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ORIGINAL RESEARCH

Tumor Necrosis Factor Inhibitor Discontinuation in Patients with Ankylosing Spondylitis: An Observational Study From the US-Based Corrona Registry

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ABSTRACT

Introduction: Tumor necrosis factor inhibitors (TNFis) have shown efficacy for the treatment of ankylosing spondylitis (AS). However, many patients may discontinue or switch TNFis due to lack of effect or adverse events. As biologics with alternative mechanisms of action become available for the treatment of AS, it is important to better understand the characteristics of patients who discontinue or have an inadequate response to TNFis to help inform treatment choices regarding initiating or switching to a biologic therapy. This study compared demographic and clinical characteristics of patients with AS who discontinued vs. continued a TNFi by their second follow-up visit in the US-based Corrona Psoriatic Arthritis and Spondyloarthritis (PsA/SpA) Registry.

Methods: All patients aged ≥ 18 years with AS enrolled in the Corrona PsA/SpA Registry between April 2013 and January 2015 who were receiving or had initiated a TNFi (index therapy) at the time of registry enrollment (baseline) and had ≥ 2 follow-up visits were included. Patient demographics, clinical characteristics, and patient-reported outcome scores at baseline were compared between cohorts of patients who discontinued or continued their TNFi by the second follow-up visit.

Results: Of the 155 included patients, 37 (23.9%) discontinued their index TNFi therapy by the second follow-up visit (mean follow-up, 17.8 months). Patients who discontinued their TNFi were older (mean age, 52.1 vs. 46.6 years; $P = 0.04$), were more likely to be obese (59.5% vs. 34.2%; $P < 0.01$), and had worse mean Bath Ankylosing Spondylitis Disease Activity Index and Bath Ankylosing Spondylitis Functional Index scores (4.8 vs. 3.5 and 4.2 vs. 2.8, respectively; $P = 0.01$ for both) at baseline than those who continued their TNFi.

Conclusions: The results of this real-world study provide insight into the demographic and clinical characteristics of patients with AS who discontinue vs. continue TNFi therapy in US clinical practice.

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PLAIN LANGUAGE SUMMARY

Tumor necrosis factor inhibitors (TNFis) are effective for improving disease outcomes in patients with ankylosing spondylitis (AS). However, up to 30% of patients may discontinue or switch TNFis within the first year of treatment due to lack of treatment effect or side effects. As biologics with new mechanisms of action become available for the treatment of AS, it is important to better understand the characteristics of patients who discontinue or have an inadequate response to TNFis to help inform treatment choices regarding initiating or switching to a biologic therapy.

This study compared demographic and clinical characteristics of patients with AS who discontinued vs continued a TNFi by their second follow-up visit in the US-based Corrona Psoriatic Arthritis and Spondyloarthritis (PsA/SpA) Registry. Approximately one-quarter of patients discontinued their TNFi by the second follow-up visit; the most commonly reported reasons for discontinuation were lack of effect and side effects. Patients who discontinued their TNFi were older, were more likely to be obese, and had higher disease activity than those who continued their TNFi. These results may help inform treatment decisions regarding initiating or switching to a TNFi in patients with active AS in US clinical practice. Additional studies are needed to evaluate the characteristics of patients who respond to TNFis compared with those who have an inadequate response.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, immune-mediated rheumatic disease that may cause destruction and fusion of the spinal vertebrae and is defined by structural changes on radiographs in the sacroiliac joints [1]. Current estimates indicate that AS affects 0.20–0.55% of the general population in the United States [2, 3]. AS occurs more frequently in male patients than in female patients, with disease onset typically occurring in the late teens through 40 years of age [4]. AS is a systemic disorder that can affect the axial skeleton, peripheral joints, entheses, eyes, skin, intestine, and cardiovascular system [1, 4, 5]. Patients with AS may suffer from extra-articular manifestations such as uveitis, inflammatory bowel disease, and psoriasis, and have an increased risk of comorbidities, including hypertension, hyperlipidemia, diabetes, peptic ulcers, headaches, depression, cancer, osteoporosis, and other cardiovascular, pulmonary, renal, and neurological complications, compared with the general population [6–10].

