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ORIGINAL ARTICLES

Non-steroidal anti-inflammatory drug use is determined by disease activity in axSpA and decreased by biologicals: a longitudinal analysis

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ABSTRACT

Objective: To evaluate non-steroidal anti-inflammatory drug (NSAID) use and Assessment in Spondyloarthritis International Society (ASAS)-NSAID scores in patients with axial spondyloarhritis (axSpA) in a longitudinal study.
Methods: In total, 429 patients with axSpA (59% male; 64% with radiographic axSpA) were included in this study. Data regarding disease activity, C-reactive protein (CRP) levels, and NSAID use and dosage were collected at 0, 12, 24, and 52 weeks retrospectively. The relationship with NSAID use /ASAS-NSAID scores and other factors were tested using generalized estimating equations (GEE).
Results: At baseline (week 0), 92.8% of patients in biologic disease-modifying anti-rheumatic drugs (bDMARDs) group and 82.1% of patients in conventional treatment group were being treated with NSAIDs. At baseline, the proportion (p=0.03) and the median (IQR) ASAS-NSAID scores were higher in bDMARDs group [100 (50-100) vs 50 (16.6-100); p<0.001]. During follow-up, NSAID use and ASAS-NSAID scores decreased significantly in patients treated with bDMARDs (p<0.001) and the reduction remained stable throughout the follow-up However, neither NSAID use (p=0.06) nor ASAS-NSAID scores changed in conventional treatment group (p=0.15). In bDMARD-treated patients, ASDAS-CRP and BASFI scores were independent determinants for NSAID use, and BASDAI and PGA were determinants for NSAID dosage. There was no independent significant predictor for ASAS-NSAID scores; PGA was the only significant predictor for NSAID use in the conventional treatment group.
Conclusion: Biologic treatment was associated with low NSAID intake in patients with axSpA, and NSAID use was determined mainly by disease activity and partly by functional during bDMARD treatment.

Keywords: Keywords: Axial spondyloarthritis; Non-steroidal anti-inflammatory drug use; ASAS-NSAID score.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic, inflammatory rheumatic disease affecting the axial skeleton, which typically leads to inflammatory back pain. Axial spondyloarthritis is subdivided into two forms –radiographic (r-axSpA) and non-radiographic axSpA (nr-axSpA) –based on the presence or absence of unequivocal radiographic changes in sacroiliac joints[1]. The disease may also cause peripheral arthritis, enthesitis, and dactylitis.

The treatment goals of axSpA are reducing symptoms, improving and maintaining spinal mobility and optimal posture, reducing functional limitations, maintaining the ability to work, and decreasing the extra-musculoskeletal manifestations and complications associated with the disease[2].

The NSAIDs are the first-line treatment options in patients with axial pain and/or stiffness[2, 3]. NSAIDs improve back pain, spinal function, morning stiffness and also peripheral joint and entheseal pain. Moreover, there is also evidence suggesting that continuous or high NSAID intake may have an impact on slowing radiographic damage of the spine[4, 5]. Thus, continuous and maximum tolerated doses of NSAIDs are recommended for patients with active, symptomatic disease[5]. The Assessment in SpondyloArthritis international Society (ASAS)/European League Against Rheumatism (EULAR) management recommendations for axSpA advised biologic disease-modifying antirheumatic drugs (bDMARDs) for active axial disease despite at least two maximum doses of NSAIDs[2].

In daily clinical practice, tapering or withdrawing NSAIDs may be expected in patients who have begun taking bDMARDs. However, there is limited data concerning dosage of NSAIDs and the determinants of

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NSAID use in patients with axSpA who have been treated with bDMARDs. To standardize the quantitation of NSAID use in patients with axSpA, the ASAS working group suggested using NSAID scores[6].

In a randomized placebo-controlled trial, baseline disease activity and ASAS-NSAID scores were similar between the groups; however, a significantly higher proportion of patients treated with etanercept vs. placebo reduced or stopped NSAID at week 8[7]. It was also shown in an observational study that treatment with tumor necrosis factor inhibitor (TNFi) was associated with a decrease in the proportion as well as the dosage of the NSAIDs in patients with axSpA in a real-life setting[8]. Recently, another observational study revealed that longitudinal NSAID use was associated with disease activity, particularly in patients treated with TNFi[9]. In addition, there is no double-blinded randomized study compared any TNFi to NSAIDs.

