normal will be identified. From histopathology data, reports will be search for key phrases including 'necrotising vasculitis', 'granuloma', 'granulomatous' and 'pauci-immune' to identify biopsies consistent with AAV.

Controls will be identified using SA Health separation summary and SA Pathology ANCA test data, with a ratio of 4 controls to 1 cohort individual. Controls will be age, sex, SEIFA and cohort year matched.

1.2.2 Diagnostic verification

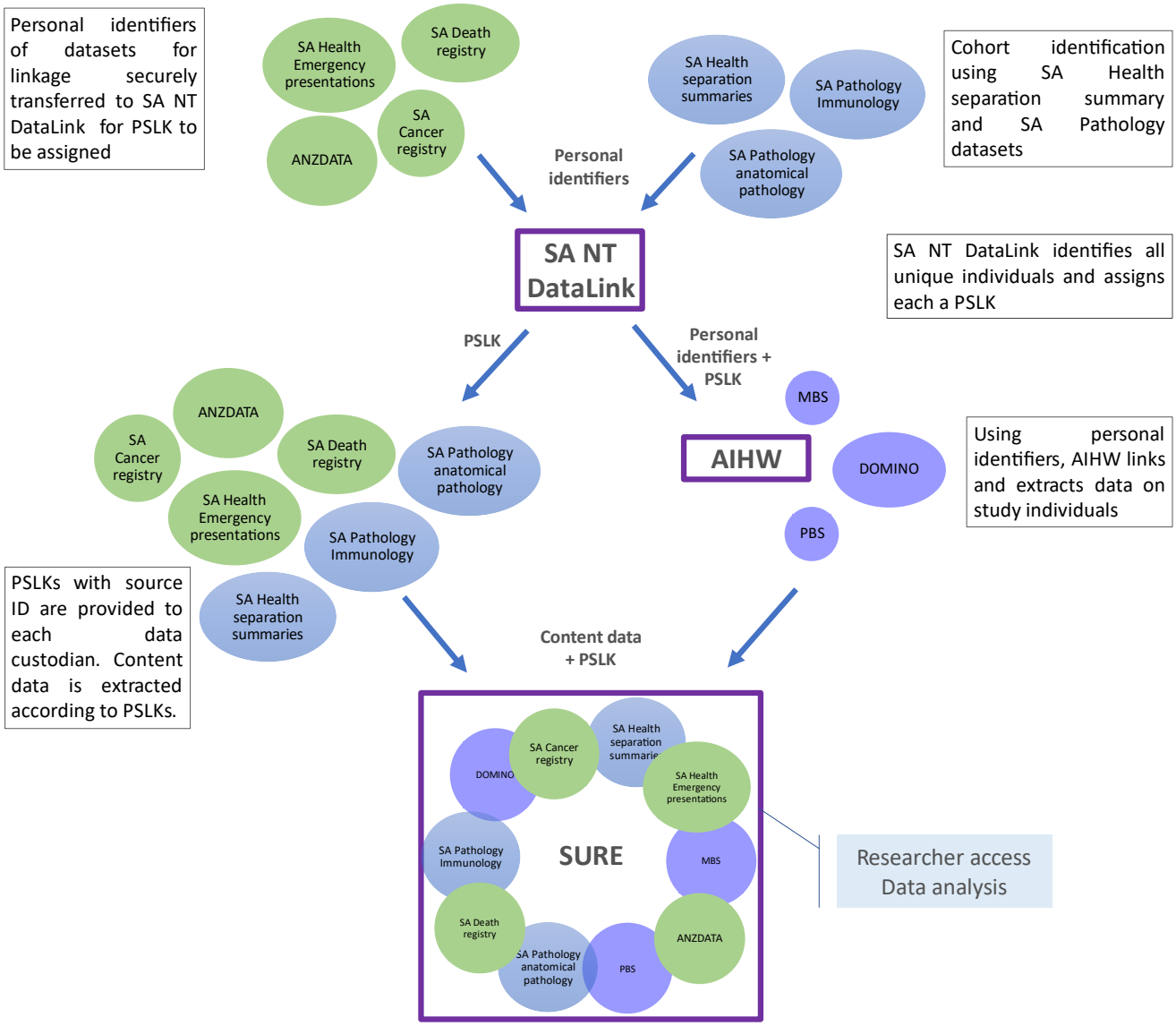
To reduce data inaccuracy and verify the diagnosis of AAV from the identified sources, we will use PBS data or death to verify the diagnosis. Diagnosis will be verified where a prescription for prednisolone, methylprednisolone, cyclophosphamide, rituximab, azathioprine, methotrexate or mycophenolate are dispensed to the person within 12 months of the first time point of source identification. When the individual has died within 12 months of the first time point of source identification, diagnosis will be confirmed if AAV or a subtype is listed as cause or contributor to death.

