The Journal of Rheumatology 2021;xx:xxxx
doi:10.3899/jrheum.201551
First Release November 1 2021

The Journal of Rheumatology

Persistence to Biologic Therapy Among Patients With Ankylosing Spondylitis: An Observational Study Using the OPAL Dataset

Hedley Griffiths[1], Tegan Smith[2], Christopher Mack[3], Jo Leadbetter[4], Belinda Butcher[5], Mustafa Acar[6], and Sabina Ciciriello[7]

ABSTRACT. ***Objective.*** To describe the treatment response and persistence to biologic disease-modifying antirheumatic drug (bDMARD) therapy in patients with ankylosing spondylitis (AS) in a real-world Australian cohort.

Methods. This was a retrospective, noninterventional cohort study that extracted data for patients with AS from the Optimising Patient outcomes in Australian RheumatoLogy (OPAL) dataset for the period of August 2006 to September 2019. Patients were classified as either bDMARD initiators if they commenced a bDMARD during the sampling window, or bDMARD-naïve if they did not. Results were summarized descriptively. Treatment persistence was calculated using Kaplan-Meier methods. Differences in treatment persistence were explored using log-rank tests.

Results. There were 5048 patients with AS identified. Of these, 2597 patients initiated bDMARDs and 2451 remained bDMARD-naïve throughout the study window. Treatment with first-, second-, and third-line bDMARDs significantly reduced disease activity. Median persistence on first-line bDMARDs was 96 months (95% CI 85–109), declining to 19 months (95% CI 16–22) in second-line therapy, and 15 months (95% CI 11–18) in third-line therapy. Median persistence was longest for the golimumab (GOL) group in all lines of therapy and shortest for the etanercept (ETN) group. Differences in persistence rates according to the time period that bDMARDs were prescribed (pre- and post-2012) were also seen for ETN and adalimumab.

Conclusion. In this cohort, all bDMARDs effectively reduced AS disease activity. Treatment persistence was sustained for up to 8 years for patients remaining on their first bDMARD, longer than on subsequent agents. Further research is needed to determine its influence on treatment recommendations.

Key Indexing Terms: ankylosing spondylitis, biologic therapy, disease-modifying antirheumatic drugs, medication persistence

Ankylosing spondylitis (AS) is a chronic, progressive, inflammatory disorder predominantly affecting the sacroiliac (SI) joints and axial skeleton.[1,2,3] Postural deformity and extraarticular manifestations can occur, resulting in disability, a reduced quality of life, and a shortened life expectancy. Treatment of AS requires a multimodal approach that includes nonpharmacologic strategies such as exercise, as well as pharmacologic therapy. In the last 2 decades, biologic disease-modifying antirheumatic drugs (bDMARDs) have proven an effective cornerstone in addressing the consequences of AS; however, with extended use of these agents, we are seeing the development of secondary failure in a number of patients. The factors mitigating the response to treatment and the failure of persistence on medication are poorly understood.[3,4]

In Australia, bDMARD agents are subsidized by the Australian Commonwealth Department of Human Services Pharmaceutical Benefits Scheme (PBS). However, bDMARD use is restricted to patients with documented, radiographically (plain radiographs) confirmed grade II bilateral sacroiliitis or grade III unilateral sacroiliitis, who have persistent disease activity (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥ 4.0) despite 3 months of treatment with daily nonsteroidal antiinflammatory drugs (NSAIDs) and a regular exercise program. There are 7 bDMARDs approved and

This study received financial assistance from Janssen-Cilag Pty Limited, Australia. The study was conducted independently by OPAL with review and input on the study start-up documents (protocol and statistical analysis plan) as well as review and input into final manuscript by a Janssen staff member (MA).

[1]H. Griffiths, MBBS, FRACP, OPAL Rheumatology Ltd, Sydney, and Barwon Rheumatology Service, Geelong; [2]T. Smith, PhD, OPAL Rheumatology Ltd, Sydney; [3]C. Mack, MBBS, FRACP, OPAL Rheumatology Ltd, Sydney, and Coast Joint Care, Maroochydore; [4]J. Leadbetter, PhD, A Stat, WriteSource Medical, Lane Cove; [5]B. Butcher, PhD, CMPP, A Stat, WriteSource Medical, Lane Cove, and University of New South Wales, Kensington; [6]M. Acar, PhD, Janssen-Cilag, Macquarie Park; [7]S. Ciciriello, MBBS, FRACP, PhD, OPAL Rheumatology Ltd, Sydney, and Royal Melbourne Hospital, Parkville, Australia.

MA is an employee of Janssen-Cilag Pty Limited, Australia. The remaining authors declare no conflicts of interest relevant to this study.