Therefore, in the present study, we aimed to evaluate NSAID use longitudinally during a 52-week period in an observational cohort of patients with axSpA and to determine factors associated with NSAIDs intake in a real-life setting.

MATERIALS AND METHODS

Study design and patient population

This retrospective observational study was conducted in a tertiary hospital between 2015 and 2020. All patients with axSpA were aged 18 years and classified according to the ASAS classification criteria for axSpA[1].

Patients who had any contraindication for NSAID use such as pregnancy, lactation, and renal failure were excluded. This study was approved by the ethics committee of Izmir Katip Celebi University (approval number of 2020-0559).

In the present cohort, bDMARD treatment was started according to the ASAS/EULAR and American College of Rheumatology/Spondylitis Association of American/Spondyloarthritis Research and Treatment Network (ACR/SAA/SPARTAN) management recommendations and local guidelines[2, 3, 10]. NSAIDs were prescribed based on ASAS/EULAR recommendations[3]. The patients who were started bDMARD at baseline visit were included in bDMARD treatment group. The patients who did not start bDMARD during follow-up (week 52) were included in the conventional treatment group. Patients who started bDMARD therapy while they were in conventional treatment group were excluded.

Collected data

Baseline information regarding socio-demographic (including age, sex, education level, smoking status, body mass index) and disease-related characteristics were recorded. During follow-up (at 0, 12, 24, and 52 weeks), data about axSpA-related features [including the presence or the development of peripheral (peripheral arthritis, dactylitis, heel enthesitis)] and extra-musculoskeletal manifestations [uveitis, psoriasis, inflammatory bowel disease (IBD)] in addition to disease activity and functional status measurements were collected.

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[11], Bath Ankylosing Spondylitis Functional Disease Index (BASFI)[12], Ankylosing Spondylitis Disease Activity score (ASDAS-CRP)[13], serum C-reactive protein (CRP) levels, and Patient Global Assessment (PGA) of disease activity[14] were collected using a structured form. In each visit, NSAID intake due to the disease, type, and the dosage and frequency of NSAIDs were also recorded to determine the ASAS-NSAID score, and NSAID dosage was adjusted according to the clinical status and disease activity of the patients.

The ASAS-NSAID score was calculated by using the following formula: (equivalent NSAID score) × (days of intake during the period of interest) × (days per week)/(period of interest in days) as suggested by the ASAS working group[6].

Statistical analysis

All statistical analyses were performed using the Statistical Package of the Social Science (SPSS) software package version 13.0 (Chicago, IL, USA). The distribution of continuous variables was investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov). Most of the continuous variables were not distributed normally; therefore, values were presented as median and interquartile range (IQR 25-75) for continuous and as percentages for categorical variables. The Mann–Whitney U test was used to compare non-normally distributed variables between the groups. The Chi-square test or Fisher's exact test was used for the comparison of categorical data.

Friedman tests were conducted to test whether there was a significant change in the ASAS-NSAID scores and disease activity measurements due to violations of parametric test assumptions (non-normal distribution). The Wilcoxon test was performed to test the significance of pair-wise differences using Bonferroni correction to adjust for multiple comparisons.

NSAIDs use and scores over time were investigated using generalized estimating equations (GEE). The GEE procedure allows the analysis of repeated measurements in longitudinal studies. Traditional statistical techniques such as linear or logistic regression cannot be used in longitudinal studies because observations are not independent of each other and special techniques such as the GEE were developed to this end[15, 16]. We analyzed

NSAIDs use (as dichotomous variable) and ASAS-NSAID scores (as a continuous variable) as dependent variables at visits during 52 weeks. Since GEE is suitable for the evaluation of the longitudinal relationship with continuous (ASAS-NSAID score) and dichotomous (NSAID use yes or no) outcome variables (dependent), and several time-dependent and independent covariates allow the use of unequal numbers of repeated measurement data, even if they deviate from normality[16].

We used only GEE (univarite and multivariate) models for longitudinal analysis in whole study. In the first step of the present study, individual longitudinal interactions between ASAS-NSAID scores or NSAID use and demographic/clinical characteristics were assessed with *p*-values of <0.10 were included in regression models. Different multivariate longitudinal models were run.

All statistical tests were two-tailed and *p*-values of <0.05 were considered as statistically significant.

