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ORIGINAL ARTICLES

Effectiveness of biologics in Australian patients with rheumatoid arthritis: a large observational study: REAL

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Key words
rheumatoid arthritis, persistence, biologic DMARD, monotherapy, OPAL-QUMI.

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Abstract

Background: The comparative effectiveness of biologic treatment regimens in a real world Australian population is unknown.
Aim: To assess the effectiveness of biological disease-modifying anti-rheumatic drugs (bDMARD) as monotherapy or in combination with methotrexate and/or other conventional DMARD (cDMARD) for the treatment of rheumatoid arthritis (RA).
Methods: A retrospective, non-interventional study was conducted that investigated the use of bDMARD in adult patients with RA in routine clinical practice. Data were extracted from the Optimising Patient Outcomes in Australian Rheumatology – Quality Use of Medicines Initiative database. Real-world effectiveness was measured using the 28-joint disease activity score (DAS28) and clinical disease activity index (CDAI) by treatment group at baseline, weeks 12 and 24.
Results: A total of 2970 patients was included with a median (min–max) age of 60.0 (19.0–94.0) years and median (min–max) duration of RA before first bDMARD treatment of 6.0 (0.2–58.3) years. A total of 1177 patients received more than one bDMARD during the analysis period of 1 January 1997 to 15 August 2015. Patients had 4922 treatment 'episodes' (defined as a cycle of continuous individual bDMARD prescribing in a single patient). Patients received a mean (SD) of 1.7 (1.0) episodes of treatment with median (min–max) treatment duration of 0.7 (0–11.8) years; median treatment duration was higher with the first treatment episode. bDMARD were most commonly initiated in combination with methotrexate (73.9% of episodes) and least commonly as monotherapy (9.9% of episodes). Median (min–max) baseline DAS28 decreased from 5.3 (0–8.7) with the first bDMARD to 3.7 (0–8.8) with the second. Median baseline CDAI similarly decreased.
Conclusions: Patients tended to persist longer on their first bDMARD treatment. bDMARD as monotherapy or in combination appear to be accepted treatment strategies in the real world.

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Introduction

Evidence from randomised controlled trials informs medication choices offered to patients with rheumatoid arthritis (RA). However, randomised clinical trials are usually restricted to investigating the effect of a single intervention on a select patient group, and clinical trial data do not necessarily extrapolate to clinical practice.

It is not known whether rheumatology practice in Australia reflects evidence-based recommendations, for example, recommendations that any biological disease-modifying anti-rheumatic drug (bDMARD) apart from rituximab can be used as first-line biological therapy[1] or that patients who fail their first bDMARD treatment should be switched to another bDMARD using a therapeutic algorithm that may or may not consider the mechanism of action.[2] The comparative effectiveness of bDMARD treatment regimens in a real-world Australian population is also unknown.

The Optimising Patient Outcomes in Australian Rheumatology – Quality Use of Medicines Initiative (OPAL-QUMI) is a point of care-derived observational registry database,[3] with more than 50 rheumatologists in 22 clinical practices in Australia contributing data. At the time this study was conducted, these rheumatologists were collectively managing approximately 18 000 patients with RA. This is one of the largest cohorts of patients with RA in the world; the Corrona RA registry in the United States is the largest and follows over 40 000 patients.[4] Also relevant is the Tocilizumab Collaboration of European Registries in RA (TOCERRA), which includes registries from 10 European countries.[5]

The aim of this retrospective, non-interventional study of patients with RA was to use data from the OPAL-QUMI registry database to assess the effectiveness over time of bDMARD as monotherapy or in combination with conventional DMARD (cDMARD) with and without methotrexate.

Methods

Study design

This was a multicentre, retrospective, non-interventional study of patients with RA treated in routine clinical practice in Australia. The objectives of the study were to assess the effectiveness of bDMARD therapy as monotherapy or in combination with cDMARD over time. bDMARD and cDMARD combination therapy that included methotrexate was investigated separately from combination therapy that did not include methotrexate.