Address correspondence to Dr. H. Griffiths, Barwon Rheumatology Service, 156 Bellerine Street, Geelong, 3220 VIC, Australia.
Email: hedley@brservice.com.au.

Accepted for publication July 22, 2021.

subsidized for the treatment of AS in Australia: 5 tumor necrosis factor inhibitors (TNFi; infliximab [IFX], etanercept [ETN], adalimumab [ADA], golimumab [GOL], certolizumab pegol [CZP]); and 2 interleukin 17 inhibitors (IL-17i; secukinumab [SEC] and ixekizumab [IXE]). IXE was not subsidized by the PBS during the time frame of this study.

In the real-world setting, persistence on treatment (defined as the duration of time from initiation to discontinuation of therapy) is often used as a surrogate for treatment effectiveness. The reported persistence rates for bDMARD treatment of AS vary considerably.[5,6] In Australia, subcutaneous TNFi persistence in a cohort of patients with AS has previously been reported[6], but the efficacy and persistence of all the currently reimbursed bDMARDs is not known.

This study used the Optimizing Patient outcome in Australian RheumatoLogy (OPAL) dataset to describe the persistence of bDMARD treatment in more than 5000 patients with AS. The demographics, clinical characteristics, and treatment response as measured by BASDAI were also captured.

METHODS

Study design and data capture. This was a multicenter retrospective, noninterventional cohort study of patients with AS treated in routine clinical practice in Australia. The OPAL dataset collects information captured during routine clinical consultations, from individual clinicians' servers. Forty-three rheumatology clinics around Australia contribute data to OPAL using purpose-built worksheets in Audit4 software (Software4Specialists) that serve as the patient's electronic medical record. All data extracted from the Australian OPAL dataset are deidentified.[7] The activities of OPAL Rheumatology Ltd have received overarching ethics approval from the University of New South Wales (UNSW) Human Research Ethics Committee (HREC) based on a patient opt-out arrangement (HC17799). This report was based on data captured for routine clinical care and did not require additional informed consent to be obtained from patients. This research protocol was approved by the UNSW HREC (HC190631).

Patient population and eligibility criteria. Patients from the OPAL dataset were included in the study if they were between 18 and 95 years of age, had a diagnosis of AS or sacroiliitis identified using the International Classification of Diseases, 10th revision (ICD-10) codes M45 or M08.1, and if they had data entered between August 1, 2006, and September 30, 2019. Patients were classified as bDMARD initiators if they commenced a bDMARD within this window, or bDMARD-naïve if they did not. A small number of patients who were on a bDMARD had no start date of a new bDMARD therapy recorded during the window and were excluded (n = 49). Patients were also excluded if they or their physicians opted out of data collection, or if they had died.

Data collection. The index bDMARD was defined as the first bDMARD (identified using Anatomical Therapeutic Chemical Classification codes) that was commenced in the study window. The index bDMARD was considered the first agent if no previous bDMARD treatment was recorded in the dataset either prior to or during the sample window, or the second agent if 1 prior bDMARD treatment was recorded.

The index date was defined as the date of first prescription of a bDMARD within the sample window. Treatment persistence is defined as the time (in consecutive days) from the index date to the date on which the medication was ceased or to the date of initiation of an alternative medication if no discontinuation date was recorded. If there was no discontinuation date and no other medication was initiated, it was assumed that the medication was ongoing up until the last visit date recorded, and patients were censored at that time.

Baseline was defined as the first assessment during the sample window or, if they were aged < 18 years, the first assessment when they were aged > 18 years within the sample selection window for both the bDMARD-naïve and bDMARD-initiator groups.

Disease activity was assessed with BASDAI after 3, 9, and 15 months of bDMARD therapy. Treatment persistence was estimated using Kaplan-Meier methods, with differences in treatment persistence by treatment or by line of therapy, explored using log-rank tests. Factors potentially influencing treatment persistence, including sex, age, disease duration, and baseline C-reactive protein (CRP) level, were explored using a Cox proportional hazards regression model.

The bDMARDs for the treatment of AS have been available for different time periods in Australia. ETN and ADA have been available since 2005 and 2006, respectively, whereas GOL, CZP, and SEC have been available since 2010, 2014, and 2016, respectively. Therefore, not all bDMARDs in this study have had the same opportunity to demonstrate persistence. To account for the different follow-up times available for the different agents, Kaplan-Meier plots reporting on the whole follow-up period as well as up to 36 months only (where the number of follow-up data available across treatments was more equal) were analyzed. The persistence of ADA and ETN prior to 2012 and post-2012 were estimated using Kaplan-Meier methods, with differences explored using log-rank tests. The 2012 timepoint was chosen to examine persistence during a period when, for the most part, only ADA and ETN were available, and another period when there were more bDMARD treatment options.