RESULTS

In total, 429 patients with axSpA (273 with r- and 156 with nr-axSpA) were included in the study. The median age was 40 (IQR: 33-51) years, 59% of patients were male and 61% were HLA-B27 positive. The median disease duration was 12 (IQR: 7-19) years. The baseline demographic and disease-related characteristics of the patients are summarized in Table I.

One hundred and thirty-nine patients with axSpA were started on bDMARDs treatment [92.1% of patients on TNFi (infliximab, adalimumab, etanercept, certoli-

TABLE I. Baseline demographic and disease characteristics

	All group (n=429)	Biologic treatment (n=139)	Conventional treatment (n=290)	p
Age, years median (IQR25-75)	40 (33-51)	39 (32-51)	41 (33-50)	0.49
Sex, male, n (%)	253 (59)	94 (68)	160 (55)	0.01
Diagnosis, n (%) r-AxSpA nr-AxSpA	 273 (63.6) 156 (36.4)	 106 (76.3) 33 (23.7)	 166 (57.4) 124 (42.6)	 <0.001
HLA-B27 positive, n (%)	209/342 (61.1)	64/95 (67.4)	146/248 (58.9)	0.15
Smoking, ever, n (%)	291/425 (68.5)	89/135 (65.9)	202 (69.7)	0.44
Duration of symptoms, median yrs (IQR25-75)	12 (7-19)	14 (9-20)	11 (7-19)	0.004
The presence of extraspinal/ extra-musculoskeletal manifestations history, n (%)				
Peripheral arthritis	127/407 (31.2)	60/123 (48.8)	67/285 (23.5)	<0.001
Enthesitis	108/377 (48)	52/99 (52.5)	129/279 (46.2)	0.30
Dactylitis	14/414 (3.4)	7/126 (5.6)	7/288 (2.4)	0.11
Hip involvement	51/366 (14.2)	18/95 (18.9)	33/271 (12.2)	0.10
Anterior uveitis	45/413 (10.9)	17/126 (13.5)	28/287 (9.8)	0.26
Psoriasis	17/411 (4.1)	5/126 (4)	12/285 (4.2)	0.91
Inflamatory bowel disease	10/369 (2.7)	5/96 (5.2)	5/273 (1.8)	0.08
Disease activity, median (IQR25-75)				
BASDAI (0 to 10)	4 (2.6-5.6)	4.9 (3.8-6.5)	3.6 (2.2-5.0)	<0.001
BASFI (0 to 10)	2.9 (1.2-5.4)	4.4 (2.6-6.3)	2.2 (0.8-4.2)	<0.001
BASMI (0 to 10)	2 (1-3)	3 (1-4)	2 (1-3)	0.009
ASDAS-CRP	2.8 (2-3.5)	3.5 (2.7-4.1)	2.4 (1.7-3.1)	<0.001
CRP (mg/dl)	1 (1-9)	7 (3-19)	1 (1-1)	<0.001
PGA of disease activity (0 to 100)	40 (20-60)	60 (50-80)	40 (20-60)	<0.001
Concomitant medications, n (%)				
Current NSAID use	367 (85.5)	129 (92.8)	238 (82.1)	0.003
Current cDMARD use	93/405 (23)	26/131 (20)	67/274 (25)	0.32

AxSpA: axial spondyloarthritis, r-axSpA: radiographic axSpA, nr-axSpA: non-radiographic axSpA, HLA-B27: Human leucocyte antigen B27, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, CRP: serum C reactive protein , ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-CRP, PGA: patient global assessment, NSAID: non-steroidal anti-inflammatory drug, cDMARD: conventional disease-modifying antirheumatic drug

zumab, golimumab) and 7.9% on secukinumab] and 290 were managed conventionally. There were a higher proportion of males and patients with r-axSpA among the biologic treatment group. Furthermore, disease duration was longer and, as expected, disease activity was higher in patients started on bDMARDs (Table I).

At baseline, 129 out of 139 (92.8%) patients started biologic and 238 (82.1%) patients treated conventionally were using NSAIDs, and the median ASAS-NSAID scores were 100 (IQR: 50-100) and 50 (IQR: 16.6-100), respectively. Both the proportion of NSAID use (Figure 1) (p=0.03) and the median ASAS-NSAID scores (Figure 2) were statistically higher in the bDMARD-treated group (p<0.001).

