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Tumor necrosis factor inhibitor (TNFi) persistence and reasons for discontinuation in a predominantly male cohort with axial spondyloarthritis

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Abstract

Although tumor necrosis factor inhibitors (TNFi) have favorably altered the treatment landscape for patients with axial spondyloarthritis (axSpA), there is limited data regarding TNFi persistence and reasons for discontinuation. This is an observational time-to-event study utilizing data collected for a prospective multiple-disease registry of US Veterans with axSpA treated with TNFi therapies and recruited over a 10 year period. Clinical, serological, and comorbid parameters were collected. Corporate Data Warehouse Pharmacy files provided courses of the 5 TNFi agents, and response to treatment was documented. Individual TNFi persistence was established utilizing univariate and multivariate Cox proportional models, and reasons for discontinuation were obtained by physician chart review. Two-hundred and fifty-five axSpA patients received 731 TNFi courses. A majority of patients (84.3%) had TNFi persistence at 12 months; 63.5% and 47.1% at 24 and 36 months, respectively. Compared to adalimumab, infliximab demonstrated greater persistence, certolizumab the least. Age, smoking status, BMI, comorbidity burden, inflammatory markers and HLA-B27 did not predict TNFi persistence or discontinuation. Stroke and peripheral arterial disease increased the probability of TNFi discontinuation. Secondary non-response (SNR) was the most common reason for discontinuation (46% of all courses); non-adherence (6%) and clinical remission (2%) were uncommon. Pain score at enrollment, myocardial infarction, African American race and inflammatory bowel disease (IBD) predicted TNFi response. While initial persistence of TNFi treatment was high, a large proportion of the patients discontinued initial TNFi therapy by 3 years, primarily due to loss of efficacy. While further research identifying potential predictors of TNFi discontinuation in axSpA is warranted, access to alternate disease-modifying therapies is needed.

Keywords Axial spondyloarthritis · TNF inhibitors · Medication persistence · Real-world

Introduction

Axial spondyloarthritis (axSpA) is characterized by inflammation of the sacroiliac joints and spine, potentially leading to bony erosion and syndesmophyte formation. For several decades, therapeutic modalities were limited to non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy, without significant protection from cumulative disease burden and poor outcomes, particularly bony erosion and fusion, chronic pain, and disability [1, 2]. The advent of biologic therapies, [tumor necrosis factor inhibitors (TNFi) and IL-17 inhibitors (IL-17i)] has revolutionized the management of axSpA, including its prototype, ankylosing spondylitis (AS). Randomized controlled trials of TNFi in AS patients report primary responses in 50–60% of recipients, and only slightly lower responses in those receiving a second TNFi following secondary failure [3–7]. Predictors of response to TNFi as measured by patient reported outcomes have been compiled from six studies and included HLA-B27 positivity, absence of enthesitis, age ≤ 40 years, elevated C reactive

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protein (CRP), low baseline Bath Ankylosing Spondylitis Functional Index (BASFI), and disease duration ≤ 2 years [8, 9]. While a number of studies report such response data, less is known about how long patients remain on these therapies in the real world.

This concept of medication persistence is crucial because multiple studies confirm that bony progression in axSpA responds slowly to therapy. Results from several cohort studies report retardation in bony progression only when TNFi users remain on therapy for 2–4 years [10–15]. This underscores the importance of long-term medication adherence and emphasizes the need to delineate the factors responsible for biologic medication discontinuation. TNFi failures in AS patients result in a substantial number (22.5%) of patients switching to another drug within a year of initiation, as was reported in the Norwegian Disease-Modifying Antirheumatic Drug (NOR-DMARD) registry [16]. This report, like several other studies, has explored the reasons for TNFi discontinuation [17], but only allows for three explanations: primary failure (drug inefficacy), secondary failure (loss of previous efficacy), and adverse events. Whether other factors contribute to TNFi discontinuation, remains to be evaluated.

More specifically, the impact of comorbid conditions on medication persistence in axSpA remains poorly defined. This is an important consideration, as osteoporosis, fragility fractures, and cardiovascular mortality are more common in axSpA than in the general population [18]. While comorbidity indices (RDCI) and specific comorbidities (hypertension and depression) are associated with higher disease activity, decreased quality of life, and greater functional impairment [19, 20], these investigations have not assessed individual morbidities with medication persistence, nor expanded the reasons for TNFi discontinuation in axSpA patients.

In light of these gaps in the literature, we assessed: (1) overall rate of TNFi persistence, (2) relative rates of persistence between specific TNFi, (3) the associations of persistence with comorbid conditions, (4) the reasons for TNFi discontinuation and (5), the association of clinical characteristics with response to TNFi in a richly characterized longitudinal cohort of US axSpA patients.

Patients and methods

A cohort analysis was performed using longitudinal data from the Department of Veterans Affairs (VA) Program to Understand the Longterm Outcomes in SpondyloARthritis registry (PULSAR). Patients who met Assessment of SpondyloArthritis International Society (ASAS) criteria for axSpA and who were evaluated and treated with TNFi from September 2007 to October 2017, qualified for study [21].