Data were analyzed using Stata MP/2 v16 (StataCorp). Values of $P < 0.05$ were considered statistically significant.

RESULTS

Patient population and treatments. There were 5048 eligible patients with AS in the OPAL dataset, of which 2597 initiated a bDMARD during the sampling window: ADA (n = 1080); ETN (n = 783); GOL (n = 354); IFX (n = 193); SEC (n = 72); and other (n = 308), consisting of CZP (n = 81), tofacitinib (n = 15), abatacept (n = 9), rituximab (n = 6), tocilizumab (n = 2), and ustekinumab (n = 2). All bDMARDs categorized as other (except for CZP) are not subsidized for AS treatment in Australia but are available for treatment of psoriatic arthritis (PsA) and/or rheumatoid arthritis (RA). For the majority of patients (97.2%), the bDMARD initiated during the study window was the first bDMARD the patient had ever received.

Demographics of included patients are reported for bDMARD-naïve and bDMARD-initiator patients (Table 1), and according to first bDMARD (Table 2). Sixty-six percent (n = 1724) of patients initiated a single bDMARD treatment, while the remaining 873 patients initiated ≥ 2 bDMARDs during the sample window. Patients in the bDMARD-treated group had a median disease duration of 21.7 months (IQR 3.0–109.9) at index.

Disease activity. For patients initiating a first-line bDMARD during the sample window, the mean BASDAI at diagnosis was 4.7 ± 3.5 (n = 378). At index date, the mean BASDAI had increased to 6.0 ± 2.9 (n = 437). After 3 months of therapy, patients treated with a first-line bDMARD demonstrated a significant ($P < 0.001$) reduction in BASDAI, which was maintained out to 15 months (Figure 1). A significant reduction in BASDAI was also seen for patients treated with a second-line bDMARD ($P < 0.001$) and a third-line bDMARD ($P < 0.05$) after 3, 9, and 15 months of therapy (Figure 1).

Table 1. Patient baseline[a] demographics for bDMARD-naïve and bDMARD-initiated groups.

	bDMARD-naïve	bDMARD-treated (Combined)
Patients, n	2451	2597
Age, yrs		
Mean (SD)	43.2 (15.5)	43.9 (13.8)
Median	41.0	43.0
IQR	31–54	33–54
Age, yrs, n (%)		
18–34	842 (34.4)	731 (28.1)
35–44	572 (23.3)	666 (25.6)
45–54	472 (19.3)	598 (23.0)
55–64	285 (11.6)	376 (14.5)
65–74	200 (8.2)	187 (7.2)
75+	80 (3.3)	39 (1.5)
Sex, n (%)		
Male	1183 (48.3)	1521 (58.6)
Female	1237 (50.5)	1058 (40.7)
Unassigned	25 (1.0)	14 (0.5)
CRP, mg/L, median (IQR)	4.0 (2.0–8.6) [n = 992]	5.0 (2.0–10.9) [n = 2100]
ESR, mm/h, median (IQR)	7.0 (4.0–15.0) [n = 978]	8.0 (5.0–17.0) [n = 2084]
PtGA, mean (SD)	35.8 (26.0) [n = 31]	36.8 (31.0) [n = 77]
PGA, mean (SD)	40.6 (23.8) [n = 30]	31.3 (28.4) [n = 76]
Baseline treatment combinations, n (%)		
NSAIDs[b]	1151 (47)	1468 (56.5)
cDMARDs	331 (13.5)	631 (24.3)
Corticosteroids	255 (10.4)	821 (31.6)

[a] Baseline date for all patients was time of diagnosis; for patients diagnosed prior to the sample window or aged < 18 years, baseline data were obtained from the start of the sample window or the time that they turned 18 years. [b] Reflects what was recorded in the patient electronic medical records. Patients taking over-the-counter NSAID medications or NSAIDs prescribed by the GP would not likely be recorded by the rheumatologist in Audit4. bDMARD: biologic disease-modifying antirheumatic drug; cDMARD: conventional disease-modifying antirheumatic drug; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GP: general practitioner; NSAID: nonsteroidal antiinflammatory drug; PGA: physician global assessment; PtGA: patient global assessment.

Persistence. Looking at up to 36 months post index for all agents combined by line of therapy, the longest persistence rates were seen for patients on first-line bDMARD treatment (Figure 2A). The median persistence was not yet reached by 36 months but was found to be 96 months (95% CI 85–109 months) on the first-line bDMARD, declining to 19 months (95% CI 16–22) with the second, and 15 months (95% CI 11–18) on the third agent when followed out to 150 months post index (Figure 2B).