At the time of data extraction, the following bDMARD were available in Australia, with a government subsidy for use in the treatment of RA as bDMARD monotherapy or in combination with a cDMARD intravenous (IV) formulation of tocilizumab, adalimumab, etanercept and certolizumab pegol. IV formulations of rituximab, infliximab and golimumab and IV and subcutaneous (SC) formulations of abatacept were subsidised only in combination with methotrexate (the minimum requirement was 7.5 mg per week). IV and SC formulations of abatacept were combined in the analyses.

The study was approved by the Bellberry Human Research Ethics Committee (HREC# 2013-04-159-A-1). This study only used aggregate data that could not be used to identify individual patients or rheumatologists; individual patient consent is based on a patient opt-out arrangement.

Patient population

Patients considered for inclusion in the study had a diagnosis of probable or definite RA (assessed by the treating rheumatologist), were being treated at an OPAL-QUMI participating centre and had data available in the period 1 January 1997 to 15 August 2015. Patients were at least 18 years old, prescribed a bDMARD, had a visit recorded within the 12 months prior to bDMARD prescription and had another visit 12–40 weeks after starting bDMARD treatment, coinciding with a continuing prescription assessment date. Patients who requested their data not to be collected for research purposes or who were taking a combination of two or more bDMARD were excluded from the analyses.

Data sources and variables

Data in this study were obtained from consecutive patients in the OPAL-QUMI registry database, captured during routine visits from 50 rheumatologists in 22 rheumatology private practices participating in the OPAL registry. The complete available dataset was used. The source data were the patients' medical records, which were subject to logic checks within the Audit4 electronic medical record (Software4Specialists, Australia). Data capture relied on physician data input; therefore, not all patients had complete datasets.

Efficacy variables included absolute change in the 28-joint disease activity score (DAS28), the clinical disease activity index (CDAI), swollen joint count and tender joint count from baseline to weeks 12 and 24. DAS28 and CDAI measures were calculated using individual component scores. For DAS28 end-points, erythrocyte sedimentation rate (ESR) values were used where

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available, and C-reactive protein values were used where ESR was missing. Demographic and baseline disease characteristics were also collected.

Statistical methods

Effectiveness was measured using DAS28 and CDAI as recorded by the treating physician. Differences in baseline patient characteristics between the treatment groups were investigated.

Descriptive statistics (mean, standard deviation, median and range) are provided for continuous variables and frequency counts for categorical variables. Missing data were not imputed except for missing end dates for last bDMARD, methotrexate or cDMARD, or for overlapping or contradictory start and stop dates for bDMARD or cDMARD. For example, where the stop date of a bDMARD was missing, the date was imputed as the day before the next bDMARD start date. Observations with missing start dates or where the stop date was prior to the start date were removed from the study data.

Visit windows were defined. Baseline was the last valid measure up to 12 months before the start date of a bDMARD regimen. Week 12 analyses included any measurement between weeks 8 and 20 after bDMARD initiation. Week 24 included any measurement between week 20 and week 32.

Data were analysed using SAS (Proprietary Software, SAS Institute Inc., Cary, NC, USA) V 9.2 by 'episodes' of treatment. An episode was defined as a cycle of continuous individual bDMARD treatment for a given patient. If the patient changed to a different bDMARD treatment, this was defined as a new episode. The median length of time patients remained on a single episode of treatment was calculated using Kaplan–Meier methodology. Treatment episodes that were still ongoing at the data cut-off point of 15 August 2015 were censored at that date. This methodology can result in both medians and upper or lower limits of the confidence intervals being indeterminable due to a lack of data.

For each type of bDMARD, analyses were conducted by category of treatment: monotherapy; combinations of the bDMARD with cDMARD, including methotrexate and combinations of the bDMARD with cDMARD, excluding methotrexate. No formal hypothesis testing was undertaken as part of this analysis. The groups being compared were non-randomised groups, and comparisons between such groups may be biased due to known or unknown baseline differences. The summaries performed should be seen as exploratory in nature.