PULSAR is a longitudinal, observational cohort that has enrolled patients from 11 VA sites (Dallas, TX; Denver, CO; Salt Lake City, UT; Albany NY, Sacramento, CA; Boston, MA; Washington, DC, Phoenix, AZ; Seattle, WA; Houston, TX, and Jackson, MS) since 2005. Study subjects receive routine standard of care and follow up visits at the discretion of the treating VA rheumatologist. Patients with ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease associated arthritis and reactive arthritis who met ASAS criteria for axSpA were included; while patients with undifferentiated spondyloarthritis and peripheral spondyloarthritis were excluded.

Standardized electronic medical record templates obtained at time of visits include the following baseline variables: sociodemographic data [age, sex, self-reported race/ethnicity, education (years)], Body Mass Index (BMI) score, smoking status (never, former, current), axSpA disease duration, and HLA-B27 status, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and numerical rating scales (NRS; 0–10) for pain [22].

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [23, 24] and Bath Ankylosing Spondylitis Functional Index (BASFI) [24] questionnaires are most often used as efficacy outcomes in randomized clinical trials, but are infrequently used in US and European clinical practices, as low as 29% in one cohort [25, 26]. In contrast, the numerical rating scale (NRS) pain score is a component of the Assessment of SpondyloArthritis international Society (ASAS) core set for clinical record keeping, is reported to be used in > 60% of reviewed AS clinical trials as a parameter of clinical response [27, 28]. While BASDAI and BASFI questionnaires were collected at enrollment in our cohort, follow up BASDAI and BASFI indices were only collected at the discretion of the treating clinician during follow-up visits. To address this, we utilized NRS pain score as a measure of response to therapy. Comorbid conditions were collected on enrollment and were based on published international classification of disease, 9th and 10th edition (ICD-9, ICD-10)-based algorithms (Quan-modified Charlson comorbidities, when available [29], and when not available, Healthcare Cost and Utilization Project [HCUP] coding [https://www.ahrq.gov/data/hcup/index.html]). The presence of these conditions relied upon coding by health care providers assigned in the 2 year interval prior to PULSAR enrollment and was reported as individual comorbidities, rather than an aggregated score.

The indication for TNFi was determined by the treating rheumatologist and based on the following: continued pain, lack of response to or contraindication to NSAIDs.

Five TNFi were evaluated: etanercept, adalimumab, golimumab, certolizumab pegol and infliximab. All 5 anti-TNFs were available to the VHA from their time of FDA approval

for AS. Corporate Data Warehouse (CDW) Pharmacy files were used to calculate start and stop dates for courses of TNFi (at least 90 days), as well as the course order when multiple TNFi were administered to individual patients (i.e. 1st line, 2nd line, 3rd line). We defined discontinuation of TNFi therapy as a greater than 90 days gap in treatment. TNFi response was defined as an improvement of NRS pain of > 2 units (on the 0–10 scale) or > 50% at most recent visit compared with NRS pain at the time of TNFi initiation. Pain scores were determined from the Patient Treatment File in the VA CDW. We defined TNF persistence as no gaps in TNFi therapy for ≥ 90 days.

The reasons for discontinuation of each course of TNFi were extracted from the medical record by direct chart review (all determined by the treating clinician) and classified as: (1) primary lack of TNFi response, (2) secondary loss of TNFi response (characterized as a loss of efficacy occurring ≥ 6 months after initiation of the current TNFi course), (3) adverse events (AE) by provider report (deemed sufficient to lead to discontinuation), (4) patient concern for or worry about risk of adverse drug reaction (but no actual adverse drug reaction), (5) financial or access barriers, (6) unnecessary due to minimal disease as assessed by provider, and (7) non-adherence (patient reported non-compliance or failure to refill medication).

The protocol was approved by the local Institutional Review Board (protocol #01,138) at each participating site, and by the independent Scientific Ethics and Advisory Committee for PULSAR (IRB/R&D Approval date 8/28/2008). Procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statistical analysis

Descriptive summary statistics were reported for the study cohort, including demographics, comorbidities, and reasons for TNFi treatment discontinuation. Baseline demographics, clinical characteristics and comorbidities were compared for those that continued and those that discontinued TNFi at 12 months, using chi-squared and *t* tests, as appropriate. The association of clinical characteristics with TNFi persistence was analyzed using multivariable Cox proportional hazards regression. Individual specific TNFi persistence was compared by Kaplan–Meier plots (adjusted for TNFi course order), as well as by Cox regression, after controlling for all potential confounders identified in the preceding analyses. Lastly, logistic regression determined characteristics associated with TNFi response. Censoring was completed on November 1st, 2017. A course order variable was created: a new course was generated every time a subject had a gap of 90 days or switch in TNF inhibitor. Two date variables were also generated, one associated with start of course and one associated with the end of course. Using these variables, the "course variable" was also arranged into course order by accounting for which TNFi came first by looking at the course start/end dates associated with each subject. The earliest course was assigned as 1, second course was assigned 2, and so forth until all courses had an assigned number. When analyses were performed, any variables with collinearity were removed, and not included in the final multivariate analysis. A p value of less than 0.05 was considered statistically significant. Statistical analysis was performed using STATA, version 15 (StataCorp) [30].