When the persistence of the groups of patients on different agents by line of therapy was investigated out to 36 months, persistence differed according to the agent used. Patients on GOL had longer median persistence when used as first-line bDMARD, whereas patients on ETN and other bDMARDs had the lowest persistence over time (Figure 2C). When treatment persistence by first-line bDMARD was analyzed out to 150 months, a similar but more notable trend was seen, with patients on GOL displaying the longest median persistence while patients on ETN and other bDMARDs had the lowest persistence over time (Figure 2D). A sensitivity analysis was conducted, censoring patients at 6 months after their last recorded prescription of their index bDMARD, and the findings were consistent. The differences in persistence among patients on different agents used in second- and third-line treatment can be found in Supplementary Table 1 (available with the online version of this article). There were differences in the types of patients prescribed each agent, and shifts in patient characteristics and treatment patterns may influence the type of patients receiving newer treatments in particular; factors such as these may also have an effect on persistence.

Treatment persistence in the overall first-line population was found to be longer in patients receiving GOL than in patients receiving other bDMARDs, and was also positively influenced by increased time from symptom onset (Table 3).

Persistence by period. Earlier initiations of bDMARD therapy (pre-2012 vs post-2012) also affected persistence of that agent. Persistence rates were higher for ADA and ETN prescribed as first line prior to 2012 when compared to those prescribed post-2012 (Figure 3). Demographics for the total population treated with first-line bDMARDs as well as that treated with first-line ETN and ADA pre- and post-2012 were also investigated. There were some changes in the overall treated population of patients over time seen in the post-2012 treated group compared to the

Table 2. Patient demographics at start of first bDMARD by agent.

	Adalimumab	Etanercept	Golimumab	Infliximab	Secukinumab	Other[a]
N	1041	783	335	183	68	113
Age, yrs						
Mean (SD)	44.3 (13.9)	44.2 (12.9)	42.7 (14.7)	45.8 (13.9)	48.6 (15)	42.6 (13.9)
Median	44	44	41	46	46.5	40
IQR	33–54	35–53	30–54	36–56	37–58.5	32–51
Age, yrs, n (%)						
18–34	294 (28.2)	192 (24.5)	113 (33.7)	39 (21.3)	13 (19.1)	38 (33.6)
35–44	255 (24.5)	216 (27.6)	78 (23.3)	48 (26.2)	17 (25.0)	31 (27.4)
45–54	238 (22.9)	210 (26.8)	64 (19.1)	45 (24.6)	17 (25.0)	22 (19.5)
55–64	156 (15.0)	108 (13.8)	50 (14.9)	33 (18.0)	9 (13.2)	12 (10.6)
65–74	82 (7.9)	47 (6.0)	25 (7.5)	15 (8.2)	9 (13.2)	7 (6.2)
75+	16 (1.5)	10 (1.3)	5 (1.5)	3 (1.6)	3 (4.4)	3 (2.7)
Sex, n (%)						
Male	657 (60.6)	464 (59.3)	209 (62.4)	99 (54.1)	42 (61.8)	27 (23.9)
Female	399 (38.3)	316 (40.4)	122 (36.4)	84 (45.9)	26 (38.2)	86 (76.1)
Unassigned	11 (1.1)	3 (0.4)	4 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
BASDAI at initiation	6.5 (2.8) [n = 165]	5.2 (2.9) [n = 116]	6.9 (2.5) [n = 79]	4.3 (3.3) [n = 22]	6.2 (2.8) [n = 23]	5.8 (2.9) [n = 32]
CRP at initiation, mg/L, median (IQR)	5.0 (2.0–12.0) [n = 821]	4.0 (2.0–9.0) [n = 633]	4.1 (1.8–11.0) [n = 288]	5.0 (2.4–11.0) [n = 123]	5.1 (2.8–11.0) [n = 60]	5.3 (2.9–16.0) [n = 102]
ESR at initiation, mm/h, median (IQR)	8.0 (5.0–20.0) [n = 813]	7.0 (4.0–15.0) [n = 627]	7.0 (4.0–15.0) [n = 283]	8.0 (5.0–20.0) [n = 122]	8.0 (5.0–16.0) [n = 60]	10 (6.0–25.0) [n = 102]
Baseline treatment combinations, n (%)						
NSAIDs	604 (58.0)	455 (58.1)	181 (54.0)	81 (44.3)	37 (54.4)	65 (57.5)
cDMARDs	242 (23.2)	163 (20.8)	76 (22.7)	63 (34.4)	15 (22.1)	44 (38.9)
Corticosteroids	347 (33.3)	290 (37.0)	108 (32.2)	64 (35.0)	24 (35.3)	56 (49.6)

