

Original article

Patterns of biologic and targeted-synthetic disease-modifying antirheumatic drug use in rheumatoid arthritis in Australia

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Abstract

Objective. The aim of this study was to describe treatment patterns in RA, including the frequency and reasons for switching or stopping biologic and targeted synthetic DMARDs (b/tsDMARDs).**Methods.** The reasons for switching or stopping b/tsDMARDs were extracted from the Australian Rheumatology Association Database (ARAD) from 2003 to 2018 for RA participants. Switching patterns for each b/tsDMARD and time on first-, second- and third-line b/tsDMARDs were evaluated using Sankey diagrams and survival methods.**Results.** A total of 2839 participants were included in the analysis. The first-line b/tsDMARDs were etanercept ($n = 1414$), adalimumab ($n = 1024$), infliximab ($n = 155$), golimumab ($n = 98$), abatacept ($n = 66$), certolizumab ($n = 38$), tocilizumab ($n = 21$) and tofacitinib ($n = 23$). Of those starting first-, second- and third-line biologic therapy, 24.0%, 31.8% and 24.4% switched to another b/tsDMARD within 12 months, respectively. Inefficacy or adverse effects were the most common reasons for stopping therapy, irrespective of line of treatment. Compared with first-line etanercept, participants were more likely to stop adalimumab [Hazard ratio (HR) 1.16, 95% CI: 1.04, 1.29] and infliximab (HR 1.77, 95% CI: 1.46, 2.16). No differences were seen for other b/tsDMARDs. For second-line therapies compared with etanercept, the risk of stopping was lower for tocilizumab (HR 0.41, 95% CI: 0.25, 0.70), rituximab (HR 0.51, 95% CI: 0.30, 0.85) and tofacitinib (HR 0.29, 95% CI: 0.15, 0.57). Participants taking rituximab, tocilizumab and tofacitinib were also less likely to stop third-line therapy in comparison with participants taking etanercept.**Conclusions.** Switching between b/tsDMARDs was common among ARAD participants with RA, most commonly due to inefficacy or adverse effects. Durability of exposure and reasons for switching varied between b/tsDMARDs.**Key words:** rheumatoid arthritis, biologics, switching, efficacy, adverse events, Sankey plots

Rheumatology key messages

- TNFi bDMARDs are common first-line therapies; switching to a different class of b/tsDMARD is common.
- Lack of efficacy is the commonest reason for stopping b/tsDMARD medications, followed by adverse events.
- There is better survival of some b/tsDMARDs used as second- or third-line therapy relative to others.

Introduction

RA is a chronic, autoimmune, inflammatory joint disease of unknown cause, which, untreated, often results in deformity and irreversible joint damage [1]. Conventional

synthetic DMARDs (csDMARDs) such as MTX, biologic DMARDs (bDMARDs), and more recently targeted-synthetic DMARDs (tsDMARDs) are now widely used to suppress synovitis, to slow or stop disease progression

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and, importantly, to minimize or eliminate structural joint damage.

The Australian Government provides universal health care through the Medicare Benefits Scheme (MBS) and Pharmaceutical Benefits Scheme. Australians can also opt for private health insurance, which provides varying cover for hospital care and some out-of-hospital ancillary health care depending upon specific policies. In Australia, b/tsDMARDs can be subsidized on the Pharmaceutical Benefits Scheme following a positive recommendation about their cost-effectiveness by the Pharmaceutical Benefits Advisory Committee (PBAC). The first b/tsDMARDs for RA listed on the Pharmaceutical Benefits Scheme were etanercept (August 2003), infliximab (November 2003) and adalimumab (December 2003), followed by rituximab (restricted to second-line use, August 2007), abatacept (March 2008), tocilizumab (August 2010), golimumab (August 2010), certolizumab (August 2010) and tofacitinib (October 2015). Etanercept and adalimumab remain the ones most commonly prescribed [2].

As with any medication, b/tsDMARDs may or may not have efficacy, or may have unintended adverse effects in the individual patient. Patients stop medications for a variety of reasons, including lack of efficacy or loss of efficacy after an initial period of response, adverse events, and a variety of other reasons such as intercurrent illness, pregnancy and occasionally remission (either drug-induced or spontaneous) [3, 4]. Patients may switch to another medication or stop use of b/tsDMARDs altogether [5, 6]. In registry-based studies, of those who stop a b/tsDMARD, 18.4–75.3% stop due to inefficacy, while adverse events account for 9.5–24.0% of cessations/changes [6–11].

Switching rates vary between different studies and different b/tsDMARDs. In recently published studies using data from administrative databases, the rate of switching varied from 7.8 to 43.5% [5, 12–14], with higher rates often observed with adalimumab [15–17], and when individuals switched or ‘cycled’ from one TNF inhibitor (TNFi) to another compared with switching from a TNFi to a non-TNFi [18]. In registry-based studies, the rate of switching has been reported to range from 28.5 to 35.0% [10, 19], with higher rates also observed after cycling from a failed TNFi to another TNFi, compared with switching to a b/tsDMARD with a different mode of action [8, 11].

Sankey diagrams are graphical visualizations of temporal pathways that can highlight patterns in data. Developed to report on the efficiency of steam engines in 1896 [20], they have recently been applied to some aspects of health and medicine, including treatment pathways, microbiological studies and medication switching [5, 21–23].

The aim of this study was to investigate b/tsDMARD switching patterns, using Sankey diagrams as well as time-to-event statistical methods, among RA participants in the Australian Rheumatology Association Database (ARAD), a large national prospective registry of people with inflammatory arthritis [24].

Methods

ARAD was established in 2002 with the aim of determining the long-term safety and effectiveness of biologic therapies in routine care. It is a voluntary national registry that collects longitudinal data from participants with inflammatory arthritis. Detailed methodology for ARAD has been described previously [24]. Participants are enrolled by a rheumatologist or can self-enrol. All participants provide permission to be contacted by ARAD investigators and give written informed consent for participation in the registry as well as having their data analysed and published. They complete questionnaires every 6–12 months in either online or paper format. The questionnaires include demographic information, medication use and patient-reported outcomes. Any data issues are investigated by ARAD staff promptly, resulting in very low rates of missing data. Participants 18 years of age and over with a confirmed diagnosis of RA and who had been exposed to a b/tsDMARD were eligible for inclusion in this analysis. ARAD has ethics approval from the Human Research Ethics Committee at Monash University (EC 00234).