Results

Patient demographics and disease characteristics

Data were extracted from the OPAL database from 1 January 1997 until 15 August 2015. There were 17 955 patients with RA, of whom 5380 adult patients received treatment with a bDMARD, and of these patients, 2970 had medication or efficacy data recorded in the period up to 12 months prior to the first bDMARD dose (the analysis population). The median (min–max) age of patients included in this study was 60.0 (19.0–94.0) years, and the median (min–max) duration of RA, prior to treatment with the first bDMARD, was 6.0 (0.2–58.3) years. Demographics and baseline characteristics are summarised in Table 1.

Episodes of treatment with bDMARD

The 2970 patients included in the study received 4922 episodes of treatment with bDMARD. Most patients had

Table 1 Demographics and baseline characteristics

	All patients
Gender, %	
Female (*n* = 2219)	74.7
Male (*n* = 743)	25.0
Missing (*n* = 7)	0.2
Joint Pattern, %	
Polyarticular (*n* = 750)	80.6
Intermittent, migratory (*n* = 114)	12.2
Monoarticular (*n* = 67)	7.2
Onset, %	
Acute (*n* = 329)	39.1
Subacute (*n* = 328)	39.0
Gradual (*n* = 184)	21.9
RhF status, %	
Positive (*n* = 1169)	66.0
Negative (*n* = 602)	34.0
CCP status, %	
Positive (*n* = 838)	55.7
Negative (*n* = 666)	44.3
Smoking status, %	
Never smoked (*n* = 624)	55.9
Ex-smoker (*n* = 351)	31.5
Current smoker (*n* = 140)	12.6
Alcohol, %	
Abstinent/rarely or social (*n* = 813)	82.5
Daily/mild/moderate (*n* = 151)	15.3
Binge/heavy (*n* = 21)	2.1
Disease activity, median (min–max)	
DAS28 (*n* = 1446)	5.3 (0–8.7)
CDAI (*n* = 1045)	33.0 (0–75.0)

CCP, cyclic citrullinated peptide; CDAI, clinical disease activity index; DAS28, 28-joint disease activity score; RhF, rheumatoid factor.

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Table 2 Median duration on bDMARD by episode of treatment

Episode of bDMARD treatment	Number of patients	Median duration (95% CI); range (years)
1	2970	1.3 (1.1–1.4); 0.0–11.8
2	1177	0.8 (0.8–0.9); 0.0–9.9
3	507	0.8 (0.7–1.1); 0.0–6.4
4	179	0.8 (0.6–1); 0.0–8.5
5	63	0.6 (0.4–1.2); 0.0–3.3
6 or greater	26	0.4 (0.3–ND); 0.0–3.5

bDMARD, biological disease-modifying anti-rheumatic drugs; CI, confidence interval; ND, not determined.

Table 3 Median duration on treatment for individual bDMARD used

bDMARD	bDMARD episodes		Median duration (95% CI); range (years)
	n	%	
Etanercept	1357	27.6	0.9 (0.8–1.0); 0.0–11.8
Adalimumab	1098	22.3	1.1 (0.9–1.3); 0.0 10.5
Abatacept	642	13.0	1.0 (0.8–1.2); 0.0–6.1
Tocilizumab	629	12.8	1.7 (1.3–2.1); 0.0–7.4
Golimumab	481	9.8	0.8 (0.7–0.9); 0.0–5.2
Certolizumab pegol	429	8.7	0.8 (0.7–0.9); 0.0–4.9
Rituximab	230	4.7	5.5 (4.3–ND); 0.0–8.5
Infliximab	56	1.1	1.1 (0.7–2.5); 0.0–8.2

bDMARD, biological disease-modifying anti-rheumatic drugs; CI, confidence interval; ND, not determined.