The goals of treatment in patients with AS are to reduce symptoms of pain, stiffness, and fatigue; maintain spinal flexibility and normal posture; reduce functional limitations; maintain work productivity; and decrease complications of the disease [11, 12]. Current treatment guidelines recommend nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line therapy in patients with active AS [11, 12]. In patients with active AS despite NSAID treatment, use of a biologic is recommended; current practice suggests use of a tumor necrosis factor inhibitor (TNFi) as the first biologic [11, 12]. Currently, there are five TNFis approved for the treatment of AS in the United States: adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab [11].

The effectiveness of TNFis in improving clinical and patient-reported outcomes (PROs) in patients with AS has been demonstrated in randomized controlled trials [13–25]. Results from several real-world observational studies support the effectiveness of TNFis in the treatment of AS in routine clinical practice [26–30]. However, prior studies found that approximately 30% of patients discontinued or switched TNFis within the first year of treatment due to lack of treatment effect or adverse events [31, 32]. Ineffective management and treatment of AS can lead to continued structural progression resulting in loss of spinal mobility, chronic

pain and fatigue, and functional disability, causing decreased quality of life and work productivity [33]. Patients may also discontinue or switch TNFis for nonmedical reasons, such as economic factors (e.g., cost of TNFi, loss or change in insurance or job) or patient preference [34]. Some evidence suggests that the efficacy of a subsequent TNFi may decrease compared with that of the initial TNFi in patients who switch TNFis due to an inadequate response [35–37]. As biologics with alternative mechanisms of action become available for the treatment of AS, it is important to better understand the characteristics of patients who discontinue or have an inadequate response to TNFis to help inform treatment choices regarding initiating or switching to a biologic therapy.

Few real-world studies have evaluated the persistency of TNFi use in patients with AS, and most prior studies have been conducted outside the United States. Limited data are available regarding the demographic and clinical characteristics of patients with AS who discontinue TNFi therapy compared with those who continue TNFi therapy in real-world clinical settings in the United States. The objective of this study was to compare patient characteristics in patients with AS who discontinued vs. continued a TNFi therapy by their second follow-up visit in the US-based Corrona Psoriatic Arthritis and Spondyloarthritis (PsA/SpA) Registry.

METHODS

Study Population

The Corrona PsA/SpA Registry is a large, independent, prospective, observational cohort of patients diagnosed with PsA or SpA by a rheumatologist. The registry includes patients recruited by 40 participating rheumatologists from 30 private and academic practice sites across 20 states in the United States. As of June 30, 2017, data on approximately 2386 patients with PsA/SpA had been collected. The Corrona PsA/SpA Registry includes information on 9700 patient visits, with a mean duration of follow-up of 2.6 years (median, 2.8 years).

This study included all patients aged $\geq$ 18 years enrolled in the Corrona PsA/SpA Registry between April 2013 and January 2015 who were diagnosed with AS and fulfilled the 1984 modified New York criteria [38] according to the treating rheumatologist, were receiving or had initiated a TNFi (index therapy) at registry enrollment (baseline), and had $\geq$ 2 follow-up visits. Patients were assigned to a cohort based on discontinued or continued use of their index TNFi by the second follow-up visit (at approximately 18 months). Patients in the "continued" cohort were those who were still on their index TNFi at the second follow-up visit. Patients in the "discontinued" cohort were those who switched from their index TNFi to a different TNFi or discontinued their index TNFi without switching by the second follow-up visit.