[a] Includes certolizumab pegol, tofacitinib, abatacept, rituximab, tocilizumab, and ustekinumab. bDMARD: biologic disease-modifying antirheumatic drug; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; cDMARD: conventional disease-modifying antirheumatic drug; CRP: C-reactive protein, ESR: erythrocyte sedimentation rate; NSAID: nonsteroidal antiinflammatory drug.

pre-2012 treated group, such as an increase in the proportion of females, decrease in time from onset to commencement of bDMARD, and increase in concomitant treatments. Similar changes were observed in the subset prescribed ADA and ETN pre- and post-2012 (Supplementary Table 2, available with the online version of this article).

DISCUSSION

This study describes treatment response and real-world persistence of bDMARD therapy in an Australian cohort of patients with AS. We show the same pattern of response as has been previously described: the first bDMARD used shows greater efficacy and persistence than the second or third agent used. This is a pattern also well recognized in other inflammatory diseases such as RA and PsA.[6,8] The median first bDMARD persistence of 96 months in this population is high compared to some reports in the literature; however, it is not out of keeping with an analysis of Greek patients with spondyloarthritis (SpA), where a high drug survival of 60% and 49% was found at 60 and 120 months, respectively.[9] Higher persistence rates of TNFi therapy are also more commonly reported for AS than for RA and PsA.[10]

There is considerable variability in reported bDMARD persistence in the literature. Previous studies support our findings of longer persistence with GOL[11] and shorter with ETN.[9] However, others have found no difference between agents.[6] This may, in part, be explained by the complex nature of drug persistence, which reflects multiple factors including tolerability, patient preference, prescribing limitations, and patient and disease characteristics, in addition to efficacy of a treatment.

Few real-world persistence data for Australian patients with AS exist. A retrospective cohort analysis using a 10% sample of all government-subsidized subcutaneous TNFi prescriptions recorded by the PBS reported no significant differences between first bDMARD persistence of ADA, ETN, or GOL in patients with AS.[6] The disparity between this and our study with regard to first bDMARD persistence is not readily explained; however, the OPAL dataset represents prescribing data, whereas the PBS represents reimbursement data. In addition, the OPAL contributors are almost exclusively in private practice, whereas the PBS cohort also captures public hospital outpatients. Some general differences exist between private and public rheumatology patients in Australia which may help explain these findings. Public sector patients generally present later for treatment,

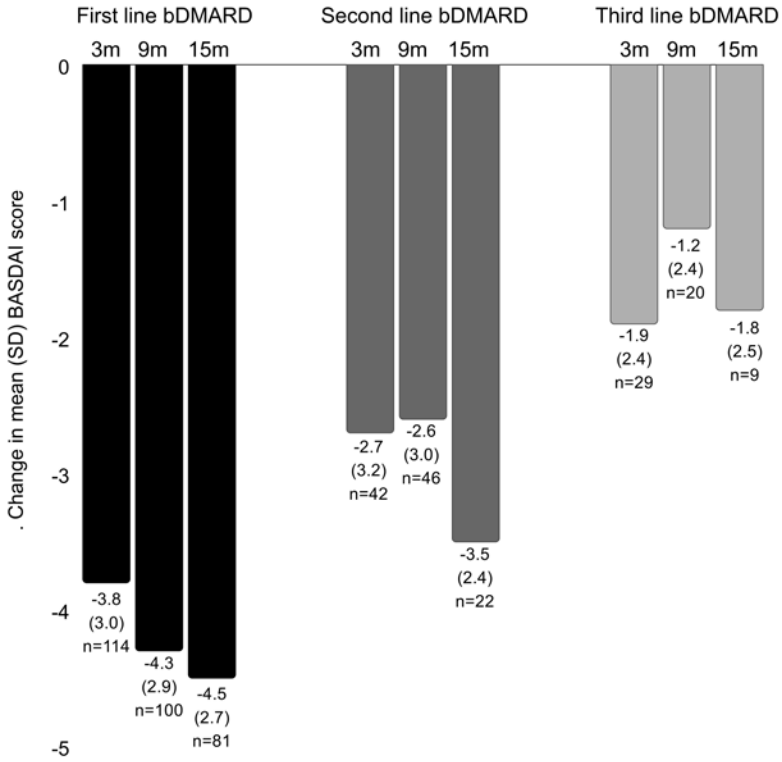

Figure 1. Changes in mean (SD) BASDAI score over time by line of therapy. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; bDMARD; biologic disease-modifying antirheumatic drug; m: months.

resulting in worse disease severity on presentation.[12] Patients seen in the public sector also tend to present with complex comorbidities, resulting in a more frequent need to cease or change bDMARDs.

