Real-World Use of Biologic Disease-Modifying Anti-Rheumatic Drugs in US Patients with Ankylosing Spondylitis: Persistence, Factors Associated with Discontinuation, and Dosing Patterns

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Presented at ISPOR 2023 | May 7–10 | Boston, MA, USA

RWD136

Objective

To report on biologic disease-modifying anti-rheumatic drug 12-month treatment persistence and dosing patterns in patients with ankylosing spondylitis using real-world data, and patient baseline characteristics that are associated with increased or decreased treatment persistence.

Background

- **Ankylosing spondylitis** (AS; i.e., radiographic axial spondyloarthritis) is a chronic, immune-mediated inflammatory disease that predominantly affects the sacroiliac joints and spine.[1,2]
- Discontinuation or switching (**non-persistence**) of biologic disease-modifying anti-rheumatic drugs (**bDMARDs**) in patients with AS is common and associated with poor clinical outcomes.[3,4,5]
- There are limited real-world data showing the association of bDMARD non-persistence with patient baseline characteristics (**variables**).[5,6]

Methods

- Merative™ MarketScan® Research Databases were used to source data on US adult patients with AS (≥1 AS ICD-9/10 code) initiating a new bDMARD from 1 January 2015–31 December 2018 (further inclusion criteria described in **Figure 1**).
- To assess 12-month treatment persistence, patients were followed for up to 12 months or until bDMARD non-persistence (≥90-day gap in therapy/change in bDMARD within 90 days) or MarketScan® disenrollment.[5]
- Persistence probabilities were estimated using Kaplan-Meier survival curves for the overall cohort and stratified by treatment history (bDMARD-naïve or -experienced) as well as by bDMARD mode of action (tumor necrosis factor inhibitors [TNFi] or interleukin-17A inhibitors [IL-17Ai]).
- The association of variables with non-persistence (discontinuation, switching, or overall) was estimated using Cox regression. Only variables with a p value below 0.25 in an initial univariate analysis were entered into the multivariate analysis. A stepwise selection method was then used with entry and stay level criteria equal to 0.05.
- Variables investigated included: age, sex, index bDMARD type, presence of extra-spinal manifestations (enthesitis, inflammatory bowel disease, psoriasis, peripheral arthritis, and uveitis), baseline comorbidities and baseline comedications. While the baseline period was a minimum of 12 months, a maximum baseline period was not defined (**Figure 1**). Patient characteristics that were first recorded following index bDMARD initiation were also investigated for their association with non-persistence as part of the multivariate analysis; however, the results are not presented here.
- As the recommended label dose of secukinumab for patients with AS is different to that in patients with other immune-mediated inflammatory diseases, dosing patterns (>5 weeks after index date) were described for patients initiating secukinumab.

Results

Patient demographics

- Eligible adult patients with AS initiating a new bDMARD (N=2,437) were identified retrospectively (**Figure 1**). Baseline demographics and characteristics are reported in **Table 1**.
- The majority of patients were bDMARD-naive (93.8%; n=2,286) during the baseline period, with most patients being prescribed TNFi (95.3%; n=2,322) versus IL-17Ai (4.7%; n=115 [secukinumab=114; ixekizumab=1]) as an index bDMARD. The inclusion of patients as bDMARD-naive may have been favored by the study design.
- Adalimumab was the most commonly prescribed TNFi (55.8%) in all patients, followed by etanercept (22.7%), infliximab (9.2%), certolizumab pegol (4.3%), and golimumab (3.3%).

Treatment persistence

- The estimated 12-month persistence was 56.4% (**Figure 2A**). The first event of non-persistence was most commonly treatment discontinuation (80.1%), compared to a switch in bDMARD therapy (19.9%).
- Persistence at 12 months was similar with TNFi (56.3%; n=2,322) and IL-17Ai (58.4%; n=115) (**Figure 2B**), and among bDMARD-naive (56.6%; n=2,286) and -experienced patients (53.5%; n=151) (**Figure 2C**).

Variables associated with non-persistence

- Variables strongly associated with non-persistence were female sex, COPD, fibromyalgia, multiple comorbidities, and baseline opioid use (**Table 2**).