During the follow-up period, 173 patients were included longitudinal analysis at 12 weeks, 155 at 24 weeks, 230 at 52 weeks in the line with the accessible visit information of the patients. The proportion of NSAID use (figure 1) and, in particular, ASAS-NSAID scores (Figure 2) decreased rapidly (as early as 12 weeks) and significantly in patients treated with biologic drugs; the reduction remained stable throughout follow-up (p<0.001) (supplementary Table I). However, neither NSAID use (p=0.06) nor ASAS-NSAID scores changed in conventionally treated patients (p=0.15) (supplementary Table I).

All disease activity measurements (BASDAI, BASFI, ASDAS-CRP, serum CRP levels, PGA of disease activity) decreased significantly in bDMARD group in week 12 (p<0.001 for all measurements) and the measurements were found to be stable throughout follow-up. However, disease activity did not change in conventionally treated patients during the follow-up period.

NSAID use as a continuous variable estimated using ASAS-NSAID scores

In the entire axSpA cohort, longitudinal univariate analysis revealed that ASAS-NSAID scores were significantly associated with treatment (B:15.01, 95%CI: [8.88 to 21.14]; p<0.001 for bDMARD), BASDAI (B:6.81, 95%CI: [5.51 to 8.10]; p<0.001), BASFI (B:5.25, 95%CI: [4.06 to 6.43]; p<0.001), PGA of disease activity scores (B:0.47, 95%CI: [0.35 to 0.59]; p<0.001), and serum CRP levels (B:0.15, 95%CI: [-0.02 to 0.33]; p=0.082) in the multivariate analysis, BASDAI (B:2.89, 95%CI: [0.44 to 5.33]; p=0.021), PGA of disease activity scores (B:0.37, 95%CI: [0.19 to 0.54]; p<0.001), and treatment type (B:14.52, 95%CI: [6.62 to 22.41]; p<0.001 for bDMARD) were independent determinants of ASAS-NSAID scores in patients with axSpA.

We repeated the longitudinal analysis in the conventional and bDMARD-treated groups separately after whole-group analysis. Univariate longitudinal analysis in the biologic treated group revealed that ASAS-NSAID scores were significantly associated with ASDAS-CRP (B:8.10, 95%CI: [0.62 to 15.59]; p=0.034), BASDAI (B:10.95, 95%CI: [9.30 to 12.59]; p<0.001), BASFI (B:7.72, 95%CI: [6.19 to 9.28]; p<0.001) and PGA of disease activity (B:0.81, 95%CI: [0.66 to 0.96]; p<0.001), BASMI (B:2.31, 95%CI: [-0.06 to 4.68]; p=0.056) and serum CRP levels (B:0.250, 95%CI: [0.05 to 0.45]; p=0.02). Therefore, we established two multivariable models to assess the associated factors/covariates with ASAS-NSAID scores over time (one with ASDAS and the other BASDAI+CRP as disease activity measures) and showed that BASDAI and PGA of disease activity were independent determinants of ASAS-NSAID scores in patients who were treated with bDMARDs (Table II).

Although univariate longitudinal analysis revealed that ASAS-NSAID scores were associated with BASDAI (B:2.81, 95%CI: [1.10 to 4.53]; p<0.001), BASFI (B:2.94, 95%CI: [1.36 to 4.52]; p<0.001), PGA of disease activity scores (B:0.30, 95%CI: [0.15 to 0.45];

TABLE II. The factors associated with ASAS-NSAID scores in biologic treated patients

	Model 1*			Model 2*		
	B	95%CI	p	B	95% CI	P
BASFI	-0.55	-4.38 to 4.28	0.98	0.94	-3.80- to 5.68	0.70
BASMI	0.95	-1.51 to 3.41	0.45	-0.10	-2.43 to 2.23	0.93
PGA	0.54	0.21 to 0.86	0.001	0.76	0.43 to 1.09	<0.001
CRP	-0.07	-0.22 to 0.08	0.38			
BASDAI	5.72	2.49 to 8.95	0.001			
ASDAS-CRP				1.77	-6.57 to 10.11	0.68

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath AS Functional Disease Index, CRP: serum C reactive protein, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-CRP, PGA: patient global assessment, BASMI: Bath Ankylosing Spondylitis Disease Activity Index, AS: Ankylosing Spondylitis

*Model 1: multivariable model to assess the associated factors/covariates with ASAS-NSAID scores over time with BASDAI and CRP

*Model 2: multivariable model to assess the associated factors/covariates with ASAS-NSAID scores over time with ASDAS- CRP

p<0.001), smoking (B:-8.39, 95%CI: [-16.85 to 0.07]; p=0.05), education (B:-0.94, 95%CI: [-1.82 to -0.05]; p=0.04) and psoriasis history (B:20.15, 95%CI: [-3.04 to -43.35]; p=0.09), there was no independent significant predictor for ASAS-NSAID scores in the conventional treatment group in multivariate analysis (Table III).