ETN and ADA were the first subcutaneous TNFi bDMARDs available for the treatment of AS in Australia in 2005 and 2006, respectively. It is interesting to note that the persistence rates of these bDMARDs differ according to the time period that they were prescribed. The increased persistence rates of ADA and ETN prior to 2012 vs the persistence rates after 2012 are most likely explained by the lack of additional options available pre-2012. As there are now more bDMARDs available for the treatment of AS, patients not achieving optimal response can be switched to an alternative treatment. In the pre- and post-2012 populations, there were differences in the patient demographics that have both positive and negative effects on persistence and do not explain the extent of the changes seen.

In Australia, bDMARDs are subsidized for AS if certain requirements are met, including radiographic change at the SI joint, BASDAI > 4, and elevated inflammatory markers (erythrocyte sedimentation rate > 15 or CRP > 10). At initiation of the first bDMARD, the BASDAI in the treated group was 6.0 ± 2.9, consistent with high disease activity. However, the median CRP was only 5.0 (IQR 2.0–10.9), suggesting that clinical assessment of disease severity and not elevated CRP as a marker of active disease is the more important factor when making the decision to prescribe a bDMARD.

Our study had several limitations. As a retrospective study of observational data, a number of missing data points were encountered. There are also differences in data maturity by agent as not all bDMARDs have been available for the same period.

The majority of the treated population in this study (1724 of 2597) had exposure to only 1 bDMARD. As a result, the sample sizes for calculating persistence for second and third bDMARD exposure were too small to draw definitive conclusions. Further, patients who received multiple bDMARDs during the sample window are included multiple times—once for each bDMARD exposure. Hence, patients with demonstrated lower persistence are overrepresented in the analysis.

Fewer real-world treatment data exist for IL-17i agents in patients with AS. SEC has only been available in Australia since October 2016 and our numbers reflect this. Nevertheless, the available data suggest IL-17i persistence follows a similar trend to the TNFi with greater persistence when used as the first bDMARD, than when used as the second or third agent.

Propensity score matching was not feasible for all agents. Differences observed between treatment groups should therefore be interpreted with caution, as this may reflect differences between the underlying patient demographics rather than between the treatments. Propensity score matching was planned to enhance comparability between the groups. However, even where a matched population was able to be generated (e.g., for the GOL and ADA pairing), the small size of the matched groups relative to the overall number of patients on each treatment indicates that there was only limited overlap between the types of patients receiving the different treatments.