Data extracted from ARAD included participant demographic and clinical characteristics, comorbidities, doctor-reported inflammatory markers at baseline, and well-validated and widely used self-reported health assessment [physical function measured by the HAQ [25] (0–3—lower score is better)] as well as health-related quality of life [measured by the Assessment of Quality of Life Questionnaire (AQoL) [26] (0–1—lower score is worse), 36-item Short-Form Health Survey (SF-36) [27] (0–100—lower score is worse) and European Quality of Life (EQ5D UK) [28] (0–1—lower score is worse)]. All data relating to b/tsDMARD use, duration of therapy, reasons for switching or stopping (drug did not work, developed side effects, arthritis improved, too sick from other illness, no longer meeting Pharmaceutical Benefits Scheme criteria, surgery, pregnancy, clinical trial finished, did not like it/worried about drug, started new drug, did not like delivery method or other), adverse events and concurrent csDMARD, oral glucocorticoid, NSAID and opioid use were also extracted.

The b/tsDMARDs examined in this analysis were etanercept ($n = 1414$), adalimumab ($n = 1024$), infliximab ($n = 155$), rituximab (second-line $n = 108$), abatacept ($n = 64$), tocilizumab ($n = 21$), golimumab ($n = 98$), certolizumab ($n = 38$) and tofacitinib ($n = 23$).

Statistical analysis

Clinical and demographic data were summarized according to participant exposure to first-line b/tsDMARD. The numbers of participants starting each b/tsDMARD were tabulated for first-, second- and third-line therapy. For those exposed to a b/tsDMARD while in ARAD, or up to 6 months before their first questionnaire, patient characteristics, including age, gender, disease duration, self-reported DMARD use, physical function and quality of life were tabulated. The quality of

life and physical function instruments were scored using standard algorithms. Groups were compared using *t*-tests, Chi-squared tests or Wilcoxon Rank Sum tests as appropriate for the data types.

Sankey diagrams were used to graphically describe the number of participants who sequentially switched or stopped first-, second- and third-line therapy, irrespective of the calendar year in which b/tsDMARDs were started and the duration of b/tsDMARD use. The bars on the left show the first-line b/tsDMARD, with subsequent b/tsDMARD use represented as progressing from left to right. The thickness and colour of the lines indicate the number switching to another b/tsDMARD or stopping b/tsDMARD use.

We also describe the percentage who switched, continued or stopped first-, second- and third-line therapy after 12, 24 and 36 month durations. Reasons for switching or stopping were taken from a single-answer question classified as drug did not work, developed side effects, or other reasons (arthritis improved, too sick from other illness, didn't meet Pharmaceutical Benefits Scheme criteria, surgery, pregnancy, clinical trial finished, did not like it/worried about drug, other, started new drug, not like delivery method or other). First-, second- and third-line b/tsDMARDs were analysed and the percentages are presented graphically. We also present reasons for switching and stopping in the first 6 months, for switching and stopping between 6 and 12 months, and for switching and stopping overall, for each line of therapy.

Hazard ratios (HRs) for switching or stopping a first-, second- and third-line b/tsDMARD (with etanercept as the reference group) were determined using Cox regression models and adjusted for age, sex, disease duration, cycling compared with switching to second- and third-line a b/tsDMARD, questionnaire year, employment, HAQ score, and current use of opioids, NSAIDs, prednisolone and/or MTX. A HR > 1 indicates a greater risk of stopping a specific b/tsDMARD compared with etanercept. Etanercept was chosen as the reference group as it was the first b/tsDMARD available for use in Australia. Time on all b/tsDMARDs was calculated from self-reported start and stop dates or date of death ascertained from record-linkage with the Australian National Death Index. The time exposed to first-, second- and third-line b/tsDMARD therapy was compared for each b/tsDMARDs using Kaplan Meier curves.

Results

Demographic and clinical characteristics

From January 2002 to May 2018 there were 2839 participants who fulfilled our inclusion criteria. The demographic characteristics are shown in Table 1; 108 participants commencing rituximab as second-line therapy are represented by their first-line b/tsDMARD in Table 1 and their data is illustrated in Fig. 1. Quality of life indicators and medications are shown in Table 2 for

2011 participants at the time of starting their first b/tsDMARD (if they started a b/tsDMARD <6 months before enrolling in ARAD, so the questionnaire can relate to the time they started a b/tsDMARD).

The median year of recruitment was 2008, 74.2% were women, the median age was 57.1 (IQR 48.2–64.7) years, and the median disease duration was 10 years (IQR 4–19). There was some variation in demographic characteristics, medications and quality of life indicators depending on which first b/tsDMARDs were commenced. For example, participants starting golimumab, certolizumab and tofacitinib but not tocilizumab, all approved in the last 10 years, had generally better function and quality of life at b/tsDMARD commencement compared with those commencing b/tsDMARDs that have been available and publicly subsidized for longer.

Patterns of b/tsDMARD use

Overall, 2839 started first-line therapy, and 1444, 743 and 314 started second-, third- and fourth-line therapy, respectively. Fig. 1 displays the flow of b/tsDMARD use from first- to fourth-line therapy in a Sankey plot. After first-line etanercept, the most common second-line b/tsDMARD was adalimumab (59.5%), while after second-line etanercept the most common were rituximab (28.8%) followed by tocilizumab (21.2%), and after third-line etanercept the most common were abatacept (60%) and tocilizumab (40%). As with etanercept, after first-line adalimumab most participants cycled to another TNFi, which was most often etanercept (39.8%). However, after that most participants switched to another class of medication. Second-line switches were also most commonly to rituximab (27.5%) followed by abatacept (23.7%) and tocilizumab (20.0%), and the most common third-line switches were to rituximab, abatacept and tocilizumab. Over time, the overall rate of switching was similar, with 38.0% switching first-line b/tsDMARD between 2002 and 2010, while 43.1% switched from first-line between 2011 and 2018.