All participating investigators were required to obtain full board approval for conducting noninterventional research involving human participants with a limited data set. The Corrona PsA/SpA Registry and its investigators have been reviewed and approved by a central institutional review board (IRB; New England Independent Review Board, NEIRB No. 120160070). For academic investigative sites that did not receive a waiver to use the central IRB, full board approval was obtained from the respective governing IRBs. All research was conducted in compliance with the Declaration of Helsinki of 1964 and all later amendments. All registry participants were required to provide written informed consent and authorization prior to participating.

Study Assessments

Data were collected using questionnaires from patients and their treating rheumatologists at office visits. Data collected at baseline included demographics (age, sex, race, and body mass index), clinical characteristics (symptom duration, human leukocyte antigen B27 positivity, family history of SpA, history of comorbidities, and prior medication use), clinical features (presence of enthesitis, Spondyloarthritis Research Consortium of Canada Enthesitis

Index score [0–16], presence of dactylitis, 68 tender joint count, and 66 swollen joint count), laboratory measurements (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]), disease activity scores (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI; 0–10], Bath Ankylosing Spondylitis Functional Index [BASFI; 0–10], spinal mobility, and Ankylosing Spondylitis Disease Activity Score), and PRO scores (pain [visual analog scale (VAS), 0–100], fatigue [VAS, 0–100], morning stiffness, Health Assessment Questionnaire for the Spondyloarthropathies [0–3], EQ-5D [0–1], EQ-VAS [0–100], and Work Productivity and Activity Impairment [WPAI] questionnaire).

Provider-reported reasons for discontinuation or switch of the index TNFi were collected for patients in the discontinued cohort. Potential reasons for discontinuation or switch included lack of effect (inadequate response or failure to maintain response), side effects (serious or minor or fear of side effects), doing well (remission or similar events), social reasons (cost, patient preference, or frequency of administration), and other.

Statistical Analysis

Categorical variables were summarized using frequency counts and percentages. Continuous variables were summarized using the number of observations, mean, and standard deviation. Reasons for discontinuation or switch of the index TNFi were summarized descriptively. Baseline demographics, clinical characteristics, and PRO scores were compared between the discontinued and continued cohorts using χ^2 tests or Fisher's exact test for categorical variables and t tests for continuous variables. All statistical analyses were performed using Stata version 14 (StataCorp LLC).

RESULTS

Of 353 patients with AS enrolled in the Corrona PsA/SpA Registry during the study period, 155 were receiving ($n = 134$) or had initiated ($n = 21$) a TNFi at enrollment and had ≥ 2 follow-up visits and were included in the analyses (Fig. 1). Overall, most patients were male (73.5%) and white (94.0%), with a mean (SD) time from symptom onset of 18.5 (12.5) years (Table 1). The majority of patients had prior biologic use (90.3%).

The mean (SD) time to the second follow-up visit was 17.8 (7.2) months (median [interquartile range], 15.4 [12.6-20.5] months). At the second follow-up visit, 118 patients (76.1%) were still receiving their index TNFi and 37 patients (23.9%) had discontinued their index

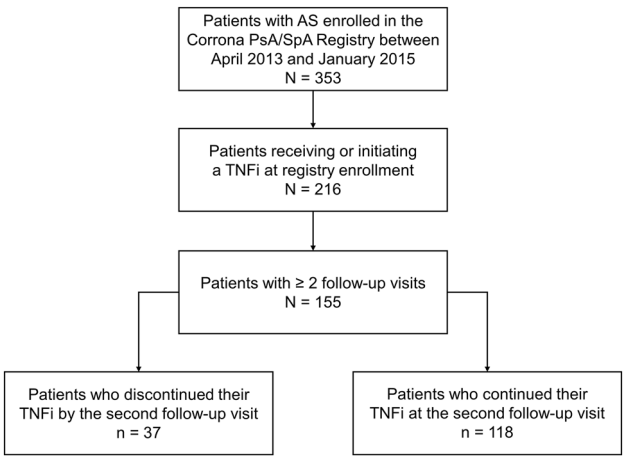

Fig. 1 Study flowchart: patients with AS who continued vs. discontinued TNFi therapy by the second follow-up visit in the Corrona Psoriatic Arthritis and Spondyloarthritis Registry. *AS* ankylosing spondylitis, *PsA* psoriatic arthritis, *SpA* spondyloarthritis, *TNFi* tumor necrosis factor inhibitor

