Predictors of Loss of Remission and Disease Flares in Patients with Axial Spondyloarthritis Receiving Antitumor Necrosis Factor Treatment: A Retrospective Study

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ABSTRACT. ***Objective.*** The aim of this study was to evaluate rate and predictive factors of loss of remission and disease flare in patients with axial spondyloarthritis (axSpA) receiving antitumor necrosis factor (anti-TNF) treatment.

Methods. In this retrospective multicenter study, patients with axSpA, according to the Assessment of Spondyloarthritis international Society (ASAS) criteria, treated with adalimumab, etanercept, or infliximab with a minimum followup of 12 months and satisfying the ASAS partial remission criteria and/or Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease were studied. Disease flare was defined as a Bath Ankylosing Spondylitis Disease Activity Index score > 4.5 or ASDAS score > 2.5 on at least 1 occasion.

Results. One hundred seventy-four patients with axSpA were studied. After a median [interquartile range (IQR)] followup of 4 years (2–6), 37 patients (21.2%) experienced a loss of remission and 28 (16.1% of the whole study group) a disease flare. Median (IQR) duration of remission in patients who lost this status was 1 year (0.625–2). Higher median erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values, continuous nonsteroidal antiinflammatory drug (NSAID) use, and an ASDAS-CRP ≥ 0.8 during the remission period were significantly associated with both loss of remission and disease flare. At the multivariate analysis, continuous NSAID intake (OR 4.05, 95% CI 1.4–11.74, p = 0.010) and ESR > 15 (OR 2.90, 95% CI 1.23–6.82, p = 0.015) were the only factors predictive of disease reactivation.

Conclusion. In this study, loss of remission and disease flares occurred, respectively, in about 21% and 16% of the patients with axSpA who achieved a state of remission while receiving anti-TNF therapy. Residual disease activity was associated with disease reactivation. (J Rheumatol First Release June 1 2016; doi:10.3899/jrheum.160363)

Key Indexing Terms:
AXIAL SPONDYLOARTHRITIS REMISSION ANTI-TNF-α DRUGS DISEASE FLARES

The spondyloarthritides (SpA) are a group of chronic inflammatory diseases that affect both the axial and peripheral skeleton. The Assessment of SpondyloArthritis international Society (ASAS) has validated classification criteria for axial SpA (axSpA)[1] that include both nonradiographic axSpA (nr-axSpA) and ankylosing spondylitis (AS). Patients with

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nr-axSpA and AS have comparable but not identical clinical manifestations and burdens of disease, which often require chronic treatment.

Tumor necrosis factor-α (TNF-α) antagonists infliximab (IFX), etanercept (ETN), and adalimumab (ADA) have proven to be effective in controlling the symptoms and signs of axSpA in specific clinical trials[2,3,4,5]. In addition, several observational studies showed that a condition of low disease activity or remission is achievable in the majority of patients treated with anti-TNF-α in a clinical practice setting[6,7]. In these studies, remission was defined according to the ASAS partial remission (PR) criteria[8], which does not differentiate between deep remission and low disease activity. The ASAS validated the Ankylosing Spondylitis Disease Activity Score (ASDAS), a new composite index for the assessment of disease activity in axSpA[9]. An ASDAS < 1.3 defines patients with inactive disease[10]. In clinical trials, PR can be achieved in about 20%–40% of patients with AS and in 15%–25% of patients with nr-axSpA treated with anti-TNF-α drugs. A state of inactive disease as defined by the ASDAS can be achieved in a similar rate of cases (about 25%–30%) in both forms of axSpA[4,11,12].