The percentages of participants continuing, stopping and switching at 12, 24 and 36 months from first-line, second- and third-line b/tsDMARDs are shown in Fig. 2 and Supplementary Table S1 (a–c, available at *Rheumatology* online). At 12 months, over two-thirds of participants (69.7%) remained on their first-line b/tsDMARD, whereas 24.0% had switched to another b/tsDMARD and 6.2% had stopped the drug. There was an increase in switching rates of patients using second-line [switched (31.8%), continued (59.2%) or stopped (9.1%)], and third-line was similar to first-line for switching [switched (24.4%), continued (66.4%) or stopped (9.3%)] b/tsDMARD. A similar pattern was evident at 24 months (with switching rates of 33.3% of patients using first-, 40.0% of patients using second- and 34.3% of patients using third-line therapy) and at 36 months (with switching rates of 38.8% of patients using first-, 45.0% of patients using second- and 37.7% of patients using third-line b/tsDMARDs switching their b/tsDMARD).

TABLE 1 Demographic characteristics at time of starting a first-line b/tsDMARD (*n* = 2839)

Factor	ETN	ADA	IFX	ABT	TCZ	GLM	CTZ	TOF	<i>P</i> -value
<i>N</i>	1414	1024	155	66	21	98	38	23	
Age, years	Mean (s.d.) 56.3 (12.6)	Mean (s.d.) 55.8 (12.5)	Mean (s.d.) 52.7 (13.1)	Mean (s.d.) 60.1 (10.9)	Mean (s.d.) 64.2 (11.6)	Mean (s.d.) 55.2 (11.5)	Mean (s.d.) 55.6 (11.9)	Mean (s.d.) 59.6 (13.8)	<0.01
Years since first symptom	13.6 (10.5)	12.1 (10.8)	14.0 (9.5)	13.1 (12.5)	13.2 (12.2)	10.4 (11.1)	11.5 (11.6)	9.1 (8.1)	<0.01
Pain of arthritis in the past week	49.7 (25.8)	47.1 (25.6)	48.0 (26.9)	46.0 (24.3)	54.4 (17.8)	46.8 (24.5)	53.6 (28.7)	54.8 (25.5)	0.14
Arthritis condition in the past week	49.2 (26.1)	46.4 (25.9)	46.8 (26.5)	43.3 (25.2)	49.3 (22.2)	47.5 (25.8)	52.1 (28.1)	56.6 (24.9)	0.09
Patient gender	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	0.94
Male	367 (26.0)	263 (25.7)	45 (29.0)	16 (24.2)	5 (23.8)	25 (25.5)	8 (21.1)	4 (17.4)	
Female	1047 (74.0)	761 (74.3)	110 (71.0)	50 (75.8)	16 (76.2)	73 (74.5)	30 (78.9)	19 (82.6)	
Diagnosis type									<0.01
RA+ve	936 (66.2)	614 (60.0)	101 (65.2)	33 (50.0)	6 (28.6)	52 (53.1)	26 (68.4)	7 (30.4)	
RA-ve	203 (14.4)	168 (16.4)	21 (13.5)	15 (22.7)	2 (9.5)	18 (18.4)	4 (10.5)	3 (13.0)	
RA	275 (19.4)	242 (23.6)	33 (21.3)	18 (27.3)	13 (61.9)	28 (28.6)	8 (21.1)	13 (56.5)	
Country of birth									0.05
Australia	1046 (74.0)	794 (77.5)	106 (68.4)	47 (71.2)	14 (66.7)	71 (72.4)	33 (86.8)	20 (87.0)	
Other	368 (26.0)	230 (22.5)	49 (31.6)	19 (28.8)	7 (33.3)	27 (27.6)	5 (13.2)	3 (13.0)	
Education									<0.01
Tertiary	521 (36.8)	368 (35.9)	74 (47.7)	23 (34.8)	9 (42.9)	46 (46.9)	18 (47.4)	14 (60.9)	
Secondary	525 (37.1)	326 (31.8)	46 (29.7)	18 (27.3)	6 (28.6)	25 (25.5)	11 (28.9)	3 (13.0)	
Not completed secondary	355 (25.1)	325 (31.7)	35 (22.6)	25 (37.9)	6 (28.6)	27 (27.6)	9 (23.7)	6 (26.1)	
Missing	13 (0.9)	5 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Employment									<0.01
Working	500 (35.4)	400 (39.1)	73 (47.1)	22 (33.3)	5 (23.8)	54 (55.1)	19 (50.0)	9 (39.1)	
Not working/Home duties/Student/Retired/Other	703 (49.7)	470 (45.9)	63 (40.6)	35 (53.0)	15 (71.4)	34 (34.7)	18 (47.4)	12 (52.2)	
Permanently unable/Ill	203 (14.4)	148 (14.5)	19 (12.3)	9 (13.6)	1 (4.8)	10 (10.2)	1 (2.6)	2 (8.7)	
Missing	8 (0.6)	6 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Socio-economic status									0.02
5 (high)	277 (19.6)	209 (20.4)	52 (33.5)	11 (16.7)	4 (19.0)	28 (28.6)	8 (21.1)	5 (21.7)	
4	272 (19.2)	191 (18.7)	29 (18.7)	6 (9.1)	3 (14.3)	16 (16.3)	4 (10.5)	4 (17.4)	
3	297 (21.0)	199 (19.4)	28 (18.1)	15 (22.7)	4 (19.0)	20 (20.4)	13 (34.2)	3 (13.0)	
2	261 (18.5)	214 (20.9)	18 (11.6)	16 (24.2)	7 (33.3)	16 (16.3)	10 (26.3)	7 (30.4)	

(continued)