Results

Baseline demographics and clinical characteristics

There were 255 axSpA patients (Table 1) for analysis. The majority were male (93%), Caucasian (74%), and 74% were HLA-B27 positive. Average axSpA disease duration was 16.5 years and the mean length of follow-up was 3.34 years (1221.17 days). There were 731 TNFi courses available for analysis. Of the 731 TNFi courses, 306 (41.86%) were adalimumab, 254 (34.75%) were etanercept, 81 (11.08%) were infliximab, 55 (7.52%) were golimumab, and 35 (4.79%) were certolizumab. At 12 months, 215 (84.3%) remained on TNFi.

Clinical characteristics associated with TNFi discontinuation at 12 months included higher baseline BASDAI (mean 5.07 vs 3.40, $p < 0.001$), and BASFI scores (mean 4.91 vs 3.83, $p < 0.001$), never smoker status (44.74 vs 26.60%, $p = 0.024$), higher number of education years (15.06 vs 14.07, $p = 0.048$) and presence of gastrointestinal ulcers (5.3 vs 0%, $p < 0.001$). No differences were noted in gender or comorbidities (including BMI) between those who continued versus discontinued TNFi at 12 months.

Predictors of TNFi discontinuation (Table 2)

Compared to those not reporting a race or reporting race as "Other", Caucasians, African Americans and Hispanics all were less likely to discontinue TNFi. Former smokers (HR 0.75, 95% CI 0.61–0.91), and those with longer axSpA disease duration (HR 0.98, 95% CI 0.97–0.99) were less likely to discontinue TNFi. More specifically, each decade of axSpA disease duration equated to a 10% decline in risk of TNFi discontinuation. While there was a trend for older

Table 1 Baseline Demographic and Clinical Characteristics of Patients with axial spondyloarthritis (axSpA) who continued versus discontinued Tumor Necrosis Factor Inhibitors (TNFi) at 12 months in the PULSAR Registry

	Overall ($N=255$)	axSpA patients who continued TNFi at 12 months ($n=215$; 84.3%)	axSpA patients who discontinued TNFi by 12 months ($n=40$; 15.6%)	p value[1]
Age in years, mean (SD)	53.01	53.09	52.60	0.837
Sex (Male), *n* (%)	93.28	93.43	92.50	0.830
Race, *n* (%)				
White	74.12	76.74	60.00	**0.026**
African-American	11.37	10.23	17.50	0.184
Hispanic	9.02	7.91	15.00	0.150
Asian-American	0.78	0.47	2.50	0.180
Other	1.18	0.93	2.50	0.398
Smoking status, *n* (%)				
Never smoked	29.46	26.60	44.74	**0.024**
Former smoker	40.25	42.86	26.95	0.056
Current smoker	30.29	30.54	28.32	0.844
Education in years, mean	14.23	14.07	15.06	**0.048**
AxSpA duration in years, mean	16.51	16.88	15.00	0.538
HLA-B27 positive, *n* (%)	74.12	72.90	80.00	0.357
CRP (mg/L), mean	10.10	10.15	8.09	0.329
ESR (mL/hr), mean	18.26	18.37	17.74	0.855
BMI Score (kg/m^2), mean	29.37	29.32	29.76	0.725
Disease activity at baseline				
BASDAI score, mean	3.65	3.40	5.07	**< 0.001**
Active disease (BASDAI ≥ 4), *n* (%)	50	46	68	**< 0.001**
BASFI score, mean	4.00	3.83	4.91	**0.002**
Pain score, mean	4.52	4.48	4.86	0.470
Comorbidities				
Cardiovascular, *n* (%)				
Angina	19.8%	19.5%	10.5%	0.184
Atherosclerosis	3.7%	3.3%	0.0%	0.259
Cerebrovascular disease/stroke	7.1%	6.5%	5.3%	0.771
Coronary artery disease	14.2%	14.0%	10.5%	0.568
Hypertension	56.8%	57.7%	42.1%	0.075
Myocardial infarction	1.9%	1.9%	2.6%	0.753
Peripheral vascular disease	2.2%	1.9%	2.6%	0.753
Venous thromboembolism	4.3%	3.7%	0.0%	0.227
Dyslipidemia, *n* (%)	48.5%	49.8%	39.5%	0.242
Depression, *n* (%)	34.6%	38.1%	34.2%	0.645
Uveitis, *n* (%)	30.6%	31.2%	31.6%	0.959
Sleep apnea, *n* (%)	24.1%	25.1%	13.2%	0.108
Inflammatory bowel disease, *n* (%)	10.5%	12.1%	5.3%	0.216
Diabetes, *n* (%)	35.5%	35.3%	36.8%	0.859
Cancer, *n* (%)	18.8%	20.5%	10.5%	0.150
Osteoporosis, *n* (%)	28.7%	32.6%	18.4%	0.081
Asthma, *n* (%)	5.2%	4.2%	7.9%	0.321
Gastrointestinal ulcers, *n* (%)	0.6%	0.0%	5.3%	**0.001**
Multiple sclerosis, *n* (%)	4.0%	3.7%	2.6%	0.738
Parkinson disease, *n* (%)	0.6%	0.0%	0.0%	N/A