To the best of our knowledge, few studies have investigated whether a status of PR or ASDAS inactive disease may be lost because of an increase in disease activity despite continuous therapy with anti-TNF-α, and few have studied which clinical/laboratory characteristics may predict these disease reactivations. While the loss of PR or ASDAS states of inactive disease is easily defined, an agreed-upon definition of flare is still a matter of debate. A study has suggested that a Bath AS Disease Activity Index (BASDAI)[13] and an ASDAS-C-reactive protein (CRP) values > 4.5 and 2.5, respectively, might be indicative of disease flare[14]. In other studies, 2 patterns of self-reported flare have been described: localized (or minor) and generalized (or major)[15,16]. Obviously, a shared validated definition of disease flare for axSpA is needed.

The objectives of our study were to investigate the rate of patients with axSpA in remission treated with anti-TNF-α therapy who experienced a reactivation of their disease, and to look into the factors predictive of loss of remission and flare.

MATERIALS AND METHODS

Study design. Ours was a retrospective study conducted in 6 Italian tertiary referral rheumatology centers involved in clinical research on axSpA. In these centers, efficacy of treatment and safety data of patients with SpA taking biologics are regularly assessed and recorded at each visit. For the purpose of our study, the data of the patients with a diagnosis of axSpA (ASAS criteria)[1] were evaluated, provided that the patients had given their written consent according to the Declaration of Helsinki. The study was approved by the local ethics committees.

Patient selection. The data of the patients with axSpA treated with ADA, ETN, and IFX between June 2004 and May 2014 and with a followup of at least 12 months were analyzed. The study group was composed of the patients satisfying the PR criteria[8] or the ASDAS state of inactive disease[9,10] for at least 2 consecutive followup visits. The ASDAS was calculated using an online calculator (www.asas-group.org).

Therapy. Anti-TNF-α drugs were given following the standard administration rules. More precisely, ADA dose was 40 mg every other week subcutaneously, ETN 25 mg twice/weekly or 50 mg/weekly subcutaneously, and IFX 3–5 mg/kg at weeks 0, 2, and 6, and then every 6–8 weeks intravenously. The treating physician, however, could increase or decrease doses or change schedules when warranted.

Data collection. Patients' data were collected at baseline and at the followup visits, which were usually performed every 3–4 months. The general data included age, sex, diagnosis (nr-axSpA and AS), disease duration, presence of extraarticular manifestations (i.e., uveitis, inflammatory bowel disease, psoriasis), and current comorbidities. The disease data encompassed the Bath AS Metrology Index (BASMI)[17], BASDAI, Bath AS Functional Index (BASFI)[18], patient's global disease activity on a 0–100 mm visual analog scale (VAS), physician's global disease activity on a 0–100 mm VAS, number of swollen (out of 66) and tender (out of 68) joints, presence of dactylitis and enthesitis, degree of radiographic sacroiliitis according to the New York criteria[19], erythrocyte sedimentation rate (ESR; mm/h), and CRP (mg/dl).

The discontinuation reasons were classified as inefficacy, adverse events, or other. Details of past (before anti-TNF-α therapy) and current antirheumatic treatments, such as synthetic disease-modifying antirheumatic drugs, corticosteroids, nonsteroidal antiinflammatory drugs (NSAID), or analgesics, were also recorded.

Definition of loss of remission and flare. Loss of PR and of the state of inactive disease was defined as a lack of the PR criteria or ASDAS ≥ 1.3, respectively. Flare was defined as BASDAI score > 4.5 or ASDAS-CRP > 2.5 on at least 1 occasion[14].

The association of disease reactivation with the main demographic and clinical variables was studied. For this purpose, the variables of interest were categorized as follows: ESR low ≤ 15 or high > 15 mm/h, CRP low < 0.5 or high ≥ 0.5 mg/dl, and ASDAS < 0.8 or ≥ 0.8 (during remission period). The cutoff value of 0.8 for the ASDAS was arbitrarily chosen to define a state of deep remission.

Statistical analysis. After testing for normal distribution of data, descriptive results were reported as mean (SD) or median [interquartile range (IQR)] for continuous variables, or number (percentages) for categorical ones.