TABLE 1 Continued

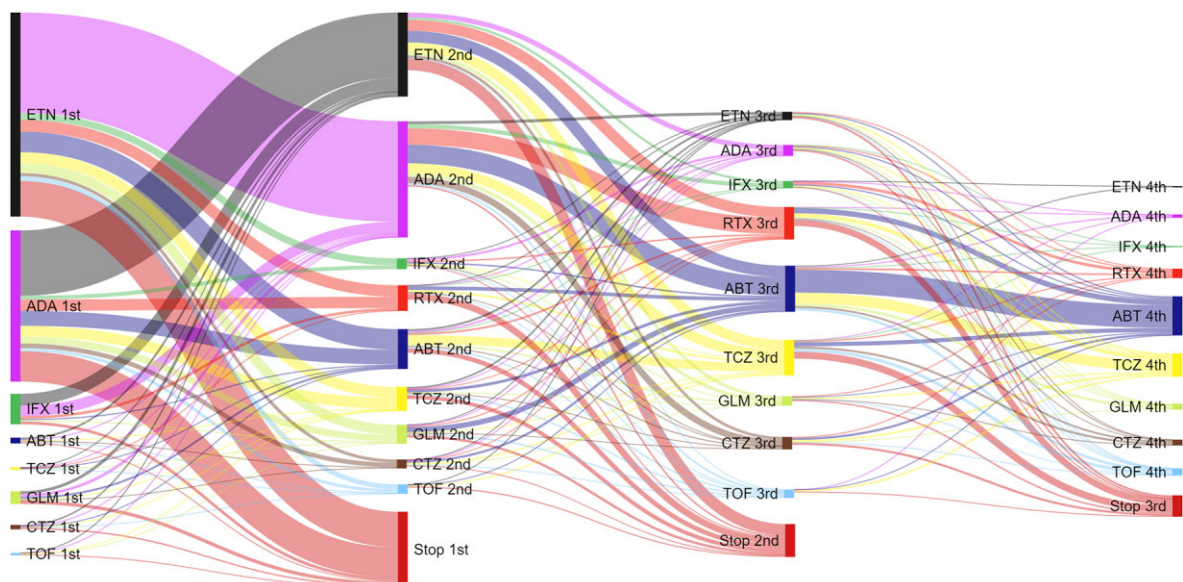
Factor	ETN	ADA	IFX	ABT	TCZ	GLM	CTZ	TOF	P-value
N	1414	1024	155	66	21	98	38	23	
1 (low)	294 (20.8)	201 (19.6)	26 (16.8)	16 (24.2)	2 (9.5)	17 (17.3)	3 (7.9)	4 (17.4)	
Missing	13 (0.9)	10 (1.0)	2 (1.3)	2 (3.0)	1 (4.8)	1 (1.0)	0 (0.0)	0 (0.0)	
Questionnaire year, median (IQR)	2007 (2005, 2000)	2008 (2006, 2010)	2007 (2004, 2007)	2012 (2010, 2015)	2012 (2010, 2016)	2012 (2011, 2014)	2012 (2011, 2012)	2016 (2016, 2016)	<0.01
Currently smoking									0.03
No	1200 (84.9)	877 (85.6)	131 (84.5)	59 (89.4)	21 (100.0)	86 (87.8)	38 (100.0)	23 (100.0)	
Yes	213 (15.1)	143 (14.0)	24 (15.5)	7 (10.6)	0 (0.0)	12 (12.2)	0 (0.0)	0 (0.0)	
Missing	1 (0.1)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Alcohol consumption									<0.01
Never	580 (41.0%)	355 (34.7%)	56 (36.1%)	15 (22.7%)	9 (42.9%)	16 (16.3%)	9 (23.7%)	10 (43.5%)	
Sometimes	663 (46.9%)	559 (54.6%)	83 (53.5%)	43 (65.2%)	9 (42.9%)	69 (70.4%)	27 (71.1%)	10 (43.5%)	
Every day	171 (12.1%)	109 (10.6%)	16 (10.3%)	8 (12.1%)	3 (14.3%)	13 (13.3%)	2 (5.3%)	3 (13.0%)	
Missing	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

ETN: etanercept; ADA: adalimumab; IFX: infliximab; ABT: abatacept; TCZ: tocilizumab; GLM: golimumab; CTZ: certolizumab; TOF: tofacitinib; n: number; IQR: interquartile range.

Overall, more participants changed at 12 months from infliximab for each line of therapy (35.5% 1st, 56.6% 2nd, 45.2% 3rd), while fewer changes were observed from second-line rituximab (16.7%), second- or third-line tocilizumab (20.8% 2nd, 16.4% 3rd) and tofacitinib (17.9% 2nd, 17.1% 3rd), and third-line golimumab (16.2%). In general, lack of efficacy was the most commonly reported reason for stopping a b/tsDMARD, irrespective of whether it was first-, second- or third-line therapy (50.7%, 58.9% and 56.7%, respectively). Stopping due to adverse events was the second-most commonly reported reason across first-, second- and third-line therapy (19.6%, 19.4% and 17.7%, respectively) (Fig. 3a–c; Supplementary Table S2a–c, available at *Rheumatology* online). The reason for stopping was time dependent for first-line use, with 53.3% stopping for lack of efficacy and 32.1% for adverse events at 6 months, and 68.2% stopping for lack of efficacy and 9.6% for adverse events at 6–12 months. Second-line use was not time dependent, with 67.8% stopping due to lack of efficacy at 6 months and 59.8% at 6–12 months, while 18.8% stopped for adverse events at 6 months and 19.3% at 6–12 months. A higher proportion stopped b/tsDMARDs completely due to adverse effects (24.7%) compared with lack of efficacy (21.3%) for first-line use, compared with who that switched first-line, where 59.8% of switching was due to lack of efficacy compared with 21.0% due to side effects. The other major reasons for stopping first-line therapies completely were being too sick from other illnesses (20.6%), surgery (7.8%) and other reasons (11.8%). For second-line stopping, 31.2% was due to lack of efficacy and 26.7% was due to adverse events, compared with those who switched (63.6% lack of efficacy, 21.0% adverse events); the results were similar for third-line stopping (35.1% lack of efficacy, 23.7% adverse events) compared with switching (65.5% lack of efficacy, 19.5% adverse events).

Risk of stopping first-, second- and third-line b/tsDMARDs

Compared with first-line etanercept, there was a trend towards an increased risk of stopping all other first-line b/tsDMARDs, with significant differences observed for adalimumab [HR 1.16 (95% CI: 1.04, 1.29)] and infliximab [HR 1.77 (95% CI: 1.46, 2.16)] (Fig. 4a; Supplementary Table S3, available at *Rheumatology* online). Compared with second- and third-line etanercept, there was a reduced risk of stopping rituximab [HR 0.51 (95% CI: 0.30, 0.85) and 0.51 (95% CI: 0.31, 0.83), respectively], tocilizumab [HR 0.41 (95% CI: 0.25, 0.70) and 0.37 (95% CI: 0.23, 0.59)] and tofacitinib [HR 0.29 (95% CI: 0.15, 0.57) and 0.26 (95% CI: 0.13, 0.52)] (Fig. 4b and c; Supplementary Table S2, available at *Rheumatology* online). The year of starting a b/tsDMARD was an independent predictor of switching, with more switching in later calendar years; overall, however, the year of starting a b/tsDMARD did not have an effect on the switching patterns. Whether subsequent switching

Fig. 1 Flow of b/tsDMARD use—switching and stopping from first-line therapy to fourth-line therapy

ETN: etanercept; ADA: adalimumab; IFX: infliximab; RTX: rituximab; ABT: abatacept; TCZ: tocilizumab; GLM: golimumab; CTZ: certolizumab; TOF: tofacitinib.

was after previous cycling or switching of a drug type was not a significant predictor of switching a second- or third-line b/tsDMARD [HR 0.82 (95% CI: 0.53, 1.25) and HR 0.94 (95% CI: 0.73, 1.20), respectively] and did not change the significance of any second- or third-line switch.