1.2.3 Data linkage procedure

Steps for linkage (depicted in flowchart- figure 1):

1. Personal identifiers of individuals meeting criteria for the study cohort will be transferred from data custodians securely to SA NT DataLink for cohort identification and generation of a project specific linkage key (PSLK).
2. SA NT DataLink assigns a PSLK for each unique individual and this is provided to the data custodian with the original identification label used by the data custodian.
3. Data custodians extract content data for individuals identified now by PSLK.
4. Data custodians transfer content data with PSLK to the secure research environment (SURE) for researcher analysis.
5. Personal identifiers will be securely transferred from SA NT DataLink to AIHW.
6. AIHW will use personal identifiers to match individuals by PSLK and extract data on these individuals from Commonwealth held datasets. The requested content data with PSLK will be transferred to SURE. Again, personal identifiers for linkage will not be available to researchers.
7. Data analysed by researchers in SURE. Analysis results only can be exported from SURE.

Figure 1



5. Statistical analysis

A capture-recapture analysis will be used to ascertain an estimate of the overall incidence and prevalence of AAV and its subtypes (GPA, MPA and EGPA), and the degree of incomplete case ascertainment through three sources (figure 2). The three sources are: SA Health public hospital separation summaries; positive ANCA ELISA results; and histopathology consistent with AAV. Three data sources have been selected in view of inherent dependency within the model. A log-linear model will be used to obtain the incidence and prevalence estimates, incorporating interaction terms to explore dependency between sources.

Using the available longitudinal data, a time series analysis will be used to forecast incidence and prevalence over time for AAV and its subtypes. Box-Jenkins method will be used to apply an

autoregressive moving average (ARMA) or autoregressive integrated moving average (ARIMA) models to forecast prevalence over time.

Descriptive statistics will be used to describe the demographic details of individuals with AAV, hospitalisations (number and length of stay), comorbidities (including cardiovascular, thromboembolic, malignancy and infection data), and outcomes (infection, renal replacement therapy or transplantation, mortality). A comorbidity index will be used when considered as potential explanatory variables in modelling of data. Descriptive statistics will be used to summarise comorbidity, mortality and health care utilisation data.

Malignancy and mortality will be compared with controls and population rates, using cox proportional models and standardised incidence ratios respectively. Where hazards are time varying, alternative survival models will be used. Hospitalisation rates and patterns will be explored using a transition state model and cox proportional hazard models.

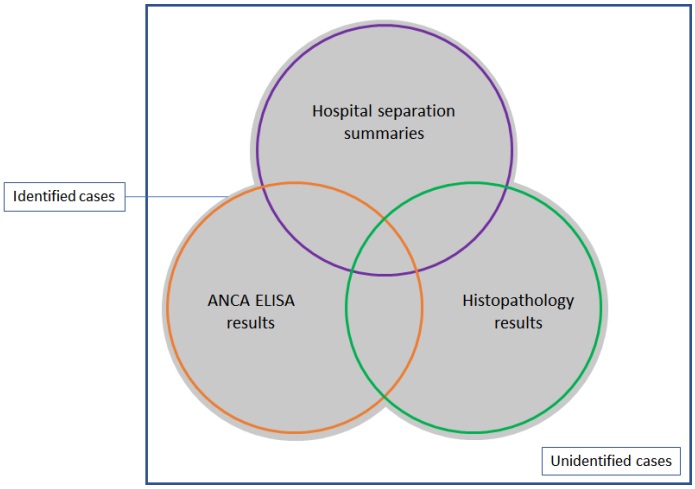
Health care utilisation data including hospitalisation data, MBS, PBS and social services support in the 10 years prior to index diagnosis will be compared between patients and controls, and by AAV subgroup. We plan to compare the health care utilisation patterns in the time prior to diagnosis, in the time period leading up to diagnosis and after diagnosis in the identified cohort. This will additionally compared with control individuals.

Additional analyses:

There will be inherent challenges in interpreting the use of coding data and sensitivity analyses will be performed with each AAV subgroup considered individually.

