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BRIEF REPORT

Nonsteroidal Antiinflammatory Drug Intake According to the Assessment of SpondyloArthritis International Society Score in Clinical Trials Evaluating Tumor Necrosis Factor Blockers: Example of Etanercept in Advanced Ankylosing Spondylitis

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Objective. **To evaluate the interest of the Assessment of SpondyloArthritis international Society (ASAS) nonsteroidal antiinflammatory drug (NSAID) score as a quality indicator and a potential outcome measure in clinical studies.**

Methods. **We used data from patients with active, advanced, axial ankylosing spondylitis refractory to NSAIDs. The study design was a 12-week, randomized, placebo-controlled period followed by a 12-week open-label extension. The ASAS-NSAID score was collected during 3 periods of interest (i.e., the 12 weeks preceding baseline, the 12 weeks of the placebo-controlled trial, and the 12 weeks of the open-label trial).**

Results. **For the 82 enrolled patients, the mean ± SD ASAS-NSAID score at baseline was similar between the 2 groups: 93 ± 76 and 74 ± 54 in the etanercept and placebo groups, respectively. There was no significant change in the ASAS-NSAID score during the first part of the trial, as recommended by the protocol. There was a statistically significant decrease in the ASAS-NSAID score during the second part of the trial with a relevant effect size (−0.56) in the placebo to etanercept group.**

Conclusion. **This study confirms the feasibility and simplicity of the ASAS-NSAID score and suggests that such a score be integrated in all studies in spondylarthritis either to check the quality of the observed data (i.e., intergroup baseline characteristics) or to evaluate the NSAID-sparing effect of other therapies.**

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) are regarded as the cornerstone of pharmacologic interventions for ankylosing spondylitis (AS), reducing pain and stiffness after 48–72 hours (1–3). Besides this dramatic symptomatic effect, recent data suggest that NSAIDs might also be effective in reducing the level of acute-phase reactants (4) and that a continuous daily intake might slow radiologic progression (5). Based on these data, a systematically continuous daily intake of NSAIDs might be of benefit to patients. However, the opposing argument is the potential

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Significance & Innovations

- The Assessment of SpondyloArthritis international Society (ASAS) nonsteroidal antiinflammatory drug (NSAID) score is a valuable technique to evaluate the magnitude of NSAID intake.
- The ASAS-NSAID score is a valuable technique to evaluate disease severity in ankylosing spondylitis.
- The ASAS-NSAID score can be used as an outcome measure to evaluate the NSAID-sparing effect of different treatment modalities.
- The ASAS-NSAID score should be integrated in all clinical/therapeutic studies/trials.

long-term gastrointestinal and cardiovascular toxicity of such therapy (6,7), particularly in these patients who are recognized as having more comorbidities than the general population (8).

In patients who have active AS (usually defined as a Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥40 on a 0–100 scale) despite NSAID treatment or in case of NSAID intolerance, tumor necrosis factor (TNF) blockers are indicated with a well-demonstrated symptomatic effect (9–11). In these patients (i.e., TNF responders), the remaining question is whether they should be advised to stop or to continue their NSAID treatment.

To be in a position to adequately evaluate the magnitude of NSAID intake in clinical studies, the Assessment of SpondyloArthritis international Society (ASAS) has recently proposed the use of a scoring system, taking into account the specific NSAIDs and the dose as well as the percentage of days with NSAID intake during a period of interest (12). This technique for collecting NSAID intake information has been used in a recently published randomized placebo-controlled trial evaluating etanercept in patients with advanced severe AS (13).

The objectives of the present study were to perform a post hoc analysis of this trial with the following aim: evaluation of 1) the feasibility of the ASAS-NSAID score calculation, 2) the changes in the ASAS-NSAID score during the randomized controlled period of the trial (i.e., 12 weeks), during which the patients were advised to maintain their NSAID intake at the same regimen, and 3) the changes in the ASAS-NSAID score during the open-label 12-week extension period, during which all of the patients received etanercept without any specific advice concerning the NSAID intake.

Patients and methods

Study design and study drug. SPINE was a therapeutic trial evaluating etanercept versus placebo in advanced severe AS comprising 2 periods: the first period (12 weeks) was a randomized placebo-controlled trial and the second period (12 additional weeks) was an open-label extension, during which etanercept was either continued or initiated (for the patients who had received etanercept or placebo during the first period, respectively).

