Adherence to Antitumor Necrosis Factor Use Recommendations in Spondyloarthritis: Measurement and Effect in the DESIR Cohort

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ABSTRACT. ***Objective.*** To evaluate a classification system to define adherence to axial spondyloarthritis (axSpA) anti-tumor necrosis factor (anti-TNF) use recommendations and examine the effect of adherence on outcomes in the DESIR cohort (Devenir des Spondylarthropathies Indifférenciées Récentes).

Methods. Using alternate definitions of adherence, patients were classified as adherent "timely" anti-TNF users, nonadherent "late" anti-TNF users, adherent nonusers ("no anti-TNF need"), nonadherent nonusers ("unmet anti-TNF need"). Multivariate models were fitted to examine the effect of adherence on quality-adjusted life-years (QALY), total costs, and nonbiologic costs 1 year following an index date. Generalized linear regression models assuming a γ-distribution with log link were used for costs outcomes and linear regression models for QALY outcomes.

Results. Using the main definition of adherence, there were no significant differences between late anti-TNF users and timely anti-TNF users in total costs (RR 0.86, 95% CI 0.54–1.36, p = 0.516) or nonbiologic costs (RR 0.72, 95% CI 0.44–1.18, p = 0.187). However, in the sensitivity analysis, late anti-TNF users had significantly increased nonbiologic costs compared with timely users (RR 1.58, 95% CI 1.06–2.36, p = 0.026). In the main analysis, there were no significant differences in QALY between timely anti-TNF users and late anti-TNF users, or between timely users and patients with unmet anti-TNF need. In the sensitivity analysis, patients with unmet anti-TNF need had significantly lower QALY than timely anti-TNF users (–0.04, 95% CI –0.07 to –0.01, p = 0.016).

Conclusion. The effect of adherence to anti-TNF recommendations on outcomes was sensitive to the definition of adherence used, highlighting the need to validate methods to measure adherence.
(J Rheumatol First Release July 1 2017; doi:10.3899/jrheum.161399)

Key Indexing Terms:
SPONDYLOARTHRITIS ANKYLOSING SPONDYLITIS ANTI-TNF
ADHERENCE ECONOMIC QUALITY OF LIFE

The Assessment of Spondyloarthritis international Society (ASAS) ankylosing spondylitis management recommendations apply to all patients with axial spondyloarthritis (axSpA)[1]. Recommendations outline the use of medication, including nonsteroidal antiinflammatory drugs (NSAID), analgesics, disease-modifying antirheumatic drugs (DMARD), glucocorticoids, and anti-tumor necrosis factor (anti-TNF) agents, as well as nonpharmacological therapy and specialist management of extraarticular symptoms. In general, recommended management aims to reduce symptoms and preserve patients' function and social participation[1]. These outcomes are also associated with costs and quality of life among patients with axSpA[2,3,4,5,6,7,8].

To our knowledge, no studies have examined to what extent axSpA care in clinical practice follows the ASAS recommendations, or how recommended care affects patient

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Accepted for publication May 5, 2017.

outcomes. One important barrier is the lack of validated methods to define or measure adherence to recommended axSpA care. Recently, we asked rheumatologists involved in the DESIR (Devenir des Spondylarthropathies Indifférenciées Récentes), a longitudinal study of patients with early axSpA[9], how adherence or nonadherence with the ASAS recommendations might be measured using observational data[10]. In a Delphi process, rheumatologists developed a classification system based on markers of nonadherence, defined as clinical actions clearly discordant with the recommendations. Adherence was then defined by the absence of markers of nonadherence. This system to define adherence, like any classification system, reflects the need to balance sensitivity and specificity according to the perceived consequences of both false-negatives and false-positives[11]. Further, as in the case of diagnostic or screening tests, there is bound to be a range of values that do not clearly indicate how to best classify the patient[12]. Using observational data alone, perfect discrimination between adherence and nonadherence to axSpA management recommendations is unlikely. However, the developed system[10] provides a means to analyze differences between patients with axSpA with and without clear markers of nonadherent management.

In our study, we aimed to evaluate the use of this classification system among DESIR patients, measuring costs and health status across groups defined by adherence to ASAS anti-TNF recommendations while controlling for adherence to other recommendations.

MATERIALS AND METHODS

Data source and study population. The DESIR cohort[9] includes 708 patients aged 18–50 years with inflammatory back pain[13,14] suggestive of SpA lasting > 3 months and < 3 years. Patients with definite diagnosis of non-SpA back pain, history of anti-TNF use, or conditions affecting informed consent were excluded. Followup occurred every 6 months in the first 2 years and every year thereafter. Our analyses included data from the first 3 years, i.e., baseline plus followup visits at months 6–36. DESIR data include clinical history, quality of life [i.e., Medical Outcomes Study Short Form-36 (SF-36)], and total health resource use and work productivity loss costs[15]. Briefly, total costs were estimated in 2013 euros using public cost data linked to self-reported, all-cause health resource use (i.e., health practitioner visits, hospitalizations, medical workups, medications) and work productivity losses, calculated as number of work days lost multiplied by daily estimated wage. Patient out-of-pocket costs were not included. Missing data were imputed using Monte Carlo Markov Chain multiple imputation, last observation carried forward, probabilistic imputation, or negative values based on clinical expertise[15]. Our current analysis included patients who satisfied the ASAS criteria for axSpA[16]. The DESIR cohort was approved by the French Departmental Directorate of Health and Social Affairs Committee for Protection of Persons (reference number 2457) and conducted in accordance with the Declaration of Helsinki and guidance for good clinical practice. All participants gave written informed consent. Secondary data analysis in the costing study was reviewed and approved by University of British Columbia Research Ethics Board (H13-01981).