NSAID use as a nominal variable

In additions to ASAS-NSAID scores, we analyzed NSAID use as a dichotomous variable in univariate and multivariate longitudinal analysis in the entire axSpA group as well as in separate treatment groups. Univariate longitudinal analysis revealed that in all patients, NSAID use was significantly associated with treatment type (B:0.89, 95%CI: [0.46 to 1.16]; p<0.001 for bDMARD), BASDAI (B:0.36, 95%CI: [0.25 to 0.47]; p<0.001), BASFI (B:0.25, 95%CI: [0.16 to 0.35], p<0.001), ASDAS-CRP (B:0.69, 95%CI: [0.39 to 0.83]; p<0.001), PGA of disease activity scores (B:0.02, 95%CI: [0.01 to 0.03]; p<0.001), and history of extra-musculoskeletal manifestations (B:0.52, 95%CI: [0.55 to 0.98]; p=0.03). In the multivariable model, assessing the associated factors/covariates with NSAID use over time showed that treatment type (B:0.66, 95%CI: [0.13 to 1.19]; p=0.02 for bDMARD), BASDAI (B:0.26, 95%CI: [0.06 to 0.46]; p=0.01), BASFI (B:0.27, 95%CI: [0.16 to 0.39]; p<0.001) and PGA of disease activity scores (B:0.01, 95%CI: [0.00 to 0.03]; p=0.03) were independent determinants of NSAID use in patients with axSpA.

Then, we repeated the univariate longitudinal analysis for the determinants of NSAID use in each treatment group and found that in the biologically treated group, NSAID use was significantly associated with BASDAI (B:0.61, 95%CI: [0.44 to 0.78]; p<0.001), BASFI (B:0.41, 95%CI: [0.27 to 0.54]; p<0.001), ASDAS-CRP (B:0.79, 95%CI: [0.51 to 1.08]; p<0.001) and PGA of disease activity scores (B:0.04, 95%CI: [0.02 to 0.05]; p<0.001). Therefore, we again established two multivariable models to assess the associated factors/covariates with NSAID use over time (one with BASDAI and the other ASDAS-CRP as disease activity measures) and showed that ASDAS-CRP and BASFI were independent determinants of NSAID use in patients with axSpA treated with bDMARDs (supplementary Table II).

Although univariate longitudinal analysis revealed that NSAID use was associated with age (B:-0.02, 95%CI: [-0.04 to -0.00]; p=0.04), symptom duration

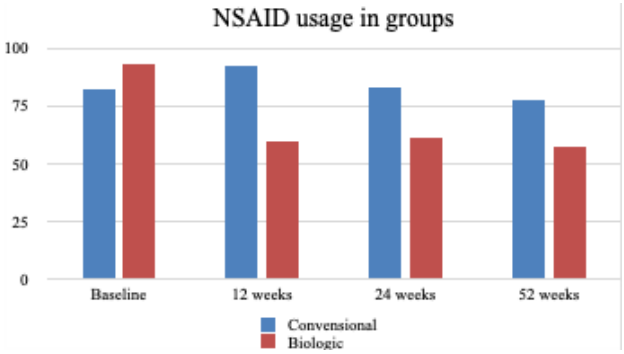

Figure 1. The proportion of NSAID use at 0, 12, 24, 52 weeks in treatment groups

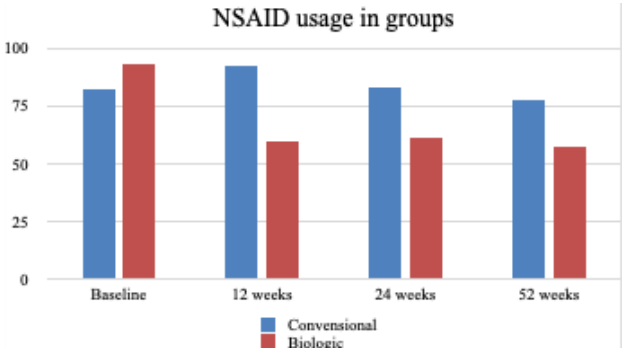

Figure 2. Median ASDAS-NSAID scores at 0, 12, 24, 52 weeks in treatment groups

TABLE III. The factors associated with ASAS-NSAID scores in conventionally treated patients