only one episode of bDMARD treatment (Table 2), although up to eight episodes of treatment were used. Patients received a median (min–max) of 1.0 (1.0–8.0) episodes of treatment. The mean (SD) treatment duration was 1.7 (1.0) years, with a median (min–max) of 0.7 (0–11.8) years. At the time bDMARD episodes were initiated, patients were also taking corticosteroids in 2810 (57.1%) episodes and taking non-steroidal anti-inflammatory drugs in 1180 (24.0%) episodes. Median (95% CI) duration of the first episode of treatment with bDMARD was 1.3 (1.1–1.4) years and was shorter for subsequent episodes of treatment (Table 2).

Usage and persistence on bDMARD

The most commonly prescribed bDMARD were etanercept (27.6% of episodes) and adalimumab (22.3% of episodes). Rituximab and tocilizumab had the longest median duration of treatment (Table 3).

bDMARD monotherapy versus combination therapy

Most of the treatment episodes were bDMARD in combination with methotrexate with or without cDMARD (other than methotrexate). Of the 4922 episodes, 1284 (26.1%) bDMARD treatment episodes did not include methotrexate. bDMARD monotherapy was administered in 9.9% of episodes (n = 488), bDMARD in combination with methotrexate with or without cDMARD (other than methotrexate) were administered in 73.9% of episodes (n = 3638) and bDMARD in combination with cDMARD without methotrexate were administered in 16.2% of episodes (n = 796). The breakdown by combination or

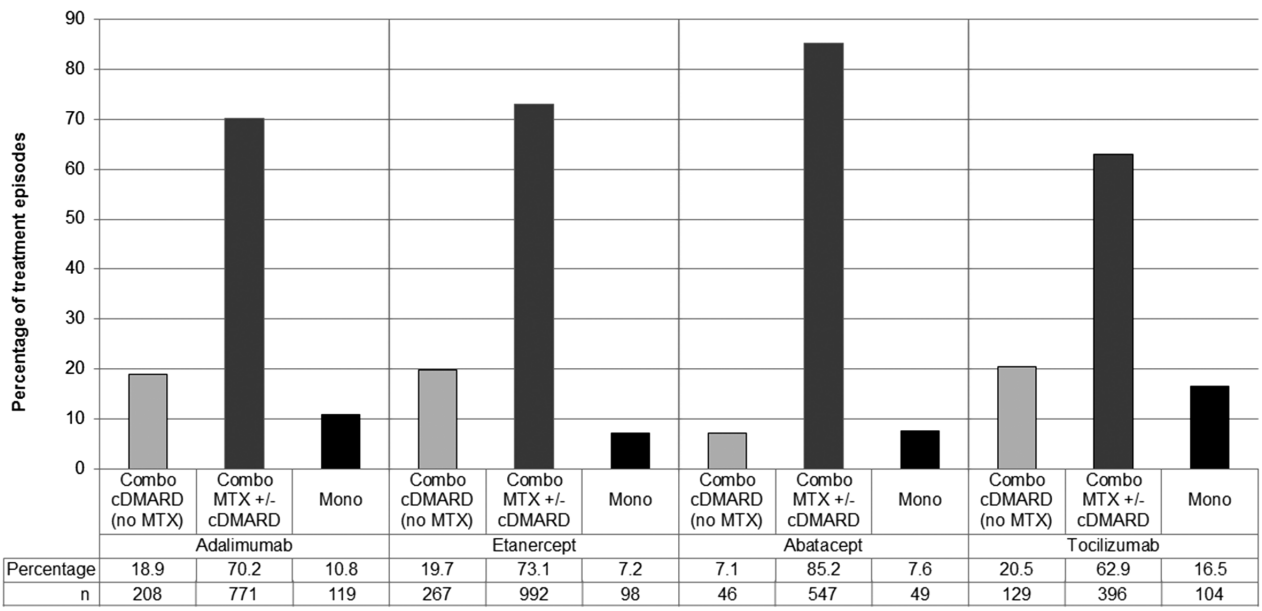

Figure 1 Individual bDMARD episodes for selected biological disease-modifying anti-rheumatic drugs (bDMARD): breakdown by monotherapy or combination therapy.