Classification of adherence. We used DESIR data to evaluate a classification system designed for use with observational data to define adherence to ASAS anti-TNF use and other care recommendations (Table 1)[10]. The definition of anti-TNF adherence considers timing of anti-TNF initiation relative to disease activity on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the physician's global assessment (PGA; a proxy for positive expert opinion cited by ASAS as a requirement for anti-TNF use). All patients who receive an adequate trial of NSAID who experience BASDAI and PGA ≥ 4 at 2 consecutive visits 6 months apart must receive an anti-TNF at the subsequent visit to be defined as adherent to recommendations; all anti-TNF use initiated before 2 consecutive visits with BASDAI and PGA ≥ 4 is also classified as adherent. The system also defines adherence relative to recommended physiotherapy, specialist care for extraarticular manifestations and comorbidities, and NSAID, glucocorticoid, and DMARD use (Table 1).

In preliminary analyses, many patients were missing data on NSAID use and few experienced ≥ 2 consecutive visits with BASDAI and PGA ≥ 4. To have an adequate number of patients for analysis, the original definition of anti-TNF adherence[10] was adapted as follows: all anti-TNF users were assumed to have had an adequate trial of NSAID and patients with BASDAI and PGA ≥ 4 at 2 consecutive visits 6 months apart had to receive an anti-TNF at the second visit (rather than the subsequent visit) to be defined as adherent. All anti-TNF use initiated before 2 consecutive visits with BASDAI and PGA ≥ 4 was considered adherent. Reasons for anti-TNF nonuse were not evaluated (data unavailable). No other adherence definitions were adapted.

In classifying patients, we aimed to group patients of similar disease severity over equal observation periods, limiting potential confounding by indication as much as possible. To do so, each patient was assigned an index date. For anti-TNF users, the index date was the date of anti-TNF initiation. For anti-TNF nonusers, the index date was the second consecutive visit with BASDAI + PGA ≥ 4, or where not applicable, the second visit within the 2 consecutive visits with highest mean BASDAI prior to Month 24; in the case of ≥ 1 pairs of consecutive visits with equal average BASDAI, the earliest pair was chosen. Classification of adherence to recommendations other than anti-TNF use was then done considering the period up to and including the index date only.

To analyze the validity of adherence groupings, an intermediate analysis was undertaken in which patients were stratified by anti-TNF use (yes/no) and the number of visits with "high disease activity" pre-index, defined as both BASDAI and PGA ≥ 4 at 0 visits, ≥ 1 nonconsecutive visits, 2 consecutive visits, or > 2 consecutive visits pre-index. Anti-TNF users and nonusers in each pre-index disease activity group were compared for significant differences on baseline disease severity markers, including baseline C-reactive protein (CRP), BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI), sacroiliitis, or spinal inflammation on radiograph, computed tomography (CT), or magnetic resonance imaging (MRI), peripheral arthritis, and CRP 1 visit pre-index using the chi-square test, Student t test, and ANOVA as appropriate. Anti-TNF users across pre-index disease activity groups were compared on positive anti-TNF response following the ASAS definition (i.e., 50% relative BASDAI change or absolute change of 2, on a 0–10 scale)[17] using the chi-square test.

In the main and sensitivity analyses (Table 2), patients were classified using 2 alternate definitions of adherence to anti-TNF recommendations (Table 3). In the main analysis, patients with high disease activity at 2 consecutive visits who received an anti-TNF agent on the second visit were classified as "adherent" users, i.e., timely anti-TNF use. In the sensitivity analysis, these patients were classified as nonadherent users, i.e., late anti-TNF use (Table 3). Descriptive statistics were produced to compare the characteristics and outcomes of patients by adherence group, as well as subsets where appropriate.

Effect of adherence classifications. Regression models were developed to estimate total costs, costs excluding anti-TNF ("nonbiologic costs"), and quality-adjusted life-years (QALY) across groups defined by adherence to anti-TNF recommendations, while controlling for adherence to other recommendations. All dependent variables were calculated over the 1 year following the patient's index date. To estimate QALY, SF-36 questionnaire data were converted into SF-6D health states and QALY were calculated using corresponding utility scores following the area under the curve method[18]. The primary independent variable in all models was adherence to

Table 1. Rheumatologist-proposed definitions of adherence* to ASAS recommendations[10].