	B	95% CI	p
BASDAI	1.37	-2.31 to 5.04	0.47
BASFI	1.08	-2.17 to 4.18	0.53
BASMI	0.28	-2.56 to 3.11	0.85
PGA	0.23	-0.02 to 0.47	0.07
Smoking (never)	-6.90	-17.32 to 3.53	0.20
Education (years)	-0.90	-2.17 to 0.38	0.17
Psoriasis (no)	11.6	-17.5 to 40.7	0.43

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Disease Index, BASMI: Bath Ankylosing Spondylitis Disease Activity Index, PGA: patient global assessment of disease activity

(B:-0.02, 95%CI: [-0.04 to -0.00]; p=0.01), PGA of disease activity (B:0.01, 95%CI: [0.00 to 0.03]; p=0.01), and history of extra-musculoskeletal manifestations (B:0.70, 95%CI: [0.10 to 1.29]; p=0.02) in the conventional treatment group, multivariate analysis showed that PGA of disease activity was the only significant predictor for NSAID use in this group of patients with axSpA (supplementary Table III).

DISCUSSION

The results of this long-term follow-up study showed that NSAID use in patients with axSpA was determined mainly by disease activity and partly by functional status. Besides, all of the activity measurements used in daily clinical practice, such as BASDAI, PGA of disease activity, and serum CRP levels were found to be associated with longitudinal NSAID use in the present cohort. However, the disease subtype had no impact on both NSAID use and dosage in patients with axSpA. In our study groups, biologic treatment was associated with both clinical improvement and a decrease in NSAID use and dosage. Using GEE analysis, we also showed that in biologic treated patients, NSAID use was determined mainly by disease activity, irrespective of treatment type during the follow-up. There are limited data evaluating the determinants of longitudinal NSAID use in patients with axSpA[7-9].

In our study, at the baseline visit, both the proportion of NSAID use and the median ASAS-NSAID scores were statistically higher in the biologically treated patients with axSpA. However, both NSAID use and dosage decreased significantly only in the advanced treatment group. Similar to our findings, NSAID use and dosage were found to be decreased in follow-up in comparison with the baseline visit in patients with axSpA treated with TNFi in the Groningen Leeuwarden Ankylosing Spondylitis (GLAS) cohort. Nevertheless, in contrast to our findings, the authors also reported that baseline NSAID use was similar in the TNFi and conventional treatment groups (79% vs 74%; p=0.131) (13). The reason for the high NSAID use in both treatment groups was not clear in this study because baseline disease activity was higher in the patients who were put on TNFi treatment.

NSAIDs are the first choice of treatment in patients with axial pain and/or stiffness and biologic agents should be considered in patients who have high disease activity despite the maximum tolerable dose of NSAIDs. In the GLAS cohort, the proportion of NSAID use was lower in the TNFi treatment group than in our study; this result might be related to the requirement of TNFi treatment for some different involvements in patients in the GLAS cohort; the higher conventional DMARD use in the patients with TNFi treatment supports this hypothesis. In both the Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort and SPARSE study, NSAID use was similar to our patients with axSpA and higher than in the GLAS cohort[7-9].

In our study, we analyzed the entire axSpA patient group as well as biologically and conventionally treated groups separately to understand the determinants of NSAID use and dosage longitudinally. In our whole axSpA cohort, longitudinal multivariate analysis revealed that, besides disease activity, therapy with bDMARDs was an independent predictor of NSAID use as well as dosage, suggesting a NSAID-sparing effect of bDMARDs in patients with axSpA. In the GLAS cohort, the authors also revealed that NSAID use was significantly related with disease activity[9]. However, they analyzed conventional and bDMARD groups separately and did not evaluate the whole group of patients. Also, they only used ASDAS-CRP, BASDAI, and serum CRP levels as disease activity measurements. In our study, we additionally analyzed functional status and PGA of disease activity for patient-reported outcomes. Furthermore, when we assessed patients in two treatment groups (conventional and biologic), we found that NSAID use was related to BASDAI, ASDAS-CRP, BASFI, and PGA of disease activity scores in biologically treated patients. By contrast, PGA of disease activity was the only determinant of NSAID use in the conventional treatment group. In addition to ASAS-NSAID scores, we analyzed NSAID use as a nominal variable. However, we believe that ASAS-NSAID scores could be a more reliable and objective marker for NSAID use in patients with axSpA because they are calculated using equivalent NSAID scores, dosage, and the percentage of days with NSAID use in a defined period. The importance of ASAS-NSAID scores was advocated previously[7].