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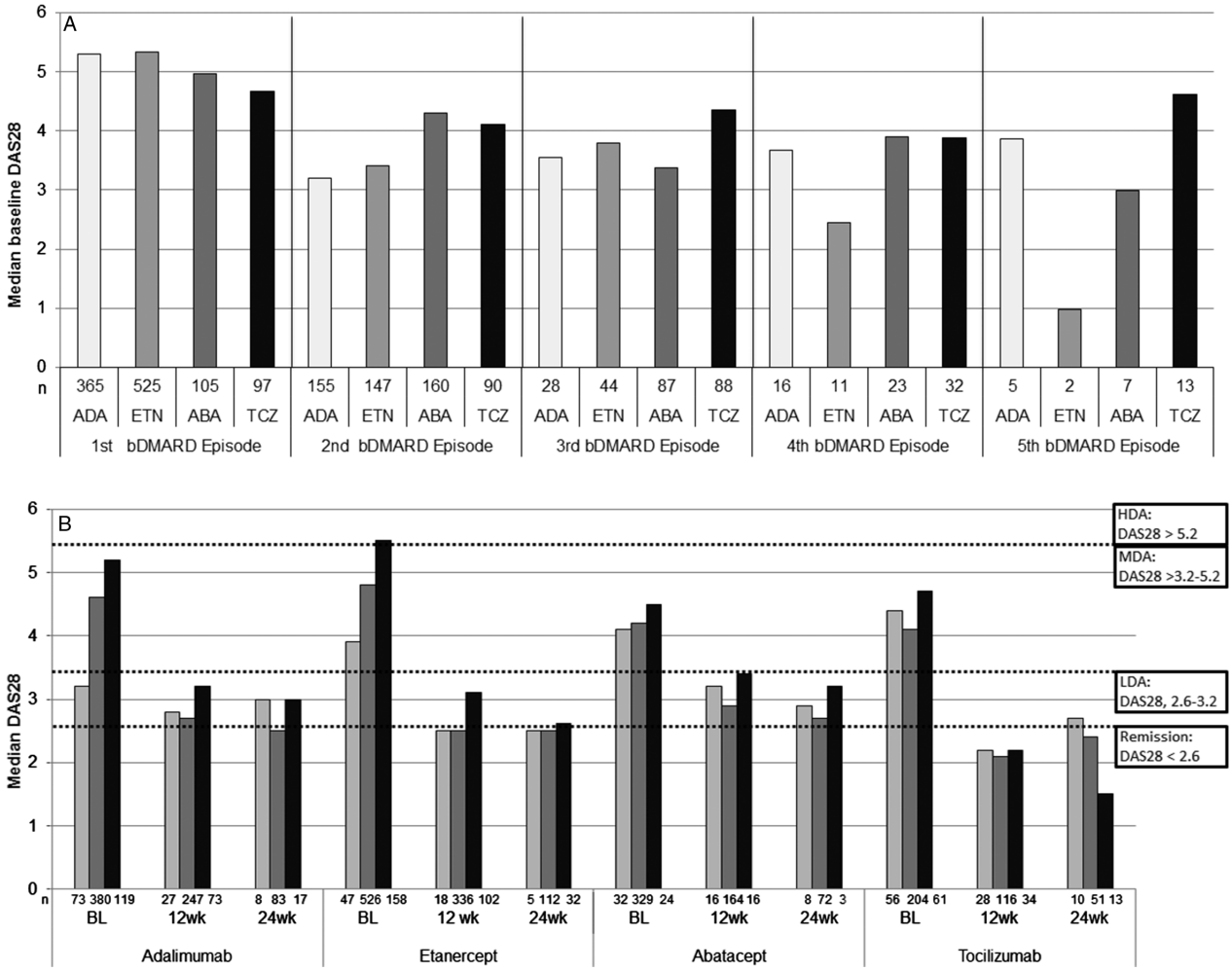