Table 1 Baseline demographics and defining clinical characteristics of all patients with AS who continued vs. discontinued index TNFi therapy by the second follow-up visit

Characteristic[a]	Overall, $N = 155$	Continued TNFi, $n = 118$	Discontinued TNFi, $n = 37$	*P* value
Age, years	47.9 (14.1)	46.6 (13.8)	52.1 (14.5)	0.04
Male, *n* (%)	114 (73.5)	87 (73.7)	27 (73.0)	0.93
Race, *n* (%)				
White	140 (94.0)	108 (94.7)	32 (91.4)	0.13
Asian	3 (2.0)	3 (2.6)	0	
Black	2 (1.3)	0	2 (5.7)	
Pacific Islander	0	0	0	
Mixed race	3 (2.0)	2 (1.8)	1 (2.9)	
Other	1 (0.7)	1 (0.9)	0	
BMI, kg/m^2	29.4 (6.6)	28.3 (5.8)	32.9 (7.8)	< 0.001
BMI (in kg/m^2) classification, *n* (%)				
Normal/underweight (< 25.0)	39 (25.8)	37 (32.5)	2 (5.4)	< 0.001
Overweight (25.0 to < 30.0)	51 (33.8)	38 (33.3)	13 (35.1)	
Obese (≥ 30.0)	61 (40.4)	39 (34.2)	22 (59.5)	
Time from symptom onset, years	18.5 (12.5)	18.5 (13.0)	18.4 (11.1)	0.99
Time from diagnosis, years	11.9 (11.7)	12.1 (12.3)	11.1 (9.9)	0.67
HLA-B27				
Patients with available HLA-B27 test result, *n* (%)	108 (69.7)	81 (68.6)	27 (73.0)	0.62
Positive test result (among patients with available test results), *n* (%)	80 (74.1)	60 (74.1)	20 (74.1)	> 0.99
Family history of SpA, *n* (%)	23 (14.8)	19 (16.1)	4 (10.8)	0.43
History of comorbidities, *n* (%)				
Cardiovascular disease[b]	18 (11.6)	15 (12.7)	3 (8.1)	0.57
Serious infection[c]	11 (7.1)	8 (6.8)	3 (8.1)	0.73
Diabetes mellitus	11 (7.1)	9 (7.6)	2 (5.4)	> 0.99
Any cancer[d]	10 (6.5)	7 (5.9)	3 (8.1)	0.70
Psoriasis	10 (6.5)	7 (5.9)	3 (8.1)	0.64
History of bDMARD use, *n* (%)[e]	140 (90.3)	108 (91.5)	32 (86.5)	0.37

Table 1 continued

Characteristic[a]	Overall, $N = 155$	Continued TNFi, $n = 118$	Discontinued TNFi, $n = 37$	P value
No. prior bDMARDs, n (%)[e]				
0	15 (9.7)	10 (8.5)	5 (13.5)	0.66
1	99 (63.9)	76 (64.4)	23 (62.2)	
≥ 2	41 (26.5)	32 (27.1)	9 (24.3)	
History of cDMARD use, n (%)[f]	55 (35.5)	39 (33.1)	16 (43.2)	0.26
No. prior csDMARDs, n (%)[f]				
0	128 (82.6)	96 (81.4)	32 (86.5)	0.37
1	21 (13.5)	16 (13.6)	5 (13.5)	
≥ 2	6 (3.9)	6 (5.1)	0	
Current medication use, n (%)				
TNFi only	58 (37.4)	45 (38.1)	13 (35.2)	0.41
TNFi + NSAID	62 (40.0)	50 (42.4)	12 (32.4)	
TNFi + csDMARD	18 (11.6)	12 (10.2)	6 (16.2)	
TNFi + csDMARD + NSAID	17 (11.0)	11 (9.3)	6 (16.2)	