All demographic and clinical characteristics will be measured at the time of TNFi treatment initiation (baseline), unless otherwise specified

Bolded p values are statistically significant

BASDAI Bath ankylosing spondylitis disease activity index, *BASFI* Bath ankylosing spondylitis functional index, *CRP* C-reactive protein, *ESR* Erythrocyte sedimentation rate, *TNFi* Tumor necrosis factor inhibitor

[1] p values calculated using appropriate statistical tests (e.g., chi-square, t tests) and compares subjects who continued at least one TNFi beyond 12 months versus subjects who discontinued all TNFi courses by 12 months)

patients to have an increased risk of TNFi discontinuation, this was not statistically significant (HR 1.14, 95% CI 0.98–1.34). Biomarkers (HLA B27 positivity, mean CRP and ESR) had no discernible impact.

Multiple sclerosis (HR 2.39, 95% CI 1.92–2.96), cerebrovascular disease (HR 2.3, 95% CI 1.49–3.63) were strongly predictive of TNFi discontinuation as were peripheral vascular disease (HR 1.93, 95% CI 1.17–3.20) and gastrointestinal

Table 2 Cox proportional hazards model for predictors of TNFi discontinuation

	Univariate HR (95% CI)	Adjusted[a] HR (95% CI)
Age	0.94 (0.88–1.01)	–
Male sex	0.96 (0.61–1.51)	–
Caucasian	0.83 (0.65–1.07)	0.42 (0.34–0.51)
African American	0.99 (0.68–1.44)	0.40 (0.27–0.57)
Hispanic	1.37 (0.18–0.70)	–
Asian	2.29 (0.25–1.16)	–
Other (referent)	1.00	–
Education (Years)	1.01 (0.93–1.02)	–
Duration of axSpA (years)	0.99 (0.97–0.99)	0.99 (0.98–0.99)
HLAB27 positivity	1.14 (0.73–1.86)	–
Mean CRP (mg/dL)	1.00 (0.98–1.01)	–
Mean ESR (mm/hr)	1.00 (0.99–1.01)	–
Course of TNFi[b]	1.15 (1.08–1.21)	1.15 (1.10–1.21)
BMI Score (kg/m^2)	1.01 (0.99–1.02)	–
Smoking status		–
Former smoker	0.81 (0.63–1.05)	–
Current smoker	0.99 (0.76–1.28)	–
Never smoker (referent)	1.00	–
Comorbidities		
Atherosclerosis	1.12 (0.26–1.86)	–
Angina	0.94 (0.53–1.67)	–
Cerebrovascular/stroke	1.78 (1.29–2.45)	2.32 (1.49–3.63)
Coronary artery disease	1.21 (0.92–1.57)	–
Hypertension	0.86 (0.71–1.05)	–
Myocardial infarction	1.20 (0.63–2.23)	0.38 (0.26–0.56)
Peripheral vascular disease	1.33 (0.94–1.89)	1.93 (1.17–3.20)
Venous thromboembolism	0.85 (0.46–1.59)	–
Dyslipidemia	1.04 (0.85–1.28)	–
Depression	1.30 (1.07–1.59)	–
Uveitis	0.99 (0.80–1.22)	–
Sleep Apnea	1.05 (0.85–1.30)	–
Inflammatory bowel disease	0.69 (0.49–0.98)	–
Diabetes	0.90 (0.72–1.12)	–
Cancer	1.05 (0.83–1.32)	–
Osteoporosis	0.86 (0.69–1.07)	–
Asthma	0.90 (0.58–1.69)	–
Multiple sclerosis	3.72 (1.75–7.91)	2.39 (1.92–2.96)
Gastrointestinal ulcer	1.39 (0.91–2.12)	1.57 (1.14–2.17)
Parkinson disease[c]	1.00	–

HR > 1.0 reflects the hazard of discontinuation. Variables were recorded at the time of registry enrollment

[a]Adjusted models were constructed with all variables from the univariate Cox proportional hazard regression, then simplified to only include those variables with HR confidence intervals excluding 1.0

[b]Reports hazard of discontinuation for first course of TNFi versus second course, and second versus third course, etc.

[c]Insufficient numbers to report hazard

ulcers (HR 1.57, 95% CI 1.14–2.17). Subsequent TNFi courses also predicted TNFi discontinuation (HR 1.15, 95% CI 1.1–1.21), so that for each additional course of TNFi, the likelihood of terminating the TNFi increased by 15% compared to the initial course. In contrast, patients with myocardial infarction were less likely to discontinue TNFi (HR 0.38, 95% CI 0.26–0.56). Adjusted models were constructed with all variables from the univariate Cox proportional hazard regression, then simplified to only include those variables with HR confidence intervals excluding 1.0. .