ASAS Item	Adherence Definition
Physiotherapy**	Define "nonadherence" by satisfaction of 1 criterion (a): a. If by the 12-month followup visit, patient has had 0 visits to the physiotherapist
Extraarticular manifestations and comorbidities	Define "nonadherence" as by satisfaction of ≥ 1 of 5 criteria: a. If at a given study visit, a patient has a new diagnosis of uveitis AND has not had an ophthalmologist consult by the next study visit b. If at a given study visit, a patient has a new diagnosis of psoriasis AND has not had a dermatologist consult by the next study visit c. If at a given study visit, a patient has a new diagnosis of pustulosis AND has not had a dermatologist consult by the next study visit d. If at a given study visit, a patient has a new diagnosis of IBD AND has not had a gastroenterologist consult by the next study visit e. If at a given study visit, a patient has a new cardiovascular event and has not had a cardiologist consult by the next study visit
NSAID	Define "nonadherence" by satisfaction of ≥ 1 of 3 criteria: a. If patient received their first DMARD before their first NSAID b. If patient has diagnosis of renal insufficiency (i.e., creatinine clearance < 30 ml/min) and NSAID use is not interrupted within 15 days of that diagnosis (as assessed at next study visit) c. If patient has history of GI event other than dyspepsia and receives an NSAID or Cox inhibitor without a concomitant PPI
Glucocorticoids	Define "nonadherence" by satisfaction of 1 criterion (a): a. If at a given study visit, a patient is receiving oral prednisone or equivalent and has no history of uveitis, peripheral arthritis, or IBD
Disease-modifying antirheumatic drugs	Define "nonadherence" by satisfaction of ≥ 1 of 3 criteria: a. If patient has synovitis ≥ 3 at 2 consecutive visits and is not prescribed a DMARD at either of these visits b. If at a given study visit, a patient is receiving MTX and has no history of peripheral arthritis or psoriasis c. If at a given study visit, a patient is receiving SSZ and has no history of peripheral arthritis, IBD, or uveitis
Anti-TNF agents	Define "nonadherence" by satisfaction of ≥ 1 of 2 criteria: a. If at 2 consecutive study visits, patient has had at least 2 adequate therapeutic trials of NSAID (i.e., minimum 2 NSAID over a 4-week period in total since symptom onset), BASDAI is ≥ 4, PGA is ≥ 4, AND an anti-TNF agent has not been prescribed at the third visit b. If patient is receiving a biological agent other than anti-TNF† (EXCEPTION: patients with psoriatic arthritis may receive a biologic other than anti-TNF, but then cannot receive a concomitant anti-TNF)

* Originally defined in Reference 10 as "compliance". ** ASAS item is "Non-Pharmacological Therapy," but was defined in Reference 10 exclusively on the basis of physiotherapy. † No DESIR patients were receiving biological agents other than anti-TNF. ASAS: Assessment of Spondyloarthritis international Society; IBD: inflammatory bowel disease; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs; GI: gastrointestinal; PPI: proton pump inhibitor; MTX: methotrexate; SSZ: sulfasalazine; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; PGA: physician's global assessment; anti-TNF: antitumor necrosis factor; DESIR: Devenir des Spondylarthropathies Indifférenciées Récentes.

anti-TNF recommendations, alternately defined in the main and sensitivity analyses. Adherence to other ASAS recommendations (i.e., physiotherapy, nonbiologic drugs, specialist care, defined in Table 1) in the period up to and including the patient's index date were also tested as independent variables. Adherence to NSAID, glucocorticoid, and DMARD recommendations was tested as a single variable called "nonbiologic drug recommendations." Adherence to recommendations for specialist care for pustulosis and cardiac events was not examined because few patients were affected. Given the risk of confounding by indication, sociodemographic and clinical variables were tested, including baseline age, sex, education, profession, smoking ("yes" vs "no/don't know"), baseline CRP and CRP 1 visit pre-index, baseline sacroiliitis or spinal inflammation on radiograph, CT, or MRI, peripheral arthritis, marital status, and number of months while being treated with anti-TNF. BASDAI and BASFI scores were not included as independent variables because preliminary analyses suggested these were identified by adherence groupings.

Generalized linear regression models using the generalized estimating equation (GEE) and assuming γ-distribution with log link were used for costs outcomes, while linear models were used for the QALY outcome. In model development, independent variables were first tested in univariate models of each outcome and those significantly associated with outcomes at $p < 0.20$ were included in multivariate models. Multivariate model selection was then done in a backward stepwise manner, beginning with all independent variables selected and removing those not associated with the outcome at $p < 0.05$ to increase goodness-of-fit based on the QIC (goodness of fit statistic for GEE models)[19,20,21]. In all models, the reference group was adherent anti-TNF users. All analyses were performed using SAS 9.4.

RESULTS

Classification of adherence. A total of 469 patients met the ASAS criteria and were included in our analysis. Table 2 shows patients' clinical characteristics by anti-TNF use and timing of initiation relative to disease activity pre-index. Among patients who had 0 visits with high disease activity pre-index, anti-TNF users had significantly more baseline peripheral arthritis (63.0% vs 38.2%, $p = 0.015$), higher baseline BASDAI (3.4 ± 1.4 vs 2.5 ± 1.4, $p = 0.003$) and BASFI (3.3 ± 1.9 vs 1.4 ± 1.4, $p < 0.0001$), higher baseline CRP (17.0 ± 16.2 vs 5.4 ± 7.3, $p = 0.002$), and CRP 1 visit pre-index than anti-TNF nonusers. Among patients who had ≥ 1 more nonconsecutive visits with high disease activity

Table 2. Patient clinical characteristics by anti-TNF use and disease activity pre-index. Values are mean ± SD or n (%) unless otherwise specified.