[a] All values were calculated based on available data and are presented as "mean (SD)" unless otherwise stated. All variables had < 20% missing data except for symptom duration ($n = 117$)

[b] Combined histories of myocardial infarction, acute coronary syndrome, coronary artery disease, congestive heart failure, peripheral artery disease, coronary revascularization procedure, ventricular arrhythmia, cardiac arrest, unstable angina, stroke, transient ischemic attack, pulmonary embolism, carotid artery disease, deep vein thrombosis, or other cardiovascular event

[c] Includes infections that led to hospitalization or intravenous antibiotics: joint/bursa, cellulitis, sinusitis, diverticulitis, sepsis, pneumonia, bronchitis, gastroenteritis, meningitis, urinary tract infection, upper respiratory tract infection, or infection of other specified site

[d] Excludes nonmelanoma of the skin

[e] Prior bDMARD use may include abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and/or ustekinumab

[f] Prior csDMARD use may include hydroxychloroquine, leflunomide, methotrexate, and/or sulfasalazine

AS ankylosing spondylitis, *bDMARD* biologic disease-modifying antirheumatic drug, *BMI* body mass index, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *HLA-B27* human leukocyte antigen B27, *NSAID* nonsteroidal anti-inflammatory drug, *SpA* spondyloarthritis, *TNFi* tumor necrosis factor inhibitor

TNFi, including 24 who switched to a different biologic (65% of patients who discontinued). Of the 37 patients who discontinued or switched their index TNFi by the second follow-up visit, 18 patients had 19 provider-reported reasons for discontinuation. Reasons for discontinuation of the index TNFi were lack of effect ($n = 6$), side effects ($n = 4$), social reasons ($n = 2$), doing well ($n = 1$), and other ($n = 6$ [1 temporary interruption, 5 unspecified]).

Patients who discontinued their index TNFi by the second follow-up visit were older (mean [SD] age, 52.1 [14.5] vs. 46.6 [13.8] years; $P = 0.04$), had a higher body mass index (mean [SD], 32.9 [7.8] vs. 28.3 [5.8] kg/m^2; $P < 0.001$), and were more likely to be obese (60% vs. 34%;

Table 2 Baseline clinical features and measures of disease activity, physical function, and spinal mobility of all patients with AS who continued vs. discontinued index TNFi therapy by the second follow-up visit

Characteristic[a]	Overall, $N = 155$	Continued TNFi, $n = 118$	Discontinued TNFi, $n = 37$	*P* value
Enthesitis, *n* (%)	45 (29.0)	34 (28.8)	11 (29.7)	0.92
SPARCC Enthesitis Index score (1–16) among patients with enthesitis	3.5 (2.8)	3.6 (2.9)	3.2 (2.6)	0.67
Dactylitis, *n* (%)	8 (5.2)	8 (6.8)	0	0.10
Dactylitis count (1–20) among patients with dactylitis	3.3 (4.0)	3.3 (4.0)	0	0.49
History of dactylitis, *n* (%)	6 (3.9)	4 (3.4)	2 (5.4)	0.58
Tender joint count (0–68)	2.5 (5.8)	2.6 (6.3)	1.9 (4.0)	0.54
Swollen joint count (0–66)	0.4 (1.4)	0.4 (1.4)	0.5 (1.2)	0.74
Patients with swollen joint count ≥ 1, *n* (%)	25 (16.5)	17 (14.8)	8 (21.6)	0.33
BASDAI score (0–10)	3.8 (2.5)	3.5 (2.4)	4.8 (2.6)	0.01
BASDAI score ≥ 4, *n* (%)	69 (44.5)	48 (42.5)	21 (60.0)	0.07
BASFI score (0–10)	3.2 (2.9)	2.8 (2.7)	4.2 (3.1)	0.01
Spinal mobility measures				
Occiput-to-wall distance, cm	4.3 (6.9)	4.4 (7.1)	4.0 (6.3)	0.76
Lateral lumbar flexion (average of right and left), cm	22.8 (18.9)	23.6 (19.6)	20.1 (16.4)	0.39
ASDAS	1.9 (0.8)	1.9 (0.8)	1.8 (0.7)	0.64
ASDAS disease activity, *n* (%)				
Inactive (< 1.3)	21 (21.0)	15 (19.7)	6 (25.0)	0.72
Moderate (≥ 1.3 to < 2.1)	45 (45.0)	35 (46.1)	10 (41.7)	
High (≥ 2.1 to < 3.5)	31 (31.0)	23 (30.3)	8 (33.3)	
Very high (≥ 3.5)	3 (3.0)	3 (4.0)	0	
CRP, mg/l	2.1 (5.8)	2.5 (6.5)	1.0 (2.1)	0.22
Elevated CRP, *n* (%)	23 (14.8)	16 (13.6)	7 (18.9)	0.42
ESR, mm/h	11.2 (15.2)	9.8 (12.9)	16.2 (20.7)	0.08