TNFi discontinuation rates and comparisons amongst individual TNFi (Fig. 1)

Persistence for all TNFi, accounting for drug course and sequence, was 84.3%, 63.5% and 47.1% at 1, 2 and 3 years, respectively. Three-year persistence was highest for infliximab, followed by etanercept. Less than 40% of patients remained on the other 3 TNFi at 3 years. Compared to the referent (adalimumab), certolizumab was the most likely to be discontinued. There was inconsistency between the Kaplan–Meier curve and the Cox proportional hazards model for certolizumab which was confirmed on repeat analyses. After adjustment for drug course and sequence, there was no difference for persistence of etanercept or golimumab versus adalimumab, though these TNFi were used less frequently thereby limiting this analysis.

Reasons for TNFi discontinuation (Fig. 2)

Secondary non-response/SNR (46%) was the most common reason for discontinuation. Adverse events and primary non-response together accounted for approximately a third of TNFi discontinuation (22%, 14%, respectively). Adverse events (AE) were defined as any patient reported side effect or complication of TNF therapy(s) that the provider felt necessitated discontinuation. These included recurrent infections, rashes, injection site reactions, headaches, paresthesia, nausea, vomiting, allergic reaction and abnormal blood counts. Patient risk aversion, non-adherence, and access barriers to medication were relatively infrequent (< 15% combined). Only 2% of patients discontinued TNFi due to sustained clinical remission, as determined by their treating physician.

Predictors of TNFi response (Table 3)

African American race, greater baseline pain score, presence of inflammatory bowel disease and osteoporosis were significant predictors of TNFi NRS response. As with TNFi discontinuation, biomarkers (HLA-B27 status, ESR, CRP) were not predictive of TNFi response. Predictors

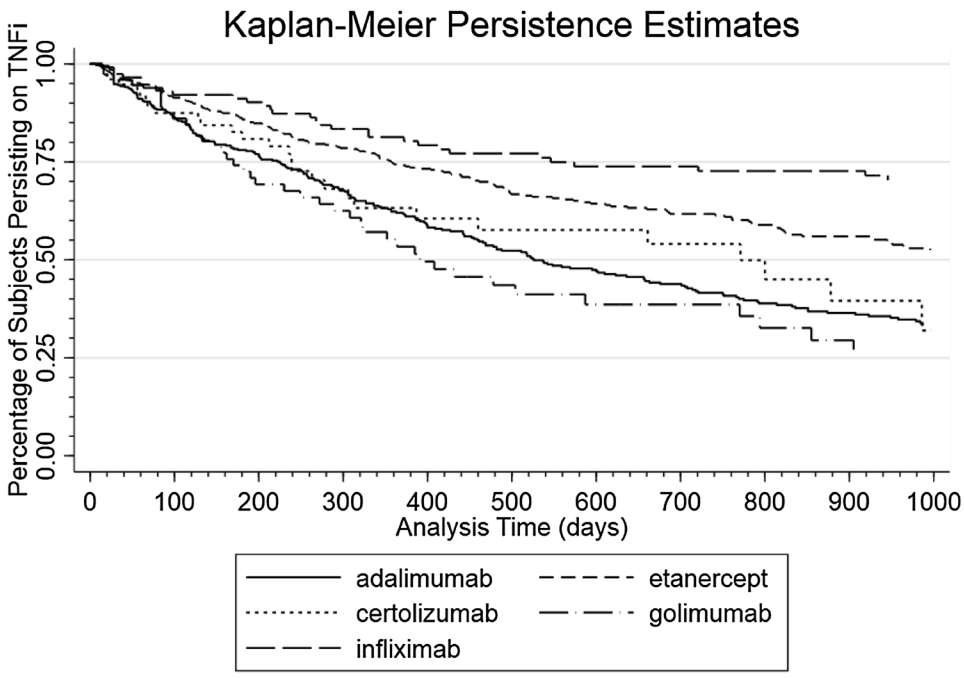

Fig. 1 Kaplan–Meier survival curve of time to TNFi discontinuation at 3 years, adjusted for TNFi course order

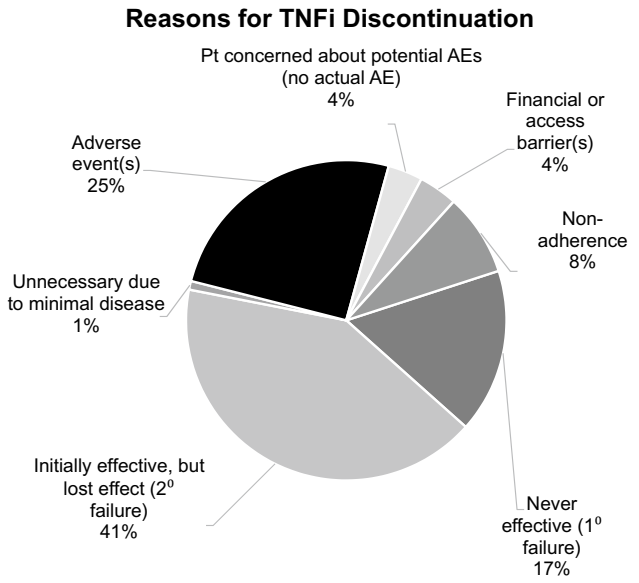

Fig. 2 Reasons for tumor necrosis factor inhibitor course discontinuation ($n = 229$ reasons)

of TNFi non-response were high BASFI scores and dyslipidemia. BMI was unassociated with TNFi response. There were no differences between individual TNFi NRS responses.