Clinical Markers	0 Visits BASDAI and PGA ≥ 4 Pre-index			≥ 1 Nonconsecutive Visits BASDAI and PGA ≥ 4 Pre-index			2 Consecutive Visits BASDAI and PGA ≥ 4 Pre-index			> 2 Consecutive Visits BASDAI and PGA ≥ 4 Pre-index	
	Anti-TNF Use, n = 30	No Anti-TNF Use, n = 173	p	Anti-TNF Use, n = 85	No Anti-TNF Use, n = 82	p	Anti-TNF Use, n = 20	No Anti-TNF Use, n = 67	p	Anti-TNF Use, n = 29	No Anti-TNF Use, n = 0
Baseline BASDAI	3.4 ± 1.4	2.5 ± 1.4	0.003	5.6 ± 1.3	5.1 ± 1.6	0.005	6.5 ± 1.0	5.5 ± 1.6	0.002	5.7 ± 1.4	NA
Baseline BASFI	3.3 ± 1.9	1.4 ± 1.4	< 0.0001	4.0 ± 2.0	3.3 ± 2.1	0.030	5.3 ± 2.7	4.0 ± 2.4	0.029	4.6 ± 2.1	NA
Peripheral arthritis = 1	17 (63.0)	66 (38.2)	0.015	56 (69.1)	52 (63.4)	0.440	17 (85.0)	35 (54.7)	0.015	17 (70.8)	NA
Baseline sacroiliitis or spinal inflammation on radiograph, CT, or MRI	21 (77.8)	105 (60.7)	0.087	63 (77.8)	48 (58.5)	0.008	10 (50.0)	32 (50.0)	1.000	14 (58.3)	NA
Baseline CRP	17.0 ± 16.2	5.4 ± 7.3	0.002	20.0 ± 24.1	9.1 ± 12.7	0.001	9.3 ± 10.5	7.0 ± 10.7	0.463	10.2 ± 12.0	NA
CRP 1 visit prior to index date	14.8 ± 16.0	4.9 ± 6.8	0.004	18.9 ± 23.8	7.5 ± 10.7	0.001	9.4 ± 10.9	6.3 ± 7.6	0.327	5.6 ± 6.1	NA
Positive anti-TNF response	12 (44.4)	NA		47 (58.0)	NA		1 (5.0)*	NA		12 (50.0)	NA
Analytic strategy for main analysis	Anti-TNF use as adherent (“timely use”)	Anti-TNF nonuse as adherent (“no anti-TNF need”)		Anti-TNF use as adherent (“timely use”)	Anti-TNF nonuse as adherent (“no anti-TNF need”)		Anti-TNF use as adherent (“timely use”)	Anti-TNF nonuse as nonadherent (“unmet anti-TNF need”)		Anti-TNF use as nonadherent (“late use”)	NA
Analytic strategy for sensitivity analysis	Anti-TNF use as adherent (“timely use”)	Anti-TNF nonuse as adherent (“no anti-TNF need”)		Anti-TNF use as adherent (“timely use”)	Anti-TNF nonuse as adherent (“no anti-TNF need”)		Anti-TNF use as nonadherent (“late use”)	Anti-TNF nonuse as nonadherent (“unmet anti-TNF need”)		Class anti-TNF use as nonadherent (“late use”)	NA

* Positive anti-TNF response in this group is significantly different from that of all other anti-TNF user groups; all pairwise comparisons at $p < 0.003$. Anti-TNF: antitumor necrosis factor; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; PGA: physician’s global assessment; BASFI: Bath Ankylosing Spondylitis Functional Index; CT: computed tomography; MRI: magnetic resonance imaging; CRP: C-reactive protein; NA: not applicable.

Table 3. Alternate definitions used to classify patients based on adherence to anti-TNF recommendations.

Disease Activity Pre-index	No Anti-TNF Use	Anti-TNF Use
Main analysis		
0 visits, ≥ 1 nonconsecutive visits, or ≤ 2 consecutive visits BASDAI and PGA ≥ 4	Adherent nonuser (no anti-TNF need)	Adherent user (timely anti-TNF use)
> 2 consecutive visits BASDAI and PGA ≥ 4	Nonadherent nonuser (unmet anti-TNF need)	Nonadherent user (late anti-TNF use)
Sensitivity analysis		
0 or ≥ 1 nonconsecutive visits BASDAI and PGA ≥ 4	Adherent nonuser (no anti-TNF need)	Adherent user (timely anti-TNF use)
≥ 2 consecutive visits BASDAI and PGA ≥ 4	Nonadherent nonuser (unmet anti-TNF need)	Nonadherent user (late anti-TNF use)

Anti-TNF: antitumor necrosis factor; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; PGA: physician's global assessment.

pre-index, anti-TNF users had significantly higher baseline BASDAI, BASFI, and CRP compared with nonusers (Table 2) and significantly more baseline sacroiliitis/spinal inflammation visible on radiographs, CT, or MRI (77.8% vs 58.5%, p = 0.008). In both the main and sensitivity analyses, patients with 0 or ≥ 1 more nonconsecutive visits with high disease activity pre-index were classified as adherent users (timely use).

Among patients who had 2 consecutive visits with high disease activity pre-index, anti-TNF users had significantly higher baseline BASDAI (6.5 ± 1.0 vs 5.5 ± 1.6, p = 0.002) and BASFI (5.3 ± 2.7 vs 4.0 ± 2.4, p = 0.029) and more baseline peripheral arthritis (85.0% vs 54.7%, p = 0.015) compared with anti-TNF nonusers (Table 2). Also, the 20 anti-TNF users with 2 consecutive visits and high disease activity had significantly lower positive response to anti-TNF therapy compared with anti-TNF nonusers with 0 visits (44.4% vs 5.0%, p = 0.003), ≥ 1 visits (58.0% vs 5.0%, p = 0.0001), or ≥ 2 visits of high disease activity pre-index (50.0% vs. 5%, p = 0.002; Table 2). The 20 anti-TNF users with 2 consecutive visits of high disease activity pre-index were classified as adherent users (timely anti-TNF use) in the main analysis, and as nonadherent users (late anti-TNF use) in the sensitivity analysis.

Patients classified as adherent nonusers are described in Appendix 1. Table 4 shows clinical characteristics, cost outcomes, and health status of patients classified as adherent users (timely anti-TNF use), nonadherent users (late anti-TNF use), and nonadherent nonusers (unmet anti-TNF need) in the main analysis and sensitivity analysis. A subset analysis of the 20 anti-TNF users classified as adherent users in the main analysis and as nonadherent users in the sensitivity analysis indicated these patients had the lowest health status post-index (0.49 ± 0.13), as well as the highest total costs (19,586 ± 8263), nonbiologic costs (7987 ± 6939), nonbiologic health resource use costs (3500 ± 3127), and productivity loss costs (4487 ± 7196).