[a] All values were calculated based on available data and are presented as "mean (SD)" unless otherwise stated. All variables had < 20% missing data except for ASDAS ($n = 100$), CRP ($n = 109$), and ESR ($n = 99$)

AS ankylosing spondylitis, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *SPARCC* Spondyloarthritis Research Consortium of Canada, *TNFi* tumor necrosis factor inhibitor

Table 3 Baseline patient-reported outcome measures of all patients with AS who continued vs. discontinued index TNFi therapy by the second follow-up visit

Characteristic[a]	Overall, $N = 155$	Continued TNFi, $n = 118$	Discontinued TNFi, $n = 37$	*P* value
Patient pain score (VAS, 0–100)	37.3 (30.1)	36.2 (30.5)	41.1 (28.8)	0.42
Patient-reported fatigue score (VAS, 0–100)	44.9 (29.5)	42.7 (28.9)	51.9 (20.7)	0.10
Morning stiffness, *n* (%)				
Yes	132 (85.2)	100 (84.7)	32 (86.5)	0.80
< 30 min	33 (25.0)	28 (28.0)	5 (15.6)	
≥ 30 min	99 (75.0)	72 (72.0)	27 (84.4)	
HAQ-S score (0–3)	0.5 (0.6)	0.5 (0.6)	0.6 (0.5)	0.14
EQ-5D score (0–1)	0.8 (0.2)	0.8 (0.2)	0.7 (0.2)	0.18
EQ-VAS score (0–100)	69.2 (22.9)	70.3 (22.4)	65.5 (24.5)	0.28
Current employment, *n* (%)	104 (68.4)	80 (69.0)	24 (66.7)	0.80
WPAI domains				
Absenteeism (work time missed), %	7.2 (18.7)	5.1 (13.4)	14.5 (29.7)	0.04
Presenteeism (impairment at work/reduced on-the-job effectiveness), %	22.6 (23.3)	21.1 (21.5)	27.9 (28.2)	0.21
Work productivity loss (overall work impairment/absenteeism plus presenteeism), %	26.1 (26.5)	24.3 (24.1)	32.1 (33.3)	0.23
Activity impairment, %	33.0 (31.4)	31.9 (31.4)	36.3 (31.8)	0.46

[a] All values were calculated based on available data and are presented as "mean (SD)" unless otherwise stated

AS ankylosing spondylitis, *HAQ-S* Health Assessment Questionnaire for the Spondyloarthropathies, *TNFi* tumor necrosis factor inhibitor, *VAS* visual analog scale, *WPAI* Work Productivity and Activity Impairment questionnaire

$P < 0.001$) at baseline than patients who continued their index TNFi (Table 1). History of comorbidities and prior and current medication use were comparable between the discontinued and continued cohorts (Table 1).