The probability of disease reactivation was analyzed using both univariate and multivariate analysis (logistic regression analysis). For these analyses, the mean values of the measures of disease activity recorded during the remission period were used.

For continuous variables, the significance of the differences was determined using the Student t test for unpaired data for variables normally distributed and the Mann-Whitney U test for unpaired samples for nonnormally distributed variables. Categorical variables were compared by the chi-square test or Fisher's exact test.

Kaplan-Meier (KM) curves were plotted to determine the rates of disease reactivation during treatment with ADA, ETN, or IFX. In KM curves calculation, we entered time until the subject was "censored" or the "event" occurred. The differences between curves were determined by the log-rank (Mantel-Cox) test.

All the statistical tests were 2-sided at the 5% level and performed using SPSS software (version 17.0; SPSS Inc.).

RESULTS

From June 2004 to May 2014, 174 of the 312 patients with axSpA treated with IFX, ADA, and ETN (152 AS, 22 nr-axSpA) reached a state of remission (defined as ASAS PR or ASDAS < 1.3) for at least 2 consecutive visits. Overall rate of drug discontinuation was 9.2% because of the lack of efficacy, loss of efficacy, and other reasons. Their male:female rate was 133:41, mean (SD) age 43.2 years

(12.7), and median (IQR) disease duration 7 years (3–14). More than half of the patients (about 59%) were receiving IFX. Table 1 shows all of the demographic, clinical, and laboratory features of this patient group.

After a median (IQR) followup of 4 years (2–6), 37 (21.2%) of the 174 patients had experienced a loss of remission and 28 (16.1% of the whole study group) had had a disease flare (BASDAI > 4.5 and/or ASDAS-CRP > 2.5). Median (IQR) duration of remission in the patients who experienced loss of remission was 1 year (0.625–2). The KM curve for loss of remission during treatment with anti-TNF-α in the 174 patients is shown in Figure 1. The difference in loss of response among ADA, ETN, and IFX is depicted in Figure 2. The log-rank test comparing the 3 curves showed that the probability of loss of remission with ADA, ETN, or IFX was not significantly different among these anti-TNF-α drugs. We did not find any statistically significant differences between patients with nr-axSpA and patients with AS regarding the probability of the loss of remission or of a disease flare.

Table 1. Demographic, clinical, and laboratory features of the patients with axSpA (n = 174) in remission and under treatment with TNF-α blockers. The measures of disease activity are the median values of the remission period. Values are median (IQR) or n (%) unless otherwise specified.

Variables	Values
Male/female, n	133/41
Age, yrs, mean (SD)	43.2 (12.7)
Disease duration, yrs	7 (3–14)
Presence of HLA-B27	122 (70.1)
CRP, mg/dl	0.3 (0.1–0.5)
ESR, mm/h	9 (4–13.75)
BASDAI	1.6 (0.9–2.4)
BASMI	2 (0–3)
BASFI	1.5 (0.7–2.4)
PtGA, cm	1.2 (0.5–2)
VAS physician, cm	0.5 (0–1.5)
VAS back pain, cm	1.3 (0.4–2)
ASDAS-CRP	1.1 (0.6–1.5)
Presence of grade IV sacroiliitis	44 (25.2)
Presence of psoriasis	18 (10.3)
Presence of IBD	20 (11.4)
Presence of uveitis	23 (13.1)
Therapy	
NSAID, continuous	21 (12.1)
sDMARD	25 (14.3)
IFX	102 (58.6)
ADA	25 (14.3)
ETN	47 (27.1)

axSpA: axial spondyloarthritis; TNF-α: tumor necrosis factor-α; IQR: interquartile range; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; PtGA: patient's global assessment; VAS: visual analog scale; ASDAS: Ankylosing Spondylitis Disease Activity Score; IBD: inflammatory bowel disease; NSAID: nonsteroidal antiinflammatory drugs; sDMARD: synthetic disease-modifying antirheumatic drugs; IFX: infliximab; ADA: adalimumab; ETN: etanercept.