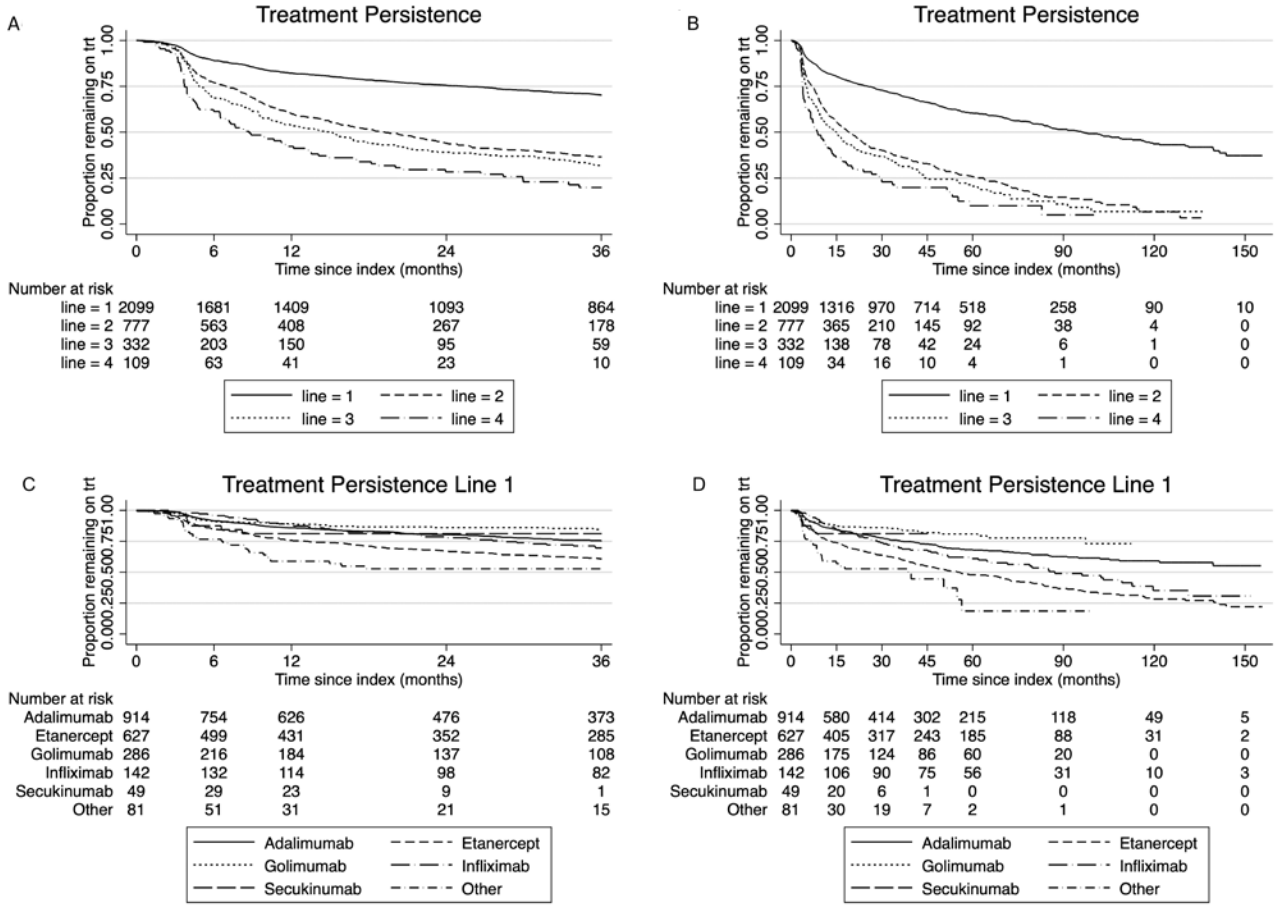

Figure 2. Median persistence for first-, second-, and third-line bDMARD-treated population (A) at 36 months and (B) up to 150 months. Subjects receiving > 1 treatment during the sample window are included multiple times, once for each line of treatment. Treatment persistence for first-line bDMARD therapy (C) at 36 months and (D) up to 150 months. bDMARD: biologic disease-modifying antirheumatic drug; trt: treatment.

Table 3. Results of Cox proportional hazards model of first-line treated population of all bDMARDs and adjusting for sex, age, time from symptom onset, bDMARD, and CRP (HRs represent hazard of treatment failure).

	Overall First-line Treated Population (n = 1510)		
	HR	95% CI	*P*
Sex[a]	1.018	0.996 to 1.041	0.12
Age	1.001	0.995 to 1.008	0.67
Time from symptom onset	0.998	0.998 to 0.999	< 0.001
bDMARD[b]			
Adalimumab	1.523	1.066 to 2.178	0.02
Etanercept	2.957	2.089 to 4.184	< 0.001
Infliximab	2.396	1.516 to 3.789	< 0.001
Secukinumab	1.493	0.628 to 3.549	0.36
Other	3.901	2.356 to 6.457	< 0.001
CRP	1.000	0.765 to 0.998	0.77

[a] Females vs males. [b] Each bDMARD is compared to golimumab. bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein.

In this real-world patient cohort, there were a number of dual diagnoses recorded. A total of 329 patients out of 2345 had a dual diagnosis, with an inflammatory condition such as psoriasis, inflammatory bowel disease (ulcerative colitis or Crohn disease), or PsA. These conditions all belong under the SpA umbrella and are to be expected as coexisting conditions in patients with AS. However, there were 62 patients (~2.6%) who had a dual diagnosis with RA, which is not to be expected. To address this, Cox regression models including dual diagnosis with an SpA-related inflammatory disorder as a factor, as well as RA as