The proportion of participants remaining on first-, second- and third-line b/tsDMARDs for each b/tsDMARD at 1-year intervals to 5 years are shown in Kaplan Meyer survival curves, noting that these absolute numbers are confounded by when each b/tsDMARD became available for subsidized use (Supplementary Fig. S1, available at *Rheumatology* online). Retention rates were generally higher for first-line b/tsDMARDs, but only significantly higher for etanercept, adalimumab, infliximab, abatacept (infusion) and certolizumab, and only etanercept was significantly different from other therapies as second- and third-line therapies.

Discussion

Most participants in ARAD between 2003 and 2018 were commenced on a TNFi, most commonly etanercept or adalimumab, reflecting their longer availability and perhaps ease of administration compared with infliximab. After failure of first-line TNFi, most participants received a second TNFi, and only received a b/tsDMARD of another class as third-line therapy. Over three-quarters of participants remained on their first-line therapy, and an even greater proportion remained on their second- and third-line b/

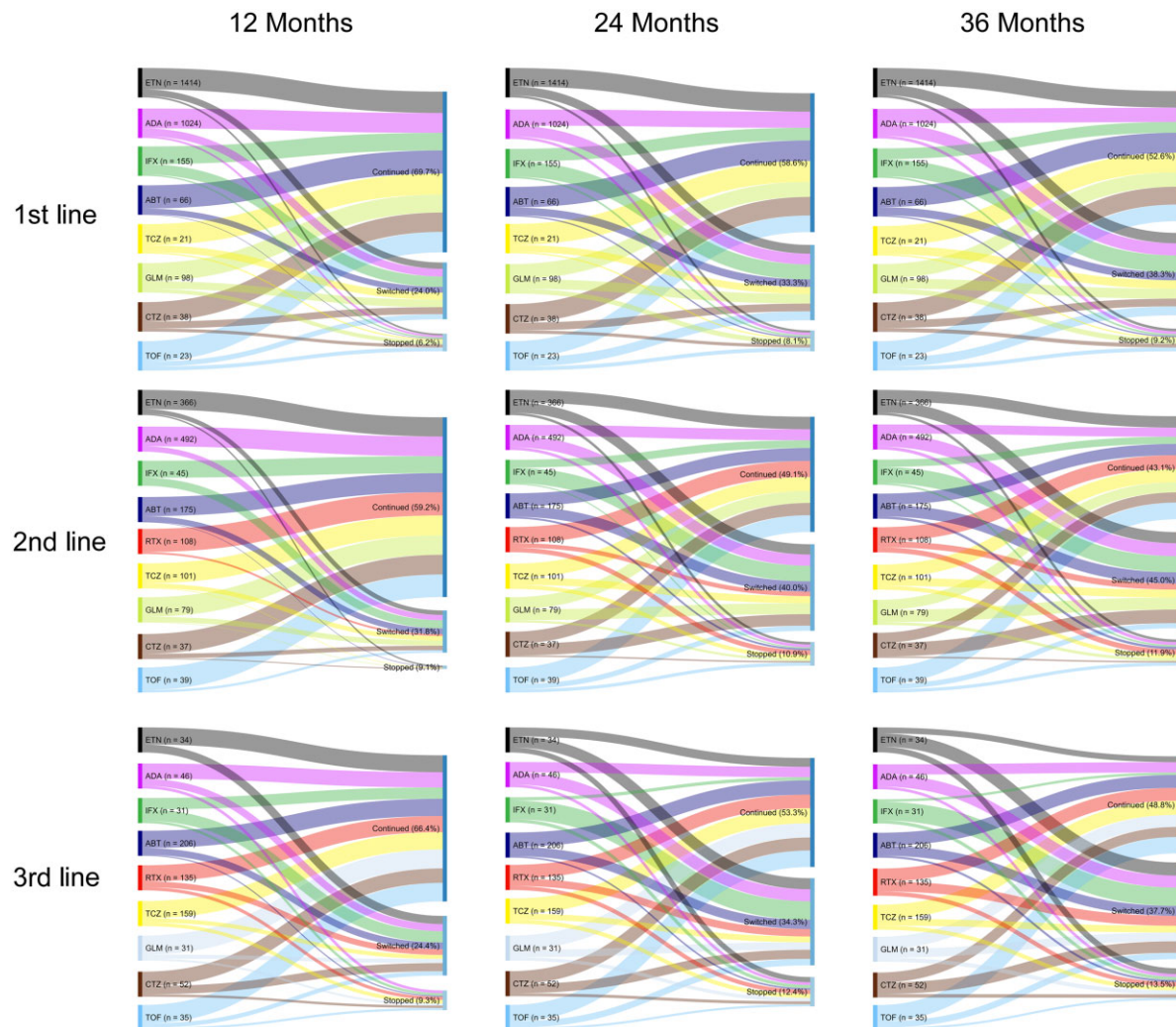
tsDMARDs. However, retention rates were lower for infliximab, irrespective of line of therapy. The most commonly cited reasons for changing or stopping a therapy were lack of efficacy (~50%) or adverse effects (~20%), irrespective of drug or line of therapy. Participants starting on more recently available Pharmaceutical Benefits Scheme-subsidized b/tsDMARDs had better function and quality of life at baseline, a potentially important confounder if comparing the benefits of b/tsDMARD therapy from registry data.