Commercially available ANCA testing was first available internationally in 1990. Increasing uptake of testing will have had an effect on proportion positive and negative over time and attribution of ANCA associated vasculitis to death. Thus, an additional analysis will be performed using data on ANCA testing and mortality from 1990 onwards to assess this trend over the time period of the full data linkage (2000 onwards).

Figure 2



6. Ethical considerations

No identifiable data will be accessible by researchers. This study will not directly impact individual patient treatment decisions as data collected involves treatment decisions already made.

Both SA NT DataLink and AIHW are physically and electronically, highly secure facilities that have established processes for data linkage projects. SA NT DataLink security procedures for the protection of personal identifiers provided for linkage are detailed and updated on the SA NT DataLink website (https://www.santdatalink.org.au/security_standards). The use of SURE for data storage and analysis allows for compliance to security standard for Commonwealth data held by AIHW.

A high standard of data management, as detailed below, is maintained to ensure patient privacy.

7. Data management

7.1 Data management and privacy

The data linkage process will be undertaken by SA NT DataLink. SA NT DataLink has well established processes to ensure that the required privacy and confidentiality of the information is preserved through the separation principle described in the figure 3 below.

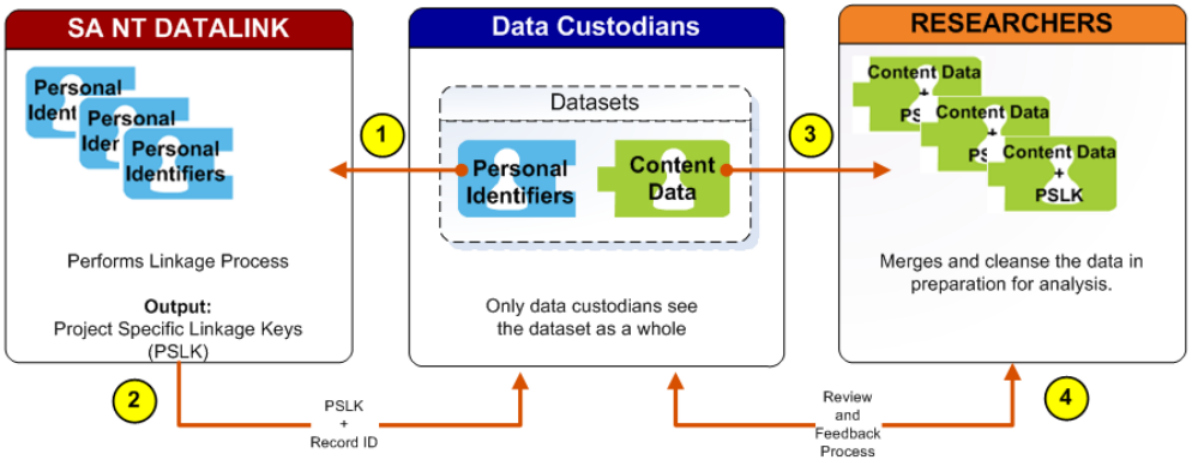
The cohort meeting the criteria outlined in the section 4.2 Study procedures will be identified by data custodians internally (SA Pathology and SA Health). The identifying information with SA Pathology and SA Health unique record identities (ID) will be sent to SA NT DataLink. SA NT DataLink will then link this information to the other datasets and return the record IDs and project specific linkage keys (PSLKs) to each data custodians. Data custodians will extract the agreed clinical and administrative information, attach the relevant PSLKs and remove any identifying information (including record IDs).

Data custodians (or SA NT DataLink's Data Integration Unit on approval or request of the data custodians) will import the de-identified data and associated PSLKs in SURE for access by approved researchers.

All data will be transferred using a secure encrypted transfer protocol such as secure unified file exchange (SUFEX). Study researchers will not have access to patient identified data.

Further detail on the privacy protecting model can be access through the SA NT datalink website (https://www.santdatalink.org.au/Privacy_Protecting_Model). Further detail on SURE can be found through the SURE introduction guide (https://www.saxinstitute.org.au/wp-content/uploads/Intro-Guide-to-SURE-V3.0-Mar17.pdf).

Figure 3: SA NT datalink privacy protecting model



Source: https://www.santdatalink.org.au/Privacy_Protecting_Model

7.2 Data storage and security

It is a Commonwealth requirement for all projects seeking to link Commonwealth data that all data must be stored in SURE. Thus, for this project, data will be provided to the researcher in SURE.

SURE is a secure remote-access computing environment located in the Sax institute, New South Wales. Data in SURE is accessible over encrypted internet connections.