Discussion

In this observational axSpA cohort study of US patients treated with TNFi, approximately two-thirds of patients had TNFi persistence after 2 years of therapy, with highest frequencies in infliximab and etanercept users. Secondary non-response, cardiovascular, gastrointestinal and multiple sclerosis comorbid disease were the most frequent reasons for discontinuation. In contrast, axSpA patients with myocardial infarction, prior smoking history, and infliximab use had greatest TNFi persistence. Our report highlights the individual comorbid conditions associated with TNFi discontinuation/persistence in a real-world cohort of axSpA patients.

Individuals switching between TNFi would be, by definition, discontinuing the first TNFi. Whereas there is substantially sparse literature regarding TNFi discontinuation, there are several studies reporting TNFi switching. A review of 21 studies of axSpA patients who underwent TNFi switching due to inefficacy or adverse events, found the second or even third TNFi had clinical benefit [17]. Drug persistence at 2 years was 58–75% for the first TNFi, 47–72% for the second TNFi, and 49% for the third TNFi, A large Swedish registry study showed a steady decline with each subsequent switch in TNFi drug, but 62% of patients were on a TNFi at 5 years, with 46% on first TNFi, 13% on second TNFi, and 3% on third TNFi [31]. Although these reports were not defined by prescription renewal, our study findings were similar: approximately 75% at 2 years for infliximab, but also lower with other TNFi, such as golimumab (< 40%). In contrast, other studies have found contrasting results: a study in Finland identified 543 patients with AS treated with TNFi, Etanercept was found to be associated with greater persistence in comparison to infliximab [32]. Potential reasons for infliximab discontinuation are theoretically increased immunogenicity due to mouse sequence in the hypervariable region and the requirement for infusion visits, rather than self-administration. However, the patients in our study represent an older demographic that may be reluctant to take injectable formulations and not only benefit from regular infusion appointments for infliximab, but also may provide an opportunity for periodic disease reminders and closer follow-up. Our cohort receives care within a healthcare system that has access to all FDA-approved therapies including infusion services, with drug choices driven by physician and patient preferences, rather than adherence to any specific protocol.

Multiple studies have reported predictors of TNFi switching and by extension, discontinuation. Patient characteristics of those who switched included female sex, older age, more severe disease, higher ESR, complete SI joint ankylosis, and enthesitis [33]. Approximately 24% of patients in a US cohort of AS patients discontinued or switched their index TNFi over a mean of approximately 18 months. The most common reasons included lack of efficacy and side effects [34]. Elevated BASDAI and BASFI at baseline were predictive of discontinuation or switching, which are in keeping with our findings. In contrast, improved clinical outcomes and thereby TNFi persistence, were reported in those with higher baseline CRP values [35], positive HLA-B27 [36], male sex, and peripheral arthritis.

In our study, higher education years correlated with TNFi discontinuation by 12 months. This contrasts with a United Kingdom study of axSpA patients where fewer years in education predicted a lower likelihood of TNFi response [37]. Possible explanations for these discordant findings include: (1) Younger and more educated patients may have had greater or different expectations of TNFi, such as functional improvement, so that patients and/or their providers were more proactive in switching therapies, and (2), less educated patients -especially those with longer disease durations—may have had different goals of treatment and expectations which may have impacted their desire to switch treatment. The interaction of higher education and specific occupations with objective measurements of functional impairment was