Baseline clinical characteristics (Table 2) and PRO scores (Table 3) were generally comparable between the continued and discontinued cohorts. However, patients who discontinued their index TNFi by the second follow-up visit had higher baseline BASDAI (mean [SD], 4.8 [2.6] vs. 3.5 [2.4]; $P = 0.01$) and BASFI scores (mean [SD], 4.2 [3.1] vs. 2.8 [2.7]; $P = 0.01$) than patients who continued their index TNFi (Table 2). Additionally, patients in the discontinued cohort reported higher baseline pain (mean [SD], 41.1 [28.8] vs. 36.2 [30.5]) and fatigue scores (mean [SD], 51.9 [20.7] vs. 42.7 [28.9]) compared with those in the continued cohort, although these differences did not reach statistical significance ($P = 0.42$ and 0.10, respectively) (Table 3). Patients who discontinued their TNFi also reported worse WPAI scores at baseline than those who continued their TNFi; in particular, patients in the discontinued cohort reported a higher percentage of absenteeism (mean [SD], 14.5% [29.7%]) compared with those in the continued cohort (mean [SD], 5.1% [13.4%]; $P = 0.04$) (Table 3).

DISCUSSION

This real-world study using the US-based Corrona PsA/SpA Registry provides insight into the characteristics of patients with AS who discontinue vs. continue TNFi therapy in routine clinical practice. Of the patients who were receiving or had initiated a TNFi at enrollment in the registry, approximately one quarter discontinued their TNFi by the second follow-up visit (mean time to the second follow-up visit, 17.8 months; median, 15.4 months). The most common provider-reported reasons for discontinuation were lack of efficacy, side effects, and other. Patients who discontinued their TNFi were older, were more likely to be obese, and had higher baseline disease activity than those who continued their TNFi.

Previous observational studies of TNFi discontinuation or switching conducted outside the United States have reported TNFi discontinuation rates of 22–53% over 1 to 2 years of follow-up among patients with AS [31, 39–43]. The most common provider-reported reasons for discontinuation or switch of a TNFi across studies were lack or loss of efficacy and adverse events [31, 39–43]. In our study, 24% of patients discontinued or switched their index TNFi over a mean of approximately 18 months of follow-up. In agreement with previous studies, the most common provider-reported reasons for discontinuation or switching were lack of efficacy and side effects.

Patient factors associated with TNFi discontinuation or switching vary between studies. Several studies have identified female sex as a predictor of TNFi discontinuation and switching [31, 39, 40, 43–49]. In a study of patients with rheumatoid arthritis, psoriatic arthritis, and AS who initiated a TNFi in the NOR-DMARD registry, additional predictors of TNFi discontinuation included higher baseline disease activity as measured by the investigator's global assessment and use of TNFi without a conventional synthetic disease-modifying antirheumatic drug (csDMARD) [40]. An analysis of TNFi-naive patients with AS who initiated a TNFi in the DANBIO registry showed that CRP < 14 mg/l and higher fatigue scores were associated with shorter time to TNFi discontinuation [42]. In the Groningen Leeuwarden Ankylosing Spondylitis (GLAS) study, a prospective longitudinal observational study of patients with AS initiating a first TNFi, factors found to be associated with TNFi discontinuation included absence of peripheral arthritis, higher baseline BASDAI score, and lower ESR or CRP level [31]. A prospective, observational study of TNFi-naive patients with AS who initiated a TNFi in the South Swedish Arthritis Treatment Group Register also identified absence of peripheral arthritis as a significant predictor of TNFi discontinuation and showed a trend toward greater likelihood of TNFi discontinuation in patients with lower CRP levels and use of TNFi without a csDMARD; however, no association was found between disease activity measures including BASDAI, BASFI, and investigator's global assessment and the likelihood of TNFi discontinuation [43]. With respect to switching, previous studies have identified older age, higher disease activity, greater symptom burden, higher ESR, complete ankylosis, and presence of enthesitis as predictors of TNFi switching [39, 44–49].