Patterns of b/tsDMARD use found in registry and administrative data studies are often difficult to describe and analyse [3]. This is because there are several competing calendar time-dependent dimensions that confound its description, and other variables that confound causation. For example, time-dependent dimensions that can confound description of b/tsDMARD use include the date the b/tsDMARD first became available for use, the date of birth of the participant (age), the date of disease onset, the date the participant entered the cohort or registry and the date of first use of a b/tsDMARD. Variables that confound causation for starting, switching or stopping a b/tsDMARD include the different prescribing rules that may be operating in different jurisdictions and any changing of these rules over time, loss of participant follow-up, and participant death. As more b/tsDMARDs become available, the abundance of choice also becomes another consideration. With time, adverse-effect profiles from real-world data become more evident and can influence initial as well as switching choices. Comorbidity, mode of administration and dosing schedule convenience can also influence these choices. Given

TABLE 2 Quality-of-life metrics, other medications and time of starting a first-line b/tsDMARD if the entry questionnaire was within 6 months of starting the b/tsDMARD ($n = 2011$)

Factor	ETN	ADA	IFX	ABT	TCZ	GLM	CTZ	TOF	P-value
N	1026	680	65	66	26	87	36	25	
	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	
HAQ score (0–3) ^a	1.2 (0.7)	1.2 (0.7)	1.3 (0.7)	1.1 (0.7)	1.2 (0.6)	0.8 (0.7)	0.7 (0.6)	0.7 (0.6)	<0.001
AQOL score (0–1) ^b	0.5 (0.2)	0.5 (0.2)	0.5 (0.3)	0.5 (0.3)	0.5 (0.2)	0.6 (0.2)	0.6 (0.2)	0.7 (0.2)	0.01
EQ5D (UK) (0–1) ^b	0.6 (0.3)	0.6 (0.3)	0.5 (0.3)	0.6 (0.3)	0.6 (0.3)	0.7 (0.2)	0.6 (0.3)	0.7 (0.2)	0.01
SF-36 physical function (0–100) ^b	18.7 (5.4)	18.9 (5.3)	18.4 (5.7)	19.2 (5.5)	17.4 (4.5)	21.7 (5.5)	21.7 (5.4)	21.6 (5.8)	<0.001
SF-36 mental health (0–100) ^b	22.2 (4.9)	21.8 (4.8)	21.5 (5.8)	21.7 (5.2)	22.3 (5.3)	23.2 (4.3)	23.7 (4.0)	23.4 (5.8)	0.03
Current medications ^c									
MTX	62.6	71.0	80.0	95.4	61.5	96.6	72.2	76.0	<0.001
HCQ	24.3	25.1	18.5	24.6	26.9	48.3	27.8	32.0	0.001
SSZ	14.3	15.7	16.9	16.9	7.7	19.5	16.7	16.0	0.09
LEF	26.2	30.4	26.2	20.0	7.7	24.1	25.0	12.0	0.03
Prednisolone	50.5	55.8	50.8	58.5	46.2	46.0	50.0	28.0	0.01
NSAID	40.5	41.4	29.2	27.7	46.2	39.1	27.8	40.0	0.16
High-potency opioid	7.9	4.4	6.2	15.2	19.2	4.6	2.8	4.0	0.01

^aLower score is better. ^bLower score is worse. ^cNo missing medication data (not reported data are 'never taken'/'stopped taking'/'don't know'). N: number; ETN: etanercept; ADA: adalimumab; IFX: infliximab; ABT: abatacept; TCZ: tocilizumab; GLM: golimumab; CTZ: certolizumab; TOF: tofacitinib; AQoL: Assessment of Quality of Life; EQ-5D (UK): European Quality of Life; SF-36 PCS: Medical Outcomes Survey Short Form—physical component score; SF-36 MCS: Medical Outcomes Survey Short Form—mental component score; b/tsDMARD: biologic/targeted synthetic DMARD.

Fig. 2 Percentage of participants continuing, switching or stopping first- to third-line therapy by each b/tsDMARD

ETN: etanercept; ADA: adalimumab; IFX: infliximab; RTX: rituximab; ABT: abatacept; TCZ: tocilizumab; GLM: golimumab; CTZ: certolizumab; TOF: tofacitinib.

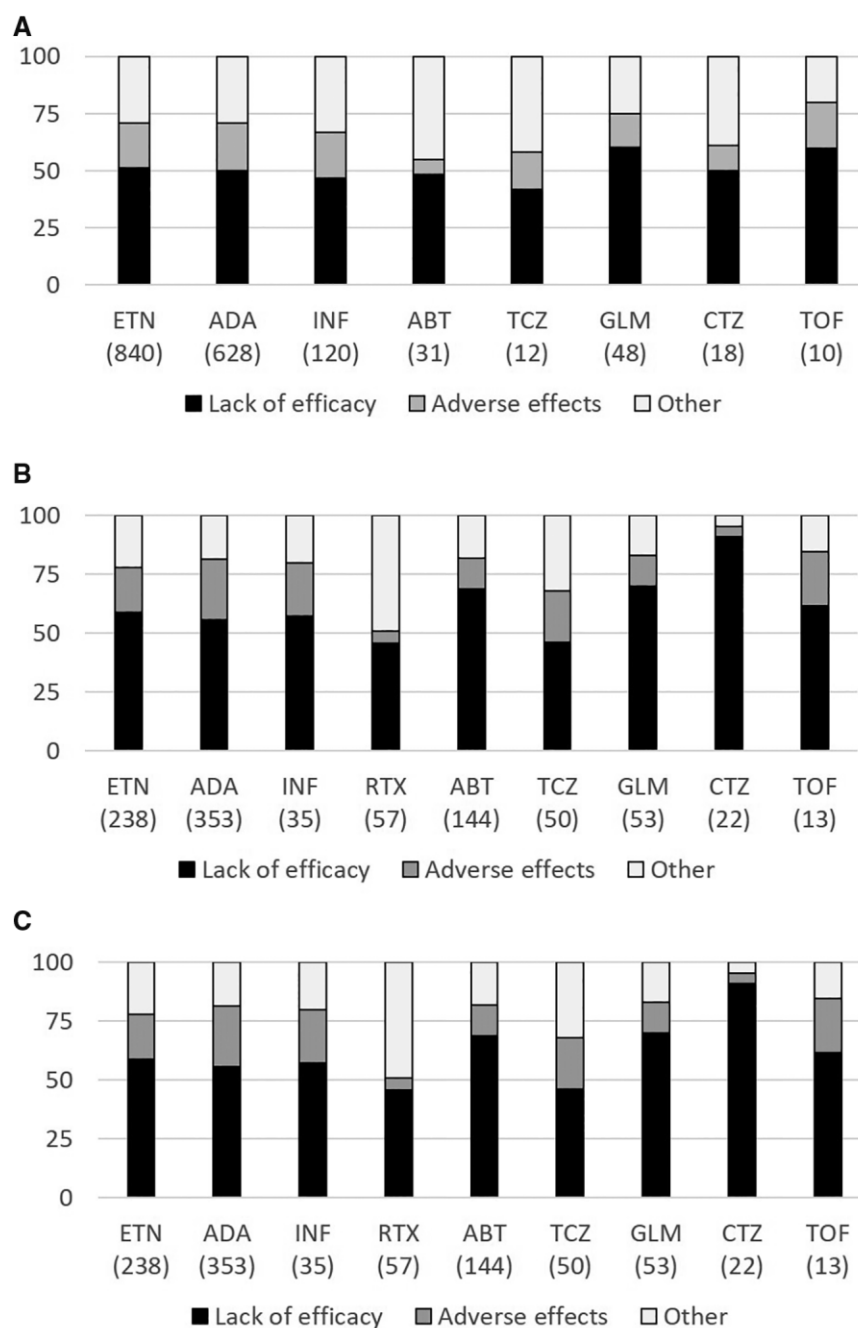
these complexities, combinations of visual and statistical analytic approaches may be desirable.