The results yielded by descriptive statistic aimed at identifying which factors were significantly associated with both loss of remission and disease flare are shown in Table 2. Median values of ESR and CRP, continuous NSAID intake, and ASDAS-CRP value ≥ 0.8 were significantly related with both loss of remission and disease flare. Of these 4 factors, only the continuous NSAID intake was independently associated with both loss of remission and disease flare at the multivariate analysis (Table 3). In our analysis, ESR was also significantly indicative of these events when using the cutoff value of 15 mm/h.

DISCUSSION

It is now widely recognized that disease remission should be the target of the treatment of all forms of axSpA[20]. Ideally, this means no sign of articular and extraarticular inflammation and no development of structural damage, but practically the aim usually is to reach clinical remission as defined by validated criteria. Both the ASAS PR criteria and the ASDAS definition of inactive disease have been validated by clinical trials[21,22]. ASAS PR is a good treatment target, but not all patients meeting the criteria for PR have a complete absence of inflammation. The ASDAS is more comprehensive because it includes an objective measure of inflammation (CRP or ESR). In addition, because this index provides a score, it allows a quantification of disease activity and therefore of depth of remission.

Anti-TNF-α agents have proven to be effective in inducing disease remission in patients with axSpA[3,4,5,6,7], but some patients may experience a loss of their state of remission despite continuing their biological therapy. This phenomenon has not been addressed by specific studies, to our knowledge. The aim of our study was to understand rate and predisposing factors of loss of remission and of disease flare in patients with axSpA taking anti-TNF-α in a clinical practice setting. Over a median (IQR) followup time of 4 years (2–6), loss of PR occurred in 37 patients (21.2%) after a median (IQR) time of remission of 1 year (0.625–2). In 28 patients (16.1% of the whole study population), the clinical picture was consistent with the provided definition of disease flare. There are no data from similar studies for comparison of our findings. Registries of patients with AS treated with anti-TNF-α agents show discontinuation rates of about 10%–15% a year[23,24], but those rates include any cause of discontinuation, and not just loss of efficacy. In addition, loss of remission does not lead to drug interruption in all cases. The rate of disease flares in patients with axSpA in PR with anti-TNF-α therapy has never been reported. In a prospective longitudinal study over a 12-month period of 200 patients with AS not taking anti-TNF-α drugs, flare rates were 36.9% and 28.3%, as reported by patients and physicians, respectively[14]. Our findings seem to indicate that in patients with axSpA in remission receiving anti-TNF-α agents, the rate of flares is relatively low.

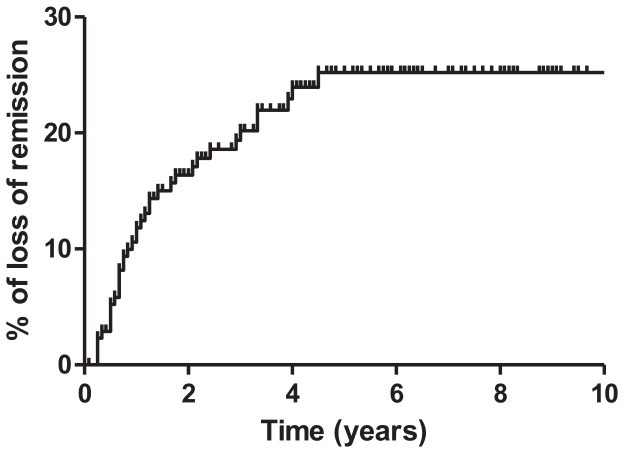

Figure 1. Kaplan-Meier curve of the loss of remission during treatment with anti-TNF agents in 174 patients with axial spondyloarthritis. Anti-TNF: antitumor necrosis factor.