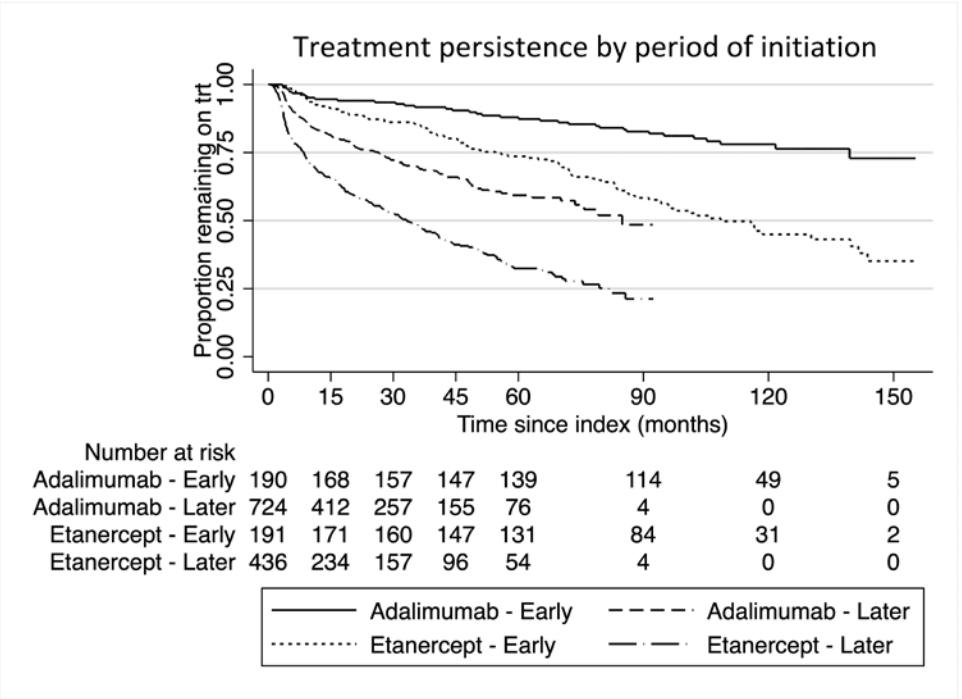

Figure 3. Persistence rates of adalimumab and etanercept pre-2012 (early) differ compared to persistence rates recorded post-2012 (later). trt: treatment.

a factor, were run. The overall effect estimates were not substantially changed by inclusion of these factors and the conclusions around persistence for patients on the different agents remain unchanged (data not shown).

This large, real-world study shows that first bDMARD therapy (either TNFi or IL-17i) effectively and rapidly reduces the mean BASDAI score of patients with AS. This benefit is sustained, with most patients (66%) remaining on their first bDMARD treatment out to 8 years. Patients who require a second or third bDMARD also respond initially, although to a lesser degree, and their persistence on treatment is reduced. Differences in treatment persistence between bDMARDs was also seen; this has the potential to influence treatment recommendations and warrants further investigation.

ACKNOWLEDGMENT

The authors acknowledge the members of OPAL Rheumatology Ltd and their patients for providing clinical data for this study, and Software4Specialists Pty Ltd for providing the Audit4 platform. The authors thank Catherine O'Sullivan, OPAL Rheumatology Ltd for assisting with the preparation of this manuscript, prepared in accordance with Good Publication Practice (GPP3) guidelines (https://www.ismpp.org/gpp3).

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Raychaudhuri SP, Deodhar A. The classification and diagnostic criteria of ankylosing spondylitis. J Autoimmun 2014;48:128-33.
2. Deodhar AA. Understanding axial spondyloarthritis: a primer for managed care. Am J Manag Care 2019;25:319-30.
3. Hunter T, Schroeder K, Sandoval D, Deodhar A. Persistence, discontinuation, and switching patterns of newly initiated TNF inhibitor therapy in ankylosing spondylitis patients in the United States. Rheumatol Ther 2019;6:207-15.
4. Braun J, van den Berg R, Baraliakos X, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis;2011;70:896-904.
5. Mahlich J, Sruamsiri R. Persistence with biologic agents for the treatment of rheumatoid arthritis in Japan. Patient Prefer Adherence 2016;10:1509-19.
6. Acar M, Juneja P, Handel M. Treatment persistence of subcutaneous TNF inhibitors among Australian patients with immune-mediated rheumatic disease (IMRD). Open Access Rheumatol Res Rev 2018;10:151-60.
7. Littlejohn G, Tymms K, Smith T, Griffiths H. Using big data from real-world Australian rheumatology encounters to enhance clinical care and research. Clin Exp Rheumatol 2019;38:874-80.
8. Lindström U, Olofsson T, Wedrén S, Qirjazo I, Askling J. Biological treatment of ankylosing spondylitis: a nationwide study of treatment trajectories on a patient level in clinical practice. Arthritis Res Ther 2019;21:1-10.
9. Flouri ID, Markatseli TE, Boki KA, et al. Comparative analysis and predictors of 10-year tumor necrosis factor inhibitors drug survival in patients with spondyloarthritis: first-year response predicts longterm drug persistence. J Rheumatol 2018;45:785-94.
10. Machado MA, Moura CS, Ferré F, Bernatsky S, Rahme E, Acurcio Fde A. Treatment persistence in patients with rheumatoid arthritis and ankylosing spondylitis. Rev Saude Publica 2016;50:50.
11. Luttropp K, Dozier M, Justo N, et al. Real-world treatment persistence of golimumab in the management of immune-mediated rheumatic diseases in Europe: a systematic literature review. BMJ Open 2019;9:e027456.
12. Furst DE. Window of opportunity. J Rheumatol 2004;31:1677-9.