Figure 2 (A) Baseline median DAS28 by biological disease-modifying anti-rheumatic drugs (bDMARD) and episode of treatment for patients included in the analyses. The median DAS28 was calculated for patients (*n* values below the x-axis) who had a recorded baseline DAS28 and who had received 1, 2, 3, 4 or 5 bDMARD episodes of adalimumab (ADA), etanercept (ETN), abatacept (ABA) or tocilizumab (TCZ) treatment. As an example, 365 patients received ADA in their first treatment episode and had a corresponding baseline DAS28, and 155 patients received ADA on their second treatment episode and had a corresponding baseline DAS28 and so on. (B) Disease outcome measure: DAS28. Median DAS28 scores presented for each biological at baseline, 12 and 24 weeks of treatment and according to concurrent treatment status. The *n* values correspond to the number of episodes of treatment. DAS28, 28-joint disease activity score; HAD, high disease activity (DAS28 > 5.2); MDA, moderate disease activity (DAS28 > 3.2–5.2); LDA, low disease activity (DAS28 2.6–3.2); remission (DAS28 < 2.6). (▨), Monotherapy; (▩), combo MXT ± cDMARD; (■), combo cDMARD only (no MXT).

monotherapy is presented in Figure 1 for adalimumab, etanercept, abatacept and tocilizumab.

Disease measures: DAS28

Overall, baseline DAS28 was higher for first-episode bDMARD treatment for all bDMARD analysed. Median (min–max) baseline DAS28 was 5.3 (0–8.7) prior to the first episode of bDMARD therapy and 3.7 (0–8.8) prior to the second and third episodes of bDMARD treatment. Median baseline DAS28 is shown by treatment episode in Figure 2A for adalimumab, etanercept, abatacept and tocilizumab.

Median DAS28 by bDMARD at baseline and 12 and 24 weeks of treatment is presented in Figure 2B for adalimumab, etanercept, abatacept and tocilizumab. At the baseline of each treatment episode, median DAS28 generally showed moderate to high disease activity, and by week 24, this had reduced to low disease activity or disease remission.

Disease measures: CDAI

Overall, the baseline CDAI score for all bDMARD analysed was higher with the first treatment episode. The median (min–max) CDAI score was 33.0 (0–75.0)