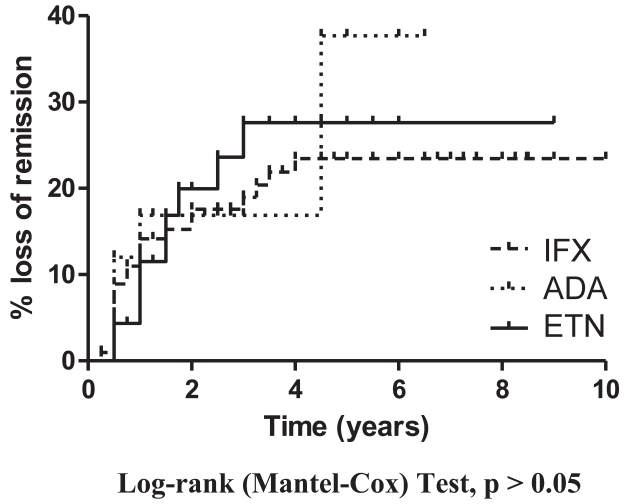

Figure 2. Kaplan-Meier curves of the loss of response of ADA, ETN, and IFX in 174 patients with axial spondyloarthritis. ADA: adalimumab; ETN: etanercept; IFX: infliximab.

In our study, persistently high values of CRP and ESR and continuous NSAID intake during the remission period were the only factors significantly associated with both loss of remission and disease flare at the univariate analysis. ASDAS-CRP median value did not show this association, but a value of this score < 0.8 was predictive of persistence of remission. At the multivariate analysis, the only factors significantly associated with both loss of remission and disease flare were persistent NSAID intake and an ESR > 15 mm/h. Demographic factors, disease duration, HLA-B27, indicators of functional damage (BASMI and BASFI), and type of anti-TNF-α drug did not show any association with disease reactivation. Altogether, these results seem to suggest that disease relapse was more likely in patients with a persistent underlying mild inflammation, as revealed by higher ESR and CRP values and the need for NSAID[25]. The association between ASDAS-CRP < 0.8 and persistence of remission seems to confirm that patients in deeper remission were less likely to relapse.

Translated into clinical practice, the findings of our study underline the importance of regular monitoring of laboratory and clinical features of patients with axSpA treated with anti-TNF-α therapy, even when they reach a state of PR. Patients with residual inflammation should be followed more closely and might benefit from a dose increase of their therapy, if feasible. On the other hand, patients with deeper remission might be candidates for a tapering regime, a strategy much discussed, especially after the data from studies in early axSpA[26,27] confirmed a poor outcome with anti-TNF-α discontinuation upon remission. However, the usefulness of these treatment strategies in the management of patients with SpA in remission treated with anti-TNF-α therapy should be proved by specific studies.

Recently, the ASAS group identified some definitions of flares based on changes in pain and the ASDAS and BASDAI indices[28], and in another study, Godfrin-Valnet, *et al* defined flares as a variation of ≥ 2.1 units in BASDAI, 0.8 units in ASDAS-ESR, or 1.3 units in ASDAS-CRP, using a different approach[29]. In this context, some authors consider relative variations and others absolute values above a significant threshold to define disease flares[30]. In our study, we identified patients with axSpA in remission with a similar disease activity at baseline, and for this reason we chose an absolute value to identify a flare.

Our present study has some limitations. First, data were taken from our database retrospectively. Second, because the number of patients with loss of remission and disease flare was relatively low, some associations might have not reached the level of statistical significance. Third, disease activity was defined only by clinical and laboratory variables. Sacroiliac joint and spine magnetic resonance imaging might have provided more precise insight on the presence and grade of residual inflammation. Despite these limitations, the results of our study convey useful information on an issue clinically relevant in daily practice.

Our study showed that over a median period of 1 year, loss of remission and disease flares occurred, respectively, in about 21% and 16% of the patients with axSpA who had achieved a state of remission while receiving anti-TNF-α therapy. Mild residual disease activity proved to be predictive of disease reactivation.