Secukinumab dosing patterns

- Of 114 patients with AS initiating secukinumab, 91 had starting and 76 had maintenance dose records. 70/91 (76.9%) patients started the recommended 150 mg dose and 18/91 (19.8%) 300 mg.
- During follow-up, 46/76 (60.5%) and 16/76 (21.1%) patients received 150 mg and 300 mg every four weeks maintenance dosing throughout, respectively, while 10/76 (13.2%) were dose-escalated (150 mg to 300 mg).
- The remaining patients had missing or otherwise unavailable data.

Summary

12-month **persistence** of **bDMARDs** in patients with ankylosing spondylitis was **56.4%**

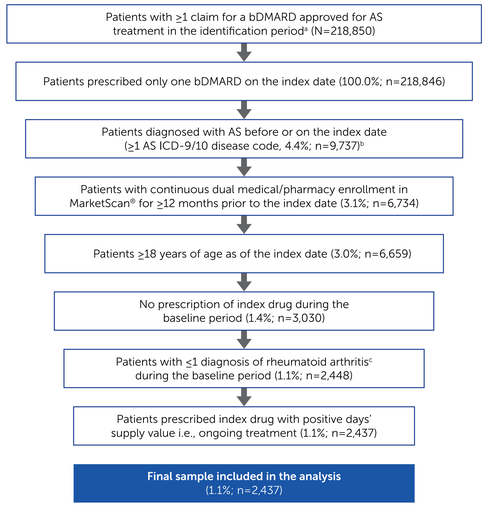
Baseline characteristics associated with *increased* persistence

History of uveitis; Comedication use

Baseline characteristics associated with *decreased* persistence

Female sex; COPD; Multiple comorbidities; Fibromyalgia; Opioid use

Figure 1 Study flow



[a]The identification or inclusion period spanned 1 January 2015–31 December 2018; [b]Patients must have had ≥1 rheumatologist-given diagnosis code for AS or 1 inpatient AS diagnosis by another provider, or 2 outpatient AS diagnoses claims by any provider type (720.0, M45, M45.0–8). The codes used may have also identified patients with other diseases related to AS; [c]Patients with ≥2 diagnosis claims (ICD-9/10 code) of rheumatoid arthritis were excluded.

Table 1 Baseline demographics and characteristics

Patient characteristic, % unless otherwise specified	All N=2,437	Patients initiating TNFi n=2,322	Patients initiating IL-17Ai n=115[a]
Age, years, mean (SD)	44.7 (13.4)	44.5 (13.4)	48.6 (13.7)
Sex, female	46.7	46.4	53.0
History of bDMARD treatment			
bDMARD-experienced	6.2	6.0	9.6
bDMARD-naïve	93.8	94.0	90.4
Extra-spinal manifestations[b]			
Enthesitis	18.9	18.7	23.5
Uveitis	15.7	15.8	12.2
Inflammatory bowel disease	9.0	9.4	1.7
Peripheral arthritis	7.3	6.7	20.0
Psoriasis	6.3	5.8	15.7
Comorbidities (all)			
None	9.7	9.9	7.0
1 comorbidity	15.6	15.8	10.4
≥2 comorbidities	74.7	74.3	82.6
Comorbidities (>10% of all patients)			
Fatigue	37.2	36.9	42.6
Hypertension	35.5	35.0	46.1
Hyperlipidemia	32.2	32.0	34.8
Depression	23.2	22.7	33.0
Anxiety	21.5	21.3	25.2
Fibromyalgia	20.9	20.5	27.8
Obesity or overweight	18.5	18.3	22.6
Sleep apnea	14.6	14.0	27.0
Asthma	14.2	14.0	17.4
Diabetes	11.4	11.2	17.4
Non-melanoma skin cancer	10.3	9.6	23.5
Other comorbidities			
SLE	2.8	2.7	6.1
Comedications (all)			
None	14.6	14.9	9.6
1 comedication	19.7	19.3	27.0
≥2 comedications	65.7	65.8	63.5
Comedications (>10% of all patients)			
NSAIDs[c]	47.4	47.6	42.6
Antihypertensives	30.1	29.6	40.0
Corticosteroids[c]	28.1	28.3	26.1
Antidepressants	26.8	26.4	33.0
Opioids	24.9	25.1	21.7
Proton pump inhibitor	19.8	19.7	21.7
Non-insulin anti-glycemic	16.0	16.1	13.9
Lipid regulators	15.0	15.0	13.9
Methotrexate	10.2	10.3	7.8

[a]Study design favored the selection of a bDMARD-naïve cohort exposed to TNFi, as few IL-17i had been approved for the treatment of AS during the study inclusion period (2015–2018) in the US; [b]Extra-spinal manifestations (ESMs) are defined as non-spinal disease symptoms in patients with AS; [c]Excluding topical preparations.