Table 3 Logistic regression model for predictors of TNFi response

	Univariate OR (95% CI)	Adjusted[a] OR (95% CI)
Age	0.99 (0.98–1.01)	–
Male sex	1.53 (0.60–3.90)	–
Caucasian	0.70 (0.45–1.07)	–
African American	1.97 (1.12–3.48)	2.09 (1.01–4.32)
Hispanic	0.95 (0.50–1.80)	–
Asian	2.25 (0.31–16.1)	–
Other race(referent)	1.00	–
Never smoker	1.35 (0.86–2.11)	–
Former smoker	0.64 (0.42–0.98)	–
Current smoker	1.22 (0.80–1.86)	–
Education (years)	0.95 (0.87–1.03)	–
Duration of AxSpA (years)	0.99 (0.98–1.01)	–
HLAB27 positivity	0.69 (0.44–1.08)	–
BASDAI score	0.93 (0.85–1.02)	–
BASFI score	0.93 (0.86–1.01)	0.81 (0.74–0.89)
Pain score	1.35 (1.24–1.47)	1.44 (1.31–1.59)
BMI score (kg/m^2)	0.98 (0.94–1.01)	–
Mean CRP (mg/dL)	0.98 (0.96–1.01)	–
Mean ESR (mm/hr)	0.99 (0.98–1.01)	–
Course of TNFi	0.98 (0.89–1.08)	–
Comorbidities		
Atherosclerosis	0.94 (0.61–1.47)	–
Angina	1.03 (0.38–2.76)	–
Cerebrovascular/stroke	0.85 (0.46–1.57)	–
Coronary artery disease	0.99 (0.62–1.57)	–
Hypertension	1.10 (0.72–1.67)	–
Myocardial infarction	4.32 (1.57–11.9)	–
Peripheral vascular disease	0.70 (0.18–2.43)	–
Venous thromboembolism	0.74 (0.20–2.76)	–
Dyslipidemia	0.56 (0.38–0.84)	0.49 (0.30–0.79)
Depression	1.10 (0.74–1.63)	–
Uveitis	1.68 (1.12–2.52)	–
Sleep apnea	0.94 (0.61–1.45)	–
Inflammatory bowel disease	2.13 (1.21–3.75)	2.96 (1.25–7.04)
Diabetes	0.78 (0.52–1.16)	–
Cancer	1.12 (0.72–1.74)	–
Osteoporosis	1.36 (0.90–2.06)	1.89 (1.15–3.10)
Asthma	1.03 (0.38–2.76)	–
Multiple sclerosis	1.00	–
Gastrointestinal ulcer	1.23 (0.59–2.56)	–
Parkinson disease[b]	1.00	–
Adalimumab (referent)	1.00	1.00
Etanercept	0.87 (0.55–1.36)	0.75 (0.45–1.25)
Infliximab	1.59 (0.73–3.42)	1.33 (0.54–3.28)
Certolizumab	0.55 (0.20–1.52)	0.52 (0.18–1.51)
Golimumab	1.32 (0.65–2.66)	1.01 (0.42–2.45)

[a]Adjusted models were constructed with all variables from the univariate Cox proportional hazard regression, then simplified to only include those variables with OR confidence intervals excluding 1.0

[b]Insufficient numbers to report Odds Ratio

not evaluated in our study, but could be explored in future cohorts.

The most common reasons reported for discontinuing or switching TNFi use is non-response, whether primary or secondary. TNFi non-response and secondary loss of response accounted for discontinuation in 65% of axSpA patients in our cohort, higher than the 56% non-response reported in Danish registry AS patients [38]. The rates of discontinuation due to low disease activity in our study were very low, likely reflecting the high rates of flares following discontinuation of TNFi in axSpA, and in keeping with recent 2019 treatment guidelines that recommend against TNFI discontinuation [39]. Our findings suggest VA providers are providing care concordant with this recommendation.

We found African American (AA) race and a high baseline pain score to be associated with TNFi response at 12 months. The signal for a response associated with AA ethnicity has not been well reported. This is of particular interest given data from the US Prospective Study of Outcomes in AS (PSOAS) cohort showing more severe disease in AA patients with AS, compared to Caucasians [40]. A recent retrospective study identified patients with AS, 8% were AA; these patients had higher inflammatory markers which was interpreted as increased disease activity [41]. However, given the small number of AA study participants in our cohort and modest significance, these findings will need to be replicated.

Patients with poor baseline function (higher BASFI scores) predicted discontinuation, similar to other reports of AS patients receiving infliximab [42]. Our findings, however, differ from other reports regarding predictors of TNFi non-response. In a Canadian AS cohort, older age, a negative HLA–B27, increased disease activity at baseline, and treatment with etanercept predicted non-response [43]. In yet other data, females had less persistence, more discontinuation and TNFi non-response, than males [35]; findings we were unable to replicate, perhaps in part a reflection of our predominantly older, male cohort.

Comorbidities have been area of intense interest with regards to the impact on disease severity and treatment response. A retrospective study in the United States using administrative claims data, confirmed the prevalence of a much greater comorbidity burden in AS patients compared to matched controls [44]. A study from the United Kingdom (UK) of newly treated AxSpA patient noted that those who had 2 or more comorbid conditions were reported to have greater TNFi discontinuation, as well as less TNFi response (disease activity, function and Quality of Life) [45]. While one would postulate increased comorbid burden would be associated with TNFI discontinuation and non-response, our findings were more nuanced. In contrast to the UK study, rather than additive comorbidities, our study analyzed individual comorbid conditions for association with TNFi persistence. It was individual rather than composite measures of comorbidities that were associated with TNFi persistence and responses. One such finding was that previous myocardial infarction predicted TNF persistence. While TNFi have been associated with reduced cardiovascular events in rheumatoid arthritis [46]; similar findings have not been reliably demonstrated in AS or nr-axSpA [47]. Numerous observational studies, meta-analyses and systematic reviews have shown a clear association between axSpA and myocardial infarctions. Extrapolating from the rheumatoid arthritis observational data [48, 49], it is suggested that providers should target systemic inflammation with TNFi, thereby decreasing myocardial infarction risks. We postulate that patients with prior MI would likely start TNFi rather than NSAIDs, the latter being relatively contraindicated. As such, patients with a history of MI–even with de novo or mild inflammatory disease–are likely to start TNFi therapy, hence the increased TNF persistence in our cohort. Further study into the impact on the possible bi-directional association of biologic therapy and cardiovascular disease would be of benefit.