Sankey diagrams are a novel way to show the flow of b/tsDMARD use in a longitudinal cohort, as they connect a series of events to give an overall pattern and can indicate dominant trends [29]. While they are a good way to present the overall picture of sequential medication switching, they cannot capture differing durations of use. Therefore, we also presented Sankey diagrams showing the status after 12 months (to be consistent with the reporting from other studies that present the status at this time point [10–12, 15, 16, 18, 30, 31]). We also present switching at 24 and 36 months, which has also been reported by some studies [14, 17, 32, 33]. One study that used Sankey diagrams mapped the flow of verified use of selected bDMARDs at the start of

each of 5 years [34]. Similarly to our study, they also showed a higher rate of switching from or stopping infliximab, with only 4% still taking the drug at 5 years. They also demonstrated a high rate of switching from or stopping adalimumab, with less than a fifth (18%) still taking the drug at 5 years, while users of etanercept remained stable over time.

We observed that 24.0% of participants had switched from their first-line b/tsDMARD by 12 months, while by 12 months 31.8% had switched from their second-line therapy. This is similar to the findings of other registry-based studies, which have reported first-line switching rates of between 17.0% [11] and 28.5% [10], but these figures are higher than those reported for some studies that used administrative data to estimate switching rates (which have rates varying between 7.8% [12] and 15.8%

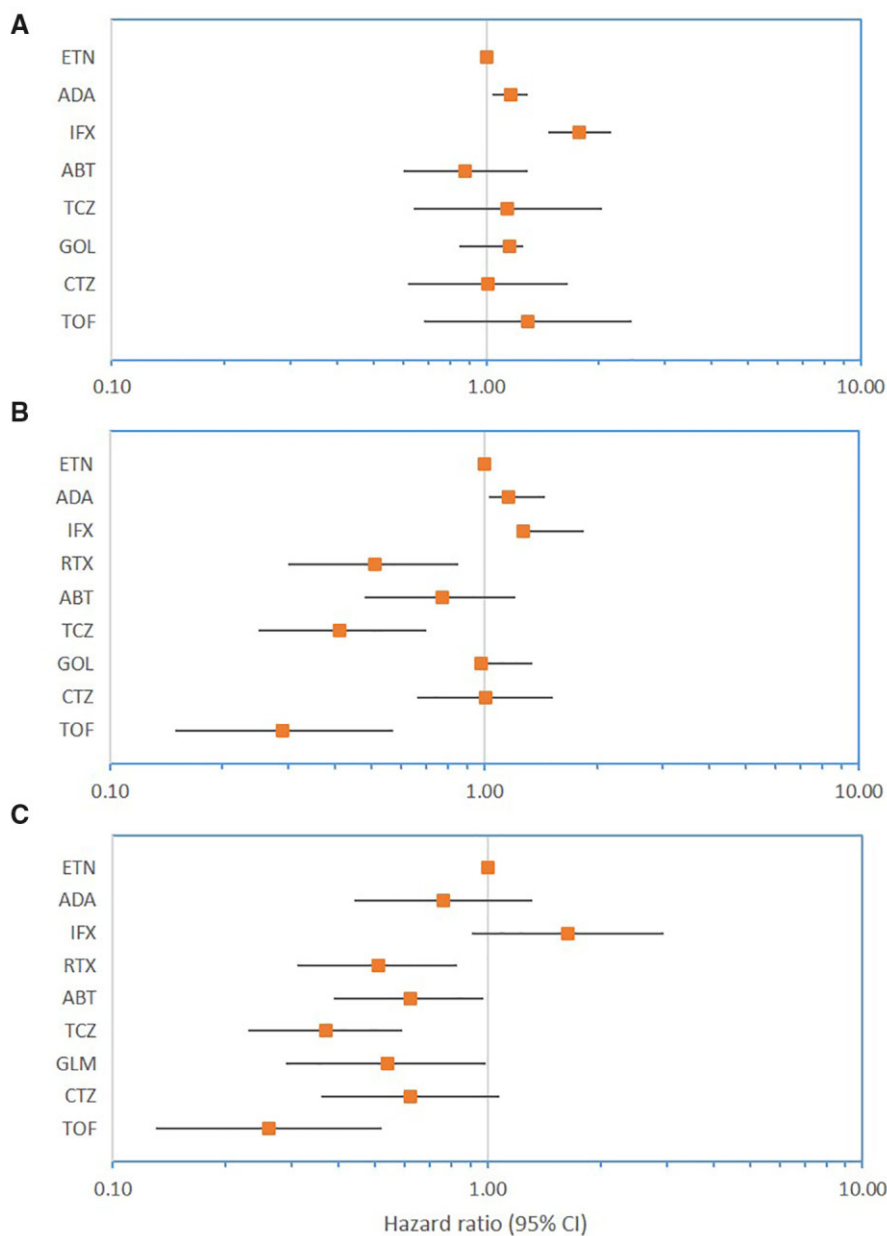
Fig. 3 Number of participants stopping each b/tsDMARD and percentage of reasons for stopping their b/tsDMARD medication



(A) First-line, (B) second-line and (C) third-line. ETN: etanercept; ADA: adalimumab; INF: infliximab; RTX: rituximab; ABT: abatacept; TCZ: tocilizumab; GLM: golimumab; CTZ: certolizumab; TOF: tofacitinib. Other includes arthritis improved, too sick from other illnesses, didn't meet Pharmaceutical Benefits Scheme criteria, surgery, pregnancy, clinical trial finished, did not like it/worried about drug, started new drug, did not like delivery method and any other reason.