In our US-based study, patients with AS who discontinued or switched their index TNFi were older and had higher baseline BASDAI, BASFI, pain, and fatigue scores than those who continued their TNFi. In our study cohort, patients who discontinued or switched their index TNFi were also more likely to be obese and reported greater work productivity and activity impairment than those who continued their TNFi. In contrast with previous studies, the proportion of patients who were female, the proportion of patients who were receiving a TNFi with a csDMARD, ESR, and CRP levels were comparable between patients who discontinued vs. continued their index TNFi. The variation in patient factors that are predictive of TNFi discontinuation may be influenced by demographics, treatment history, and choice of TNFi among patients included in a specific study population.

Limited data are available regarding TNFi discontinuation in patients with AS seen in clinical practice in the United States. Prior studies using US healthcare claims data have

evaluated persistency, treatment patterns, healthcare resource utilization, and healthcare-associated costs of biologic treatment in patients with rheumatoid arthritis, psoriasis, psoriatic arthritis, and AS; these studies found overall biologic discontinuation rates of 11–35% [32, 34, 50–52]. However, this is the first study to compare baseline characteristics between US patients with AS who discontinued their TNFi and those who continued their TNFi, presenting important insights into the characteristics of patients who discontinue TNFis and the reasons for TNFi discontinuation in routine clinical practice in the United States.

A general limitation of observational studies is the concern that patients enrolled in registries may not be representative of patients seen elsewhere in general practice. Patients in this study are routinely seen and treated by rheumatologists voluntarily participating in the Corrona PsA/SpA Registry; these patients may not be representative of all patients with AS in the United States, many of whom are not being treated by a rheumatologist. The small sample size necessitated the pooling of TNFis for analysis; therefore, no conclusions can be drawn regarding the persistency of specific TNFi agents among patients with AS. Finally, only about half of the patients (18 of 37) who discontinued their index TNFi had provider-reported reasons for discontinuing or switching, providing limited information on the reasons for TNFi discontinuation in this study population.

CONCLUSIONS

This real-world study provides insight into the demographic and clinical characteristics of US patients with AS who discontinue vs. continue TNFi therapy in routine clinical practice. Approximately one-quarter of patients discontinued their TNFi by the second follow-up visit; the most common provider-reported reasons for discontinuation were lack of effect and side effects. Patients who discontinued their TNFi were older, were more likely to be obese, and had higher disease activity than those who continued their TNFi. This study helps to address a knowledge gap by contributing information on the characteristics of patients who discontinue TNFis and the reasons for TNFi discontinuation in the United States. These results may help inform treatment decisions regarding initiating or switching to a TNFi in patients with active AS in US clinical practice. Additional studies are needed to evaluate the characteristics of patients who respond to TNFis compared with those who have an inadequate response.

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Compliance with Ethics Guidelines. Ethics approvals for this study were obtained from a central institutional review board (IRB; New England Independent Review Board, NEIRB No. 120160070). For academic investigative sites that did not receive a waiver to use the central IRB, full board approval was obtained from the respective governing IRBs and documentation of approval was submitted to the Sponsor prior to initiating any study procedures. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. The Corrona dataset is based on a large US multicenter study adhering to a number of institutional review boards, with complex logistics. Patients did not provide consent to raw data sharing during the data collection for this purpose, and the Corrona data sharing policies do not permit raw data sharing for this purpose. An aggregated limited dataset from the current analyses is available to qualified investigators with an approved protocol. Data requests may be sent to Corrona, represented by Dr. Jeffrey D. Greenberg, MD, MPH, NYU School of Medicine, New York, NY; e-mail: jgreenberg@corrona.org.

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