On the other hand, peripheral vascular disease and cerebrovascular disease surprisingly, predicted TNFi discontinuation. We postulate that this may reflect a greater comorbidity burden or concern for potential adverse events in these specific patients, lowering the threshold for subsequent discontinuation of TNF. Given the correlation of certain comorbidities on TNFi treatment response, there is need for further study of individual chronic conditions, specifically the cardiovascular disease spectrum.

In our cohort, former smoking was protective against TNFi discontinuation, in contrast with results from the Danish AS registry, in which current and former smokers with AS had shorter treatment adherence and poorer treatment response compared to never smokers [50]. However, a large UK cohort of axSpA showed no difference in response to the first TNFi related to baseline smoking status, whether current, former, or never smokers [51]. These equivocal reports require further exploration. Lastly, the association of de novo or worsening multiple sclerosis and TNF discontinuation is in keeping with prior studies [52].

Our report is significant for the large axSpA patient population with rheumatologist-confirmed diagnoses, multi-site US recruitment, collection of sociodemographic data, HLA-B27 testing, patient-reported outcomes utilizing the standardized electronic medical records, and availability of all FDA-approved TNFi to participants with limited financial or other access barriers. In addition, we evaluated a predominantly older cohort, which is a traditionally under-studied population in axSpA. Our inclusion of comorbidity data adds important parameters to assessing risks for TNFi discontinuation, although further studies will be needed to focus on specific coexistent conditions. Our analysis included TNFi courses and

the merged administrative pharmacy data with patient reported outcomes and provider-based assessments to ascertain the TNF persistence rates at specific time periods. Additionally, to explore causes of TNFi discontinuation, utilizing real world data reflecting TNFi prescription practices for axSpA among US veterans. Our data are also the first to show no preferential TNFi discontinuation related to race. Non-adherence, adverse events, access barriers, and fear of potential adverse events were relatively uncommon, suggesting that TNFi are well tolerated and safe in most axSpA veterans.

Limitations of our study include our analysis of a well-established predominantly male, elderly subjects compared to the usual reports of younger, newly diagnosed patients. ASDAS, a more robust measure of disease activity, was not routinely collected as part of this study. While BASDAI on enrollment was collected and reported, only a subset had repeat BASDAI longitudinally correlating with TNFi courses to provide further analysis. Race was self-reported rather than biological race which must be taken into consideration, and further studies exploring the impact of biologic race on TNF persistence in this patient population may be relevant. We did not categorize the cohort based on disease activity or phenotype, e.g.: presence of coexisting peripheral arthritis, uveitis, etc., which may have impacted response or lack thereof to TNFi therapy. Patients with co-existing peripheral arthritis or enthesitis may have used concomitant disease-modifying antirheumatic drugs (DMARDs) or NSAIDs which may have augmented/influenced TNFi response or persistence, and the residual channeling bias related to the selection of therapies must be considered in the interpretation of our results. The impact of anti-TNF antibodies was not evaluated in this study and remains an area for further inquiry. Finally, there are the inherent limitations of administrative data, including missing variables. We also acknowledge but are unable to explain the conflicting results which were unresolved despite repeat statistical analyses.

In conclusion, we found a significant proportion of a predominantly male cohort with axSpA discontinued TNFi therapy within 2–3 years, primarily as a result of secondary non-response, additionally, specific comorbid conditions led to TNFi discontinuation including cerebrovascular and peripheral vascular disease. Higher pain scores (NRS) at baseline, African American Race, Inflammatory Bowel Disease and Osteoporosis predicted TNFi response. Our findings provide additional parameters to be considered in treatment options for axSpA patients. Research identifying potential predictors for treatment responses and discontinuation continue to be areas of interest and future study.

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Data availability The Veterans Health Administration has sole ownership of the data gathered for this study and data are not available for sharing or public viewing.

Code availability Not applicable.

Declarations

Conflict of interest The other authors have disclosed no conflicts of interest. Dr. Kerr has received current and prior grant funding from Novartis, BMS and Pfizer. She currently serves on the advisory board for Janssen. Dr. Walsh has received consulting fees from AbbVie, Lilly, Novartis and UCB (all less than $10,000). She has also received research funding from AbbVie and Pfizer. Dr. Clegg has received VA Merit Review funding. Dr. Reimold has served as a consultant for Lilly (less than $10,000).

Ethical approval Approval obtained by the local Institutional Review Board at each participating site, and by the independent Scientific Ethics and Advisory Committee for the Department of Veterans Affairs (VA) Program to Understand the Longterm Outcomes in SpondyloARthritis registry (PULSAR). Ethics Approval MIRB number: 01138. Initial approval: 08/28/2008.

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