[18]). Similarly to other studies [6, 10, 35], we observed a preference for first-line TNFi over other classes, although this is confounded by the order in which these

b/tsDMARDs became available for use in Australia. However, even when studies limited their registry analysis to after 2010, when b/tsDMARD from other classes

Fig. 4 Risk of stopping therapy compared with ETN for each b/tsDMARD

(A) First-line, (B) second-line and (C) third-line. HR: hazard ratio, NA: not applicable. Adjusted for age, sex, disease duration in years, cycling compared with switching b/tsDMARD, year of starting b/tsDMARD, employment, HAQ score and current use of opioids, NSAIDs, prednisolone and MTX.

became available, over 70% of patients started on a TNFi [36, 37].

We used Cox regression models, adjusting for switching or cycling from the previous b/tsDMARD, concomitant medications (MTX, prednisolone, high potency opioids and NSAIDs), demographics (age, sex, questionnaire year, disease duration, and employment status) and function (HAQ), all covariates that may influence changing or stopping b/tsDMARDs. Not all studies assessing b/tsDMARD use have adjusted for

concomitant medications and other confounders in their analysis [6, 10, 11, 19, 35]. Some studies have adjusted for confounders, particularly when using survival-based statistical analyses [7, 38, 39], and some have also included propensity scores [40], or presented both adjusted and unadjusted results [41]. Compared with etanercept, we observed a lower risk of stopping second- and third-line therapy with rituximab, tocilizumab and tofacitinib. This is consistent with the findings of other studies, which have also reported improved

retention rates with second-line rituximab and tocilizumab [11, 37, 40, 42]. Few studies provide retention rates for tofacitinib, as it is relatively new to the market. However, one study reported a primary failure rate of this drug of 67%, compared with a primary failure rate of 38% for TNFs, 34% for abatacept and 20% for tocilizumab, although it had similar retention rates to tocilizumab as a second-line therapy [37]. Nevertheless, as in our study, tofacitinib numbers were small, and these estimates need to be confirmed in other studies.

One important advantage of registry-based data is that we can ascertain reasons for switching and stopping b/tsDMARDs. Across all b/tsDMARD, we observed that of the participants who stopped a b/tsDMARD, loss of efficacy accounted for 55.4% of primary reasons for discontinuing drug use, while adverse effects accounted for 18.9%. These proportions are similar to observations on data from other registries. For example, the NOR-DMARD registry ($N=2778$) data revealed that of the 209 patients stopping a monotherapy bDMARD over 24 months, 39.2% and 31.0% stopped therapy due to lack of efficacy and adverse events, respectively [9], while the Corona RA Registry ($N=6209$) data revealed that 35.8% and 20.1% of participants who stopped cited loss of efficacy and safety concerns as the reason, respectively [6]. Similarly, in the ANSWER cohort study, which examined cessation of b/tsDMARD by 36 months in 4466 treatment courses across seven bDMARDs, of the 2540 who stopped treatment, 1154 (45.4%) of cessations were due to lack of efficacy and 532 (20.9%) were due to adverse events [7]. The KOBIO registry data revealed that, among those participants who switched therapies, 75.3% of switches were due to inefficacy and 14.5% to adverse events [10].

Our data are similar to the data in other registry-based studies with respect to reasons for switching therapies. The UK BSRBR-RA study found that, among participants starting their third-line bDMARD, 24.0% ceased therapy due to adverse events [8]. One study reported a higher rate of adverse events in subsequent therapies compared with first-line therapy [35]. In these registries, from Europe, Japan and North America, switching rates were up to ~28% with about two-thirds of switches being due to lack of efficacy and one-third to side effects [6, 10, 31].

Based upon the results of our study, one implication for practice is that etanercept may be preferred over adalimumab and infliximab as first-line bDMARD therapy in view of its lower risk of cessation, although its risk of cessation did not differ from that of other TNF inhibitors or other b/tsDMARDs with a different mode of action. For second- and third-line therapy, some biologics (including rituximab, tocilizumab and tofacitinib) appeared to have a significantly lower risk of cessation than other biologic agents. However, other important factors, including patient characteristics, an individual's risk of adverse events, patient preferences, and the environmental context, are also important in influencing drug choice.

Strengths and limitations

Strengths of this study include the longitudinal design, the long period of observation, and the very low proportion of participants for whom there is missing data (almost 80% of participants have completed at least three questionnaires). ARAD is a large dataset, so there was more than adequate power to perform multistage analysis of treatment outcomes. Weaknesses include the self-reported nature of some of the data; however, it should be noted that there was a very high agreement (κ 0.85–0.94), positive predictive value (0.83–0.97) and sensitivity (0.84–0.96) for b/tsDMARDs when linking ARAD to the Pharmaceutical Benefits Scheme for the years 2012–2018, which attests to the accuracy of the patient reporting in respect to b/tsDMARD use [43].

As our data starts in 2002, when TNFi bDMARDs were the only such agents available, and since the median year of recruitment was 2008, ARAD has fewer numbers of the b/tsDMARDs introduced in more recent years. Although we had low numbers of participants taking tofacitinib, we could still see a pattern of continued use after 1 year for both first-line users and those who switched to tofacitinib for second- or third-line therapy. However, we were unable to describe patterns of use of other JAK inhibitor (JAKi) therapies such as baricitinib or upadacitinib due to lower numbers. Orally active JAKi agents are popular in Australia, and as JAKi usage increases over time, there will be scope to make more robust comparisons for these agents through ARAD.

Conclusion

Based upon ARAD data, the pattern of b/tsDMARD use in Australia is complex. Switching between b/tsDMARDs was common among participants with RA, and durability of exposure and reasons for switching varied. Sankey diagrams and survival curves can complement numerical data by providing visual insights into these complex trends.

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Data availability 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.

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