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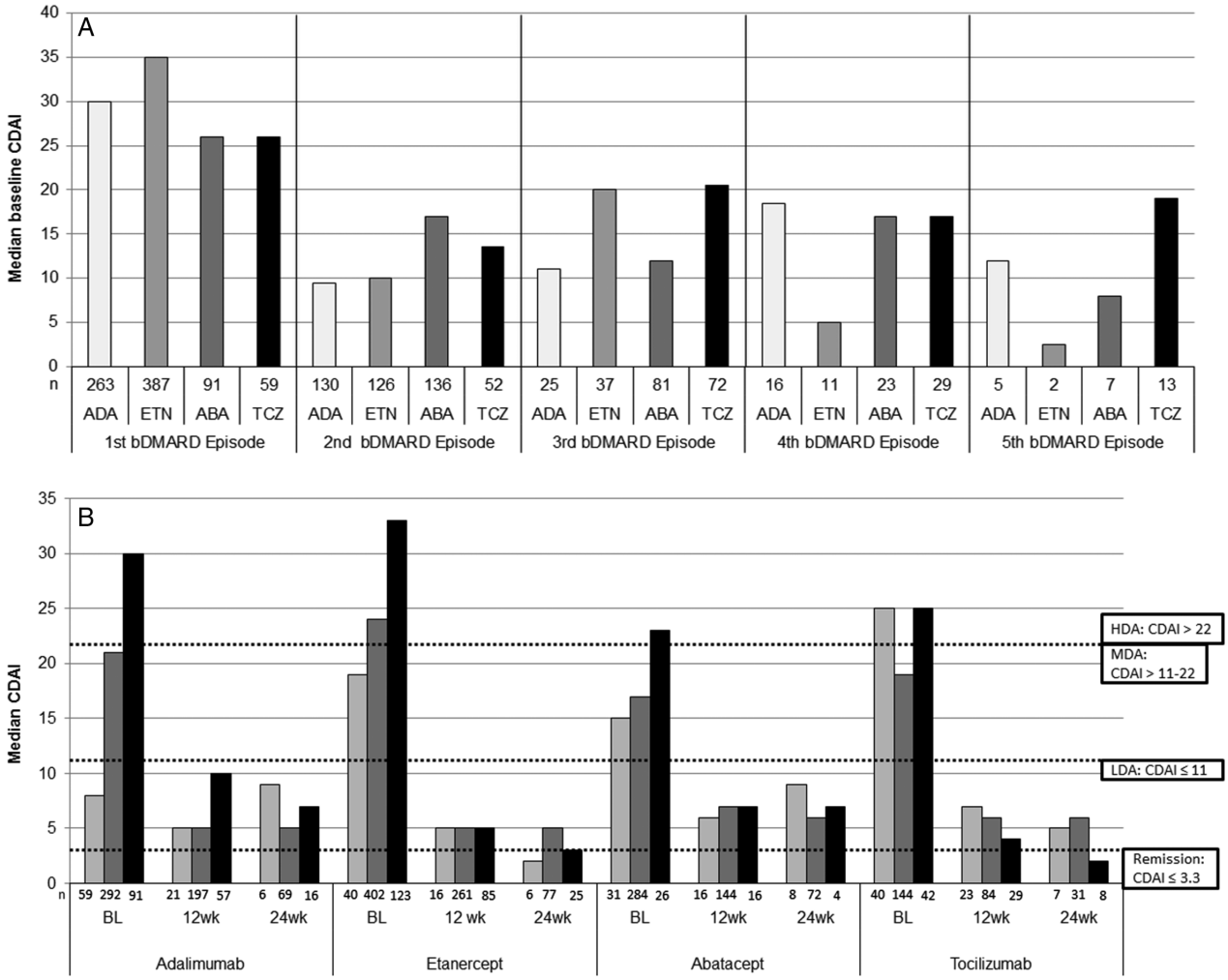

Figure 3 (A) Baseline median clinical disease activity index (CDAI) by biological disease-modifying anti-rheumatic drug (bDMARD) and episode of treatment for patients included in the analyses. The median CDAI was calculated for patients (*n* values below the x-axis) who had a recorded baseline CDAI and who had received 1, 2, 3, 4 or 5 bDMARD episodes of adalimumab (ADA), etanercept (ETN), abatacept (ABA) or tocilizumab (TCZ) treatment. As an example, 263 patients received ADA on their first treatment episode and had a corresponding baseline CDAI, and 130 patients received ADA on their second treatment episode and had a corresponding baseline CDAI and so on. (B) Disease outcome measure: CDAI. Median CDAI scores presented for each biological at baseline, 12 and 24 weeks of treatment and according to concurrent treatment status. The *n* values correspond to the number of episodes of treatment. HAD, high disease activity (CDAI >22); MDA, moderate disease activity (CDAI >11–22); LDA, low disease activity (CDAI ≤11); remission, (CDAI ≤3.3). (▨), Monotherapy; (▩), combo MXT ± cDMARD; (■), combo cDMARD only (no MXT).

prior to first episode of treatment, 12.0 (0–68.0) prior to second episode of treatment and 14.0 (0–70.0) prior to third episode of treatment. Median treatment baseline CDAI is shown by episode and bDMARD in Figure 3A.

Median CDAI by biological at baseline and 12 and 24 weeks of treatment is presented in Figure 3B. At the baseline of each treatment episode, median CDAI generally showed moderate to high disease activity, and by week 12, this had reduced to low disease activity or disease remission, which was maintained till week 24.