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Table 2. Association of main demographic and clinical variables with loss of remission and disease flare in patients with axSpA in remission with anti-TNF-α therapy. Values are median (IQR) or n (%) unless otherwise specified.

Variables	Loss of Remission			Disease Flare		
	Yes, n = 37	No, n = 137	p	Yes, n = 28	No, n = 146	p
Male vs female	28 (75.7)	105 (76.6)	0.902	22 (78.6)	111 (76)	0.771
Age, yrs, mean (SD)	44.1 (13.5)	43.1 (12.6)	0.699	44.2 (13.9)	43.1 (12.5)	0.662
Disease duration, mos	108 (36–192)	82 (36–155)	0.289	88 (36–153)	84 (36–168)	0.732
ESR, mm/h	12 (10–19)	7 (4–12)	0.001	12 (9–19)	7 (4–13)	0.001
CRP, mg/dl	0.5 (0.2–0.6)	0.2 (0.03–0.5)	0.010	0.5 (0.2–0.6)	0.2 (0.05–0.5)	0.022
NSAID, concomitant use vs sporadic use	9 (24.3)	12 (8.9)	0.011	8 (28.6)	13 (9)	0.004
HLA-B27, presence vs absence	28 (75.7)	94 (68.6)	0.405	21 (75)	101 (69.2)	0.538
ASDAS-CRP	1.22 (0.88–1.62)	0.98 (0.42–1.51)	0.107	1.28 (0.91–1.65)	0.99 (0.42–1.51)	0.056
ASDAS-CRP > 0.8 vs ≤ 0.8	29 (78.4)	78 (57.8)	0.022	23 (82.1)	84 (58.3)	0.017
EAM, presence vs absence	12 (32.4)	43 (31.4)	0.903	9 (32.1)	46 (31.5)	0.947

axSpA: axial spondyloarthritis; TNF-α: tumor necrosis factor-α; IQR: interquartile range; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NSAID: nonsteroidal antiinflammatory drugs; ASDAS: Ankylosing Spondylitis Disease Activity Score; EAM: extraarticular manifestations.

Table 3. Association of main demographic and clinical variables with loss of remission and disease flare in patients with axSpA in remission while taking anti-TNF-α therapy (logistic regression).

Variables	Loss of Remission			Disease Flare		
	OR	95% CI	p	OR	95% CI	p
~~0.976~~						
Age, yrs	1.005	0.970–1.041	0.780	1.014	0.976–1.054	0.463
Male vs female	0.797	0.301–2.110	0.648	1.089	0.348–3.407	0.883
Disease duration, mos	1.002	0.998–1.006	0.278	1.000	0.995–1.005	0.947
IFX vs ADA + ETN	1.034	0.410–2.606	0.943	1.192	0.420–3.383	0.741
ADA vs IFX + ETN	1.152	0.294–4.515	0.839	1.250	0.267–5.840	0.777
ESR, > 15 vs ≤ 15	2.901	1.233–6.824	0.015	2.691	1.044–6.937	0.040
NSAID continuous use	4.054	1.400–11.738	0.010	4.540	1.532–13.454	0.006

axSpA: axial spondyloarthritis; TNF-α: tumor necrosis factor-α; IFX: infliximab; ADA: adalimumab; ETN: etanercept; ESR: erythrocyte sedimentation rate; NSAID: nonsteroidal antiinflammatory drugs.

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Correction

Predictors of Loss of Remission and Disease Flares in Patients with Axial Spondyloarthritis Receiving Antitumor Necrosis Factor Treatment: A Retrospective Study

Lubrano E, Perrotta FM, Manara M, D'Angelo S, Addimanda O, Ramonda R, et al. Predictors of loss of remission and disease flares in patients with axial spondyloarthritis receiving antitumor necrosis factor treatment: a retrospective study. J Rheumatol 2016;43:1541-6. In the author affiliation section, Fabio Massimo Perrotta should be listed as F.M. Perrotta. We regret the error.

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