The results of the present study provide additional evidence regarding the substantial efficacy of TNFi in patients with axSpA because all disease activity measures decreased significantly after as little as 12 weeks of follow-up. Furthermore, in our biologic treatment group, the proportion of patients using NSAIDs and median ASAS-NSAID scores decreased in 12 weeks and remained stable at the 24 and 52-weeks follow-up visits. The authors of the GLAS cohort study showed that ASAS-NSAID scores significantly decreased with TNFi therapy in 6-12 weeks[9]. In the SPARSE study, NSAID use was reduced or stopped at week 8 in patients treated with etanercept[15]. The percentage of patients with axSpA, in whom NSAID scores decreased or NSAID treatment was ceased, was higher among the TNFi treatment group, also in the DESIR cohort[8].

Our study has some limitations. First, the retrospec-

tive design, inevitably resulted in missing data in the follow-up period. Second, we coul not evaluate the different treatment groups (TNFi agents and secukinumab in addition to COX-2 inhibitors and traditional NSAIDs) as a sub-analysis due to the low number of patients. In addition, we did not have information about comorbidities, which are crucial factors associated with the reduced use of NSAIDs in clinical practice.

The main strengths of the study were the patient populations and sample size because patients with both r- and nr-axSpA were included in the study. This is the first study showing that in addition to biologic treatment, disease activity might affect NSAID use and dosage in patients with both r- and nr-axSpA. Additionally, we used GEE for longitudinal analysis, which is a robust evaluation of the relationship with continuous as well as dichotomous outcome variables and several time dependent and independent covariates.

CONCLUSION

This is the first study evaluating the relationship between NSAID use and disease activity of all subtypes of axSpA in a longitudinal analysis. Our results showed that NSAID use and dosage were significantly higher in patients with axSpA who were indicated bDMARD treatment. Our results indicate that NSAID use may decrease significantly over time under biological treatment, thus clinicians should be aware of patients' NSAIDs needs and reconsider modifications. In addition, as disease activity has an independent impact on NSAIDs use, disease activity measurements should be considered for NSAIDs prescriptions. However, it was stable in conventionally treated patients with axSpA. Calculating ASAS-NSAID scores may be a more appropriate outcome than nominal NSAID use to investigate NSAID use in patients with axSpA.

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SUPPLEMENTARY MATERIAL

TABLE I. ASAS-NSAID scores and the percentage of NSAID use in follow-up

ASAS-NSAID scores, median (IQR)	Baseline	Week 12	Week 24	Week 52
bDMARDs group	100 (50-100)	14.3 (0-50)	13.7 (0-50)	9 (0-50)
Conventional group	50 (16.6-100)	100 (50-100)	100 (25-100)	50 (8.3-100)
NSAID use, yes, %				
bDMARDs group	92.8	59.8	61.3	57.9
Conventional group	82.1	92.3	87.8	77.2

TABLE II. The factors associated with NSAID use in biologic treated patients

	Model 1*			Model 2*		
	B	95%CI	p	B	95% CI	p
BASDAI	0.25	-0.04 to 0.53	0.09			
PGA	0.02	-0.00 to 0.04	0.07			
BASFI	0.03	-0.20 to 0.27	0.79	0.23	0.05 to 0.40	0.01
ASDAS-CRP				0.53	0.17 to 0.88	0.03

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, AS: Ankylosing Spondylitis, PGA: patient global assessment of disease activity, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score of C reactive protein
*Model 1: multivariable model to assess the factors/covariates with NSAID use with BASDAI and PGA
*Model 2: multivariable model to assess the factors/covariates with NSAID use with ASDAS-CRP

TABLE III. The factors associated with NSAID use in conventionally treated patients

	B	95% CI	p
PGA	0.02	0.00 to 0.03	0.01
Age (years)	-0.02	-0.05 to 0.02	0.39
Symptom duration (years)	-0.02	-0.06 to 0.01	0.15
History of EMM	0.42	-0.40 to 1.24	0.32

PGA: patient global assessment of disease activity, EMM; extra-musculoskeletal manifestations