Discussion

This study sampled the entire OPAL-QUMI database, which includes data from more than 17 900 patients and 22 rheumatology practices in Australia. Patients were community-based and had to be at least 18 years old with a diagnosis of RA to be eligible for inclusion in the study. The results from this study may provide a good representation of the adult Australian population with RA.

Our results show a relatively short period of persistence on individual bDMARD, with a median of approximately 0.7 (ranged from 0 to 11.8) years. The observed

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persistence on individual bDMARD is slightly lower than what has previously been reported by Dalen *et al.* (2016),[6] where the median persistence on adalimumab, etanercept and certolizumab pegol was 1.3 years and the persistence on golimumab was 1.5 years.

The wide range in treatment persistence is a reflection of the diversity in the approach to patient management in real-world rheumatology, potentially driven by an aggressive treat-to-target approach. Other drivers of this wide range in treatment persistence may include differences in government-reimbursed access to studied agents in Australia, with etanercept obtaining reimbursement approval in 2003; adalimumab in 2004; abatacept IV and SC in 2007 and 2011, respectively and tocilizumab in 2010. Our results also reflect the current continuation restrictions that apply to reimbursed supply, which require physicians to provide documented proof of adequate response to treatment.[7] The Pharmaceutical Benefits Scheme restrictions allow patients to swap between bDMARD without having to requalify. Cessation of treatment around 8–9 months (0.7 years) probably reflects primary failure and a desire to achieve a state of low disease activity or remission.

Persistence on rituximab and tocilizumab was longer than on other bDMARD even though, in clinical practice, they are generally reserved for later lines of treatment. An explanation for this may be that patients who are primary non-responders to anti-tumour necrosis factor (TNF) therapy may respond better to a bDMARD with a different mechanism of action.[2] This is supported by a Slovenian registry study that found a statistically significant retention advantage in second-line bDMARD treatment for non-TNF inhibitors compared to second-line TNF inhibitors.[8]

Combination therapy (bDMARD + cDMARD ± methotrexate) is commonly used in clinical practice, supported by our study in which 90% of episodes of treatment were given as combination therapy. Despite this, treatment with either monotherapy or combination therapy resulted in clinical improvements in disease severity, indicating that bDMARD as monotherapy or in combination are both valid treatment options. Disease severity (as measured by DAS28 and CDAI) was the highest in patients receiving their first episode of a bDMARD therapy but improved as treatment progressed. This suggests that rheumatologists are adopting a treat-to-target approach that is widely endorsed in the treatment of RA[1,9] and aims for low disease activity or remission through switching bDMARD.

While this study reports on evidence available from a database that collects routine clinical data, exported directly from patients' medical records, there is a high proportion of missing data, and it is unclear whether these data are missing at random. For example, we are not able to explain from this dataset why abatacept was used in some patients as a monotherapy despite the Australian government's requirements for co-administration with methotrexate for reimbursement.

There is a potential for a selection bias in treatment as patients prescribed TNF inhibitors as monotherapy often have less severe disease at baseline compared to those prescribed the IL-6 receptor inhibitor tocilizumab or CD80/86 and CD28 interaction co-stimulation modulator abatacept. No descriptive or statistical comparisons of pretreatment disease activity, prior treatment and clinical characteristics or drug retention rates have been made between bDMARD monotherapy and the planned combination therapies.

Conclusion

The majority of patients received one line of bDMARD and tended to persist longer on the first prescribed bDMARD and on non-TNF inhibitor bDMARD. Baseline disease activity scores were higher for the first episode of bDMARD treatment, with the baseline scores for second and subsequent episodes relatively stable, suggesting that rheumatologists aim for low disease activity or remission by switching bDMARD. bDMARD as monotherapy or in combination with or without methotrexate appear to be effective and accepted treatment strategies in the real world.

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