Figure 2 Persistence of bDMARD therapy in the first 12 months of treatment (A), by index bDMARD type (B), by history of bDMARD treatment (C)

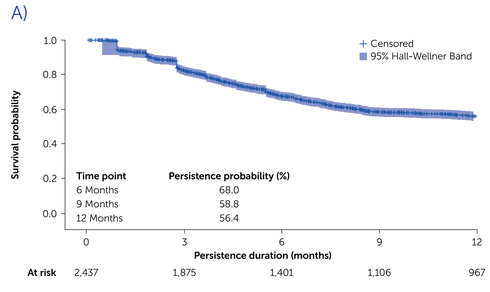


Table 2 Baseline variables associated with non-persistence of bDMARD therapy in the first 12 months of treatment

Persistence vs non-persistence: multivariate analysis[a] (reference)	Baseline variable	Discontinuation N=2,248[b] HR (95% CI)	Switch N=1,676[c] HR (95% CI)	Overall non-persistence N=2,437[d] HR (95% CI)
Sex (male)	Female	1.59 (1.37–1.85)	2.01 (1.49–2.70)	1.63 (1.42–1.86)
Index bDMARD type (TNFi)	IL-17Ai	–	0.22 (0.05–0.87)	–
Extra-spinal manifestation (no enthesitis)	Enthesitis	1.20 (1.01–1.44)	–	–
Extra-spinal manifestation (no uveitis)	Uveitis	0.59 (0.47–0.74)	0.42 (0.25–0.69)	0.56 (0.45–0.69)
Comorbidity (none)	1 comorbidity	–	–	0.99 (0.75–1.31)
	≥2 comorbidities	–	–	1.35 (1.06–1.73)
Comorbidity (no COPD)	COPD	1.70 (1.21–2.39)	–	1.47 (1.06–2.03)
Comorbidity (no fibromyalgia)	Fibromyalgia	1.41 (1.19–1.67)	–	1.27 (1.09–1.49)
Comorbidity (no SLE)	SLE	1.54 (1.08–2.21)	–	–
Comedication (none)	1 comedication	–	–	0.74 (0.59–0.93)
	≥2 comedications	–	–	0.76 (0.62–0.93)
Comedication (no opioid)	Opioid	–	1.43 (1.04–1.96)	1.25 (1.08–1.46)

[a]Additional variables, including those first recorded following index bDMARD initiation, were included in multivariate analyses but not presented in the above table. Only sex, index bDMARD type, enthesitis, uveitis, baseline comorbidities, and baseline comedications were considered here. Cells denoted with '–' were not tested in the multivariate model. [b]Patient population consisted of patients who discontinued bDMARD treatment (n=761) and patients who were persistent (n=1,487); [c]Patient population consisted of patients who switched bDMARD treatment (n=189) and patients who were persistent (n=1,487); [d]Patient population consisted of patients who discontinued or switched bDMARD treatment (n=950) and patients who were persistent (n=1,487).

Conclusions

Real-world data of US patients with AS showed that just under half of patients are estimated to be non-persistent on bDMARD therapy after 12 months. The baseline characteristics evaluated here as being associated with bDMARD non-persistence (female sex, COPD, multiple comorbidities, fibromyalgia, and opioid use) may help to identify patients with AS who have unmet needs and ultimately, improve their care.

AS: ankylosing spondylitis; **bDMARD:** biological disease-modifying antirheumatic drugs; **CI:** confidence interval; **COPD:** chronic obstructive pulmonary disease; **HR:** hazard ratio; **IL-17i:** interleukin-17 inhibitor; **IL-17Ai:** interleukin-17A inhibitor; **NSAIDs:** non-steroidal anti-inflammatory drugs; **SD:** standard deviation; **SLE:** systemic lupus erythematosus; **TNFi:** tumor necrosis factor inhibitor.

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