Within SURE, only investigators listed in the research ethics for a study are able to access data, and study specific data remain independent from each other. All researchers must undertake training in the use of SURE before they may access this research environment.

SURE is accessed remotely using secure passwords provided to individuals users in addition to an authentication token. Within this environment there is no access to internet including email, or the ability to copy data onto removable data storage media such as memory sticks.

Data in SURE cannot be removed. Only analytical results can be exported through a curated gateway. Data is reviewed by AIHW prior to export to ensure data integrity and to minimise the risk of reidentification of individuals from extracted data (data pertaining to subgroups with fewer than 5 individuals will be amalgamated to form a larger subgroup or not extracted).

8 Publication

Analysis results will be disseminated in relevant special society academic meetings and written up for publication in the academic literature. These results may also be presented at the Australia and New Zealand Vasculitis society meeting, attended by relevant consumer groups.

Funding will be sought as an unrestricted grant(s), without contingencies placed on study design, analysis method or results dissemination. Any funder(s) will be acknowledged in the presentation and publication of study results.

9 References

1. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. The New England journal of medicine. 2010;363(3):221-32.
2. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. New England Journal of Medicine. 2010;363(3):211-20.
3. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med. 2009;150(10):670-80.
4. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis. 2011;70(3):488-94.
5. Walsh M, Flossmann O, Berden A, Westman K, Hoglund P, Stegeman C, et al. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012;64(2):542-8.
6. Fujimoto S, Watts RA, Kobayashi S, Suzuki K, Jayne DR, Scott DG, et al. Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K. Rheumatology (Oxford, England). 2011;50(10):1916-20.
7. Furuta S, Chaudhry AN, Arimura Y, Dobashi H, Fujimoto S, Homma S, et al. Comparison of the phenotype and outcome of granulomatosis with polyangiitis between UK and Japanese cohorts. Journal of Rheumatology. 2017;44(2):216-22.
8. Furuta S, Chaudhry AN, Hamano Y, Fujimoto S, Nagafuchi H, Makino H, et al. Comparison of phenotype and outcome in microscopic polyangiitis between Europe and Japan. Journal of Rheumatology. 2014;41(2):325-33.
9. Stamp LK, Chapman PT, Francis J, Beckert L, Frampton C, Watts RA, et al. Association between environmental exposures and granulomatosis with polyangiitis in Canterbury, New Zealand. Arthritis Research & Therapy. 2015;17(1):333.
10. Lane SE, Watts R, Scott DG. Epidemiology of systemic vasculitis. Curr Rheumatol Rep. 2005;7(4):270-5.
11. Hissaria P, Cai FZ, Ahern M, Smith M, Gillis D, Roberts-Thomson P. Wegener's granulomatosis: epidemiological and clinical features in a South Australian study. Internal medicine journal. 2008;38(10):776-80.
12. Ormerod AS, Cook MC. Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales. Internal medicine journal. 2008;38(11):816-23.
13. Gibson A, Stamp LK, Chapman PT, O'Donnell JL. The epidemiology of Wegener's granulomatosis and microscopic polyangiitis in a Southern Hemisphere region. Rheumatology (Oxford, England). 2006;45(5):624-8.
14. Jones G-R, Lyons M, Plevris N, Jenkinson PW, Bisset C, Burgess C, et al. IBD prevalence in Lothian, Scotland, derived by capture–recapture methodology. Gut. 2019:gutjnl-2019-318936.
15. van der Maas NAT, Hoes J, Sanders EAM, de Melker HE. Severe underestimation of pertussis related hospitalizations and deaths in the Netherlands: A capture-recapture analysis. Vaccine. 2017;35(33):4162-6.
16. Schielke A, Takla A, von Kries R, Wichmann O, Hellenbrand W. Marked Underreporting of Pertussis Requiring Hospitalization in Infants as Estimated by Capture-Recapture Methodology, Germany, 2013-2015. The Pediatric infectious disease journal. 2018;37(2):119-25.
17. Braeye T, Verheagen J, Mignon A, Flipse W, Pierard D, Huygen K, et al. Capture-Recapture Estimators in Epidemiology with Applications to Pertussis and Pneumococcal Invasive Disease Surveillance. PLOS ONE. 2016;11(8):e0159832.
18. Pearce FA, Lanyon PC, Grainge MJ, Shaunak R, Mahr A, Hubbard RB, et al. Incidence of ANCA-associated vasculitis in a UK mixed ethnicity population. Rheumatology. 2016;55(9):1656-63.