Across all groups defined in the main analysis, a total of 208 patients (44.3%) were treatment nonadherent to physiotherapy recommendations, i.e., did not receive ≥ 1 physiotherapy visit in the first year. A total of 39 patients (8.3%) had treatment nonadherent to 1 or more nonbiologic drug recommendations. Nonadherence to specialist care for uveitis, psoriasis, or inflammatory bowel disease was infrequently observed (Table 4 and Supplementary Table 1).

Cost outcomes. Table 5 shows the multivariate models of cost outcomes produced in the main and sensitivity analyses. In the main analysis, nonadherent users (late anti-TNF use) and adherent users (timely anti-TNF use) showed no significant differences in total costs (RR 0.86, 95% CI 0.54–1.36, p = 0.516) or nonbiologic costs (RR 0.72, 95% CI 0.44–1.18, p = 0.187). Relative to adherent users, nonadherent nonusers (unmet anti-TNF need) had significantly lower total costs (RR 0.11, 95% CI 0.08–0.15, p < 0.0001) and significantly lower nonbiologic costs (RR 0.56, 95% CI 0.39–0.79, p < 0.001). In the main analysis, age and female sex were associated with increased total and nonbiologic costs; being unmarried was associated with decreased nonbiologic costs (Table 5). Other independent variables tested in univariate models, including nonadherence to other recommendations, were not significant in multivariate models in the main or sensitivity analyses.

In the sensitivity analysis, nonadherent users (late anti-TNF use) and adherent users (timely anti-TNF use) showed no significant differences in total costs (RR 0.94, 95% CI 0.65–1.37, p = 0.753). However, nonadherent, i.e., "late," anti-TNF users had significantly increased nonbiologic costs (RR 1.58, 95% CI 1.06–2.36, p = 0.026) relative to adherent users. Relative to adherent users (timely anti-TNF use), nonadherent nonusers (unmet anti-TNF need) had significantly lower total costs (RR 0.11, 95% CI 0.08–0.15, p < 0.0001) and significantly lower nonbiologic costs (RR 0.68, 95% CI 0.48–0.98, p = 0.036).

Health outcomes. Table 6 shows the multivariate model of QALY outcomes in the main and sensitivity analyses. In the main analysis, there were no significant differences in health

Table 4. Characteristics and outcomes of patients defined as adherent users, nonadherent users, and nonadherent nonusers. Values are mean ± SD or n (%).

Characteristics	Adherence Classification 1: Main Analysis			Adherence Classification 2: Sensitivity Analysis		
	Adherent User: Timely Anti-TNF Use, n = 135	Nonadherent User: Late Anti-TNF Use, n = 29	Nonadherent Nonuser: Unmet Anti-TNF Need, n = 67	Adherent User: Timely Anti-TNF Use, n = 115	Nonadherent User: Late Anti-TNF Use, n = 49	Nonadherent Nonuser: Unmet Anti-TNF Need, n = 67
Baseline age, yrs	33.8 ± 9.7	33.8 ± 7.5	33.7 ± 7.9	33.5 ± 10.0	34.7 ± 7.8	33.7 ± 7.9
Male	64 (50.0)	9 (37.5)	24 (37.5)	57 (52.8)	16 (36.4)	24 (37.5)
Postsecondary education	65 (50.8)	11 (45.8)	34 (53.1)	58 (53.7)	18 (40.9)	34 (53.1)
Married	74 (57.8)	18 (75.0)	43 (67.2)	59 (54.6)	33 (75.0)	43 (67.2)
Academic or executive-level occupation	18 (14.1)	4 (16.7)	11 (17.2)	16 (14.8)	6 (13.6)	11 (17.2)
Peripheral arthritis	90 (70.3)	17 (70.8)	35 (54.7)	73 (67.6)	34 (77.3)	35 (54.7)
Baseline disease duration	1.6 ± 0.9	1.6 ± 1.0	1.5 ± 0.9	1.6 ± 0.8	1.6 ± 0.9	1.5 ± 0.9
Baseline sacroiliitis or spinal inflammation on radiograph, CT, or MRI	94 (73.4)	14 (58.3)	32 (50.0)	84 (77.8)	24 (54.5)	32 (50.0)
Baseline CRP	17.8 ± 21.2	10.2 ± 12.0	7.0 ± 10.7	19.2 ± 22.2	9.8 ± 11.2	7.0 ± 10.7
Baseline HLA-B27–positive	97 (75.8)	20 (83.3)	47 (73.4)	81 (75.0)	36 (81.8)	47 (73.4)
No comorbidities at baseline	99 (77.3)	19 (79.2)	46 (71.9)	81 (75.0)	37 (84.1)	46 (71.9)
Mean BASDAI pre-index	53.6 ± 17.4	64.5 ± 10.5	58.2 ± 11.0	51.3 ± 17.7	64.5 ± 10.3	58.2 ± 11.0
Mean BASFI pre-index	39.5 ± 20.8	48.6 ± 21.0	40.9 ± 21.4	37.0 ± 19.8	50.0 ± 21.0	40.9 ± 21.4
Baseline physician's assessment of disease activity	3.4 ± 2.7	3.9 ± 2.4	5.5 ± 1.3	2.8 ± 2.5	5.0 ± 2.3	5.5 ± 1.3
Nonadherent on physiotherapy recommendations	48 (37.5)	12 (50.0)	21 (32.8)	42 (38.9)	18 (40.9)	21 (32.8)
Nonadherent on nonbiologic drug recommendations	15 (11.7)	5 (20.8)	3 (4.7)	13 (12.0)	7 (15.9)	3 (4.7)
Nonadherent on specialist care for uveitis	0 (0)	1 (4.2)	0 (0)	0 (0)	1 (2.3)	0 (0)
Nonadherent on specialist care for psoriasis	7 (5.5)	0 (0)	2 (3.1)	7 (6.5)	0 (0)	2 (3.1)
Nonadherent on specialist care for IBD	1 (0.8)	0 (0)	0 (0)	1 (0.9)	0 (0)	0 (0)
Positive response to anti-TNF therapy	60 (46.9)	12 (50.0)	NA	59 (54.6)	13 (29.5)	NA
Time on anti-TNF, mos, 1 yr from index	10.3 ± 3.3	10.0 ± 3.9	NA	10.5 ± 3.2	9.7 ± 3.7	NA
QALY	0.586 ± 0.155	0.595 ± 0.122	0.572 ± 0.135	0.604 ± 0.153	0.548 ± 0.136	0.572 ± 0.135
Total costs	16,061 ± 7686	14,281 ± 8529	2092 ± 2880	15,408 ± 7433	16,692 ± 8730	2092 ± 2880
Nonbiologic costs	3341 ± 4835	2350 ± 2607	2092 ± 2880	2481 ± 3796	4913 ± 5742	2092 ± 2880
Nonbiologic HR costs	2014 ± 2384	1717 ± 1689	1265 ± 1392	1739 ± 2127	2527 ± 2579	1265 ± 1392
Work productivity costs	1327 ± 4215	633 ± 1169	827 ± 2234	742 ± 3112	2385 ± 5232	827 ± 2234

Anti-TNF: antitumor necrosis factor; CT: computed tomography; MRI: magnetic resonance imaging; CRP: C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; IBD: inflammatory bowel disease; QALY: quality-adjusted life-years; HR: health resource; NA: not applicable.

status between adherent users (timely anti-TNF use) and nonadherent users (late anti-TNF use), or between adherent users and nonadherent nonusers (unmet anti-TNF need). Baseline postsecondary education was associated with a significantly higher health status, while smoking and female sex was associated with significantly lower health status (Table 6). Other independent variables tested in the main analysis, including nonadherence to other recommendations, were not significant in multivariate models. In the sensitivity analysis, nonadherent anti-TNF users (late anti-TNF use) had significantly lower health status relative to adherent users (timely use; –0.06, 95% CI –0.09 to –0.03, p = 0.0005). Nonadherent nonusers (unmet anti-TNF need) also had significantly lower health status than adherent "timely" users (–0.04, 95% CI –0.07 to –0.01, p = 0.016).

DISCUSSION

The ASAS recommendations advise that anti-TNF therapy should be prescribed to patients with 4 or more weeks of high disease activity[1]. To measure adherence to these recommendations using observational data over 6-month intervals, a definition of adherence must specify the number of consecutive visits with high disease activity that should be interpreted as evidence of sustained activity over 4 weeks. A recent classification system proposed 1 such definition[10], which we analyzed using DESIR data to compare patient

Table 5. Models of effect of adherence classifications on cost outcomes.

Outcome	Variable	EST (SE)	EST (95% CI)	p	RR* (95% CI)
Adherence classification 1: main analysis					
Total cost	Age at baseline, yr increase	0.02 (0.01)	0.02 (0.01–0.04)	< 0.0001	1.03 (1.01–1.04)
	Female vs male	0.52 (0.10)	0.52 (0.32–0.72)	< 0.0001	1.69 (1.38–2.06)
	Baseline smoking status, yes vs no	–0.05 (0.10)	–0.05 (–0.25 to 0.16)	0.6605	0.96 (0.78–1.17)
	Adherent nonuser vs adherent user	–2.75 (0.12)	–2.75 (–2.98 to –2.52)	< 0.0001	0.06 (0.05–0.08)
	Nonadherent nonuser vs adherent user	–2.24 (0.17)	–2.24 (–2.57 to –1.92)	< 0.0001	0.11 (0.08–0.15)
	Nonadherent user vs adherent user	–0.15 (0.24)	–0.15 (–0.61 to 0.31)	0.5156	0.86 (0.54–1.36)
Nonbiologic costs	Age at baseline, yr increase	0.03 (0.01)	0.03 (0.02–0.05)	< 0.0001	1.03 (1.02–1.05)
	Female vs male	0.64 (0.11)	0.64 (0.43–0.85)	< 0.0001	1.90 (1.53–2.35)
	Unmarried vs married	–0.30 (0.12)	–0.30 (–0.54 to –0.06)	0.0131	0.74 (0.58–0.94)
	Baseline smoking status, yes vs no	0.09 (0.11)	0.09 (–0.13 to 0.31)	0.4256	1.09 (0.88–1.36)
	Adherent nonuser vs adherent user	–1.05 (0.13)	–1.05 (–1.30 to –0.80)	< 0.0001	0.35 (0.27–0.45)
	Nonadherent nonuser vs adherent user	–0.59 (0.18)	–0.59 (–0.94 to –0.24)	0.001	0.56 (0.39–0.79)
	Nonadherent user vs adherent user	–0.33 (0.25)	–0.33 (–0.83 to 0.16)	0.1873	0.72 (0.44–1.18)
Adherence classification 2: sensitivity analysis					
Total cost	Age at baseline, yr increase	0.02 (0.01)	0.02 (0.01–0.04)	< 0.0001	1.03 (1.01–1.04)
	Female vs male	0.52 (0.10)	0.52 (0.32–0.72)	< 0.0001	1.69 (1.38–2.06)
	Baseline smoking status, yes vs no	–0.04 (0.10)	–0.04 (–0.25 to 0.16)	0.6704	0.96 (0.78–1.17)
	Adherent nonuser vs adherent user	–2.74 (0.12)	–2.74 (–2.99 to –2.50)	< 0.0001	0.06 (0.05–0.08)
	Nonadherent nonuser vs adherent user	–2.24 (0.17)	–2.24 (–2.57 to –1.90)	< 0.0001	0.11 (0.08–0.15)
	Nonadherent user vs adherent user	–0.06 (0.19)	–0.06 (–0.43 to 0.31)	0.753	0.94 (0.65–1.37)
Nonbiologic costs	Age at baseline, yr increase	0.03 (0.01)	0.03 (0.02–0.05)	< 0.0001	1.03 (1.02–1.05)
	Female vs male	0.61 (0.11)	0.61 (0.39–0.82)	< 0.0001	1.84 (1.48–2.28)
	Unmarried vs married	–0.29 (0.12)	–0.29 (–0.52 to –0.05)	0.0174	0.75 (0.59–0.95)
	Baseline smoking status, yes vs no	0.07 (0.11)	0.07 (–0.15 to 0.29)	0.5588	1.07 (0.86–1.33)
	Adherent nonuser vs adherent user	–0.85 (0.13)	–0.85 (–1.11 to –0.59)	< 0.0001	0.43 (0.33–0.55)
	Nonadherent nonuser vs adherent user	–0.38 (0.18)	–0.38 (–0.74 to –0.03)	0.0359	0.68 (0.48–0.98)
	Nonadherent user vs adherent user	0.46 (0.21)	0.46 (0.05–0.86)	0.0263	1.58 (1.06–2.36)

* Rate ratio obtained by [exp (EST)]. Adherent nonuser: no anti-TNF need. Nonadherent nonuser: unmet anti-TNF need. Adherent user: timely anti-TNF use. Nonadherent user: late anti-TNF use. EST: estimate; anti-TNF: antitumor necrosis factor.

Table 6. Models of effect of adherence classification on QALY outcome.

Outcome	Variable	EST (SE)	EST (95% CI)	p
Adherence classification 1: main analysis				
QALY	Postsecondary education vs none	0.04 (0.01)	0.04 (0.02–0.06)	< 0.0001
	Female vs male	–0.03 (0.01)	–0.03 (–0.05 to –0.01)	0.001
	Baseline smoking status, yes vs no	–0.04 (0.01)	–0.04 (–0.06 to –0.02)	< 0.0001
	Adherent nonuser vs adherent user	0.07 (0.01)	0.07 (0.04–0.09)	< 0.0001
	Nonadherent nonuser vs adherent user	–0.02 (0.02)	–0.02 (–0.05 to 0.01)	0.1444
	Nonadherent user vs adherent user	–0.01 (0.02)	–0.01 (–0.06 to 0.03)	0.4962
Adherence classification 2: sensitivity analysis				
QALY	Postsecondary education vs none	0.04 (0.01)	0.04 (0.02–0.05)	0.0002
	Female vs male	–0.03 (0.01)	–0.03 (–0.04 to –0.01)	0.0025
	Baseline smoking status, yes vs no	–0.04 (0.01)	–0.04 (–0.05 to –0.02)	0.0002
	Adherent nonuser vs adherent user	0.05 (0.01)	0.05 (0.03–0.07)	< 0.0001
	Nonadherent nonuser vs adherent user	–0.04 (0.02)	–0.04 (–0.07 to –0.01)	0.0164
	Nonadherent user vs adherent user	–0.06 (0.02)	–0.06 (–0.09 to –0.03)	0.0005

Adherent nonuser: no Anti-TNF need. Nonadherent nonuser: unmet anti-TNF need. Adherent user: timely anti-TNF use. Nonadherent user: late anti-TNF use. QALY: quality-adjusted life-years; EST: estimate; anti-TNF: antitumor necrosis factor.

characteristics and outcomes across groups defined by anti-TNF use and high disease activity (BASDAI + PGA ≥ 4) over 6-month intervals.

Because rheumatologists proposed that "early" anti-TNF users are best defined as adherent[10], a goal of our study was to evaluate the validity of classifying as adherent all anti-TNF users who received an anti-TNF before experiencing high disease activity at 2 consecutive visits. Comparing anti-TNF

users and nonusers within strata of patients with 0 or ≥ 1 nonconsecutive visits of high disease activity pre-index, we found that anti-TNF users had significantly higher disease activity than anti-TNF nonusers. This supports rheumatologists' proposal to classify early anti-TNF users as adherent. However, its failure to distinguish premature anti-TNF use, and its excess costs, is a crucial flaw of the proposed classification system.

We also evaluated the validity of classifying as adherent patients who experienced high disease activity at 2 consecutive visits, but who received an anti-TNF on the second visit. Importantly, the 2-consecutive visit cutoff permits patients to experience up to 6 months of high disease activity before anti-TNF initiation, which could result in classifying as adherent some patients whose anti-TNF initiation might otherwise be considered late. In our intermediate analysis, we found that the 20 anti-TNF users who experienced high disease activity at exactly 2 consecutive visits pre-index had the lowest rate of positive anti-TNF response of all anti-TNF users. We chose to classify these 20 patients as adherent users in the main analysis, but as nonadherent "late" users in the sensitivity analysis. A subset analysis suggested that these 20 patients had poorer outcomes compared to the overall groups defined as nonadherent users in the main and sensitivity analyses. These findings suggest that the difference in results between the main and sensitivity analyses was driven by these 20 patients, raising the question of whether anti-TNF initiation among these patients was indeed later than optimal.

The discrepancy between the main and sensitivity analyses here suggests that the effect of adherence to anti-TNF recommendations is highly sensitive to the definition of adherence used. In the main analysis, with patients permitted up to 2 consecutive visits with high disease activity, no benefit of adherence was apparent. However, in a sensitivity analysis allowing only 0 or ≥ 1 nonconsecutive visits with high disease activity, specific benefits of adherence were demonstrated: adherent "timely" anti-TNF users had significantly lower nonbiologic costs compared with nonadherent "late" anti-TNF users, and they had significantly better health status than both nonadherent "late" anti-TNF users and nonadherent nonusers. We interpret the findings of the sensitivity analysis as preliminary evidence that adherence to anti-TNF use recommendations may reduce nonbiologic costs and increase quality of life among patients who warrant anti-TNF therapy. The findings of our main analysis suggest that the previously proposed definition of adherence to anti-TNF recommendations[10] has the potential to misclassify as "adherent" some anti-TNF users whose therapy initiation may have been later than optimal.

Our study has limitations. For one, we required patients to receive an anti-TNF sooner than proposed by rheumatologists[10]. While, *a priori*, this raised the concern that some patients would be prematurely classified as "nonadherent," the results of the sensitivity analysis suggested that the opposite concern (i.e., misclassification of late users as adherent) was more pertinent. Also, we could not explain why patients did not receive an anti-TNF agent, though possible reasons include patient refusal, contraindication to treatment, or lack of "positive expert opinion." Importantly, although ASAS cites positive expert opinion as a requirement for anti-TNF use, the criteria that should inform the expert's opinion are not defined quantitatively. This is problematic in developing a method to detect positive expert opinion using observational data. We used PGA as a proxy for positive expert opinion because this reflects the physician's opinion on disease severity. Given the inclusion of this proxy, results pertaining to patients classified as nonadherent nonusers should be understood as the consequences of not receiving an anti-TNF agent for any reason, despite having high disease activity as assessed by the rheumatologist. However, the PGA variable may not identify all reasons for a lack of positive expert opinion; consequently, no anti-TNF nonusers can be classified with certainty as being "nonadherent" to recommendations using the system analyzed here. For the purpose of further research, the description of "positive expert opinion" should be elaborated by ASAS because this undefined criterion acts as a strong barrier to measuring adherence.

As in all studies using observational data to compare patients on the basis of treatment, the results of our study are limited by potential confounding by indication. We note that disease severity markers, including BASDAI, BASFI, CRP, and baseline sacroiliitis/spinal inflammation, were insignificant in multivariate models, meaning disease severity was effectively identified by adherence groupings. Nonetheless, possible residual confounding by indication should be considered when interpreting our findings. As well, radiographic progression in SpA occurs slowly[22], and our study's limited 1-year observation period means that the full effect of anti-TNF therapy on longterm outcomes has not been identified. Because placebo-controlled studies of anti-TNF use among patients with axSpA have generally lasted only 12–16 weeks[23,24], our study provides comparatively longterm data on the effect of anti-TNF agents. However, longer-term assessment of anti-TNF users will be needed to understand the effect of adherence over time.

Our study has examined the measurement of adherence to the ASAS anti-TNF use recommendations. The results show that the effect of adherence is highly sensitive to the definition of adherence used. A classification system proposed for defining adherence[10] has substantial limitations, including failure to define premature anti-TNF use and to distinguish anti-TNF nonusers who are adherent to recommendations despite high disease activity. While benefits of adherence to anti-TNF use recommendations were not demonstrated when using 1 definition of adherence, benefits were observed when using an alternate definition. This discrepancy highlights the need to refine and validate

methods to measure adherence to axSpA anti-TNF recommendations and its corresponding effect.

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APPENDIX 1. Characteristics of adherent nonusers (n = 255). Values are mean ± SD or n (%).

Patient Characteristics	Values
Baseline age, yrs	32.3 ± 8.3
Male	142 (55.7)
Postsecondary education	180 (70.6)
Married	162 (63.5)
Academic or executive-level occupation	76 (29.8)
Peripheral arthritis	118 (46.3)
Baseline disease duration	1.5 ± 0.9
Baseline sacroiliitis or spinal inflammation on radiograph, CT, or MRI	153 (60.0)
Baseline CRP	6.7 ± 9.6
Baseline HLA-B27–positive	230 (90.2)
No comorbidities at baseline	203 (79.6)
Mean BASDAI pre-index	3.3 ± 1.8
Mean BASFI pre-index	1.8 ± 1.7
Baseline physician's assessment of disease activity	2.9 ± 1.9
Nonadherent on physiotherapy recommendations	127 (49.8)
Nonadherent on nonbiologic drug recommendations	16 (6.3)
Nonadherent on specialist care for uveitis	0 (0)
Nonadherent on specialist care for psoriasis	9 (3.5)
Nonadherent on specialist care for IBD	2 (0.8)
Positive response to anti-TNF therapy	NA
Time on anti-TNF, mos, 1 yr from index	NA
QALY	0.674 ± 0.156
Total costs (2013 euros)	1108 ± 1848
Nonbiologic costs (2013 euros)	1108 ± 1848
Nonbiologic HR costs	898 ± 1391
Work productivity costs	214 ± 1070

CT: computed tomography; MRI: magnetic resonance imaging; CRP: C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; anti-TNF: antitumor necrosis factor; QALY: quality-adjusted life-years; HR: health resource; NA: not applicable.