Inclusion criteria. The characteristics of the patients have been previously published (13). Briefly, all of the patients had to have active (BASDAI score ≥40), advanced, severe (presence of intervertebral bridges on spinal radiographs) AS refractory to NSAIDs (according to the modified New York criteria) to be eligible for the study.

Outcome measures. Apart from the conventional measures (e.g., BASDAI, Bath Ankylosing Spondylitis Functional Index [BASFI], Bath Ankylosing Spondylitis Metrology Index [BASMI], C-reactive protein [CRP] level, Ankylosing Spondylitis Disease Activity Score [ASDAS] endorsed by the ASAS), NSAID intake was collected in accordance with the ASAS recommendations (i.e., name, mean dose, number of days of intake during a period of time). Thereafter, the ASAS-NSAID score was calculated considering not only the daily dose of a specific NSAID (e.g., a score of 100 is given to naproxen 1,000 mg, diclofenac 150 mg, etc.) but also the percentage of days of intake of such NSAIDs during a given period of time. For example, a patient taking naproxen 1,000 mg during 45 days in a period of 90 days was scored at 50.

Statistical analysis. The ASAS-NSAID score has been calculated in accordance with the ASAS recommendations (12).

In order to evaluate the changes in the ASAS-NSAID score, 3 periods of interest were considered, i.e., the 12 weeks preceding baseline, the first period (12 weeks of the randomized placebo-controlled trial), and the second period (12 weeks of the open-label extension).

In order to approach the concept of sensitivity to change, the effect size was compared in the conventional outcome measures (e.g., BASDAI, BASFI, BASMI, ASDAS-CRP) and the ASAS-NSAID score during the open-label part of the study in those patients who received placebo during the first period of the study.

The primary analysis was modified intent-to-treat with the last observation carried forward used for missing variables.

For all of the continuous variables, the means and SDs were calculated. The intra- and intergroup comparisons of the continuous variables were performed according to the nonparametric Wilcoxon signed rank 2-tailed test. Moreover, in order to estimate the magnitude of the sensitivity to change, the standardized response mean was calculated (i.e., the ratio between the mean changes over the baseline SDs of the changes).

Results

Patients and study course. Of the 82 recruited patients (mean ± SD age 47 ± 10 years, 93% men, 83% B27 positive, mean ± SD BASDAI score 61 ± 13, mean ± SD BASFI score 60 ± 19, mean ± SD BASMI score 5.7 ± 1.3, mean ± SD ASDAS 3.8 ± 0.8), 43 received etanercept and 39 received placebo during the first 12 weeks of therapy, during which 5 patients withdrew from the study, result-

Table 1. ASAS-NSAID score changes during the 3 study periods by treatment group*

Treatment group	Period of interest†				Intertreatment group comparison in a period of interest, *P*‡			Intratreatment group comparison between 2 periods of interest, *P*‡	
	W−12/W0 (n = 82)§	W0/W12 (n = 82)¶	W0/W12 (n = 77)¶	W12/W24 (n = 77)#	W−12/W0 (n = 82)§	W0/W12 (n = 82)¶	W12/W24 (n = NA)#	W−12/W0 vs. W0/W12 (n = 82)	W0/W12 vs. W12/W24 (n = 77)
Etanercept to etanercept					0.291	0.60	NA	0.93	0.0052
Mean ± SD	93 ± 76	87 ± 53	87 ± 54	70 ± 51					
Median (IQR)	99 (41–100)	100 (50–100)	100 (50–100)	76 (30–100)					
Min–max	0–423	0–200	0–200	0–200					
Placebo to etanercept								0.009	0.0003
Mean ± SD	74 ± 54	82 ± 56	83 ± 57	59 ± 56					
Median (IQR)	75 (33–100)	100 (50–100)	100 (50–100)	54 (0–100)					
Min–max	0–200	0–233	0–233	0–200					

* ASAS = Assessment of SpondyloArthritis international Society; NSAID = nonsteroidal antiinflammatory drug; W = week; NA = not applicable; IQR = interquartile range.
† Period of interest is the period during which the ASAS-NSAID score has been calculated, in particular.
‡ Statistical significance determined by Wilcoxon's signed rank test.
§ During the 12 weeks preceding the study (W−12/W0), patients were receiving NSAIDs without any study drug/biologic agents.
¶ During the first 12 weeks of the trial (W0/W12), patients received either etanercept or placebo.
# During the last 12 weeks of the trial (W12/W24), all patients received etanercept.

ing in 77 patients enrolled in the open-label period (38 and 39 in the etanercept to etanercept group and the placebo to etanercept group, respectively). During the open-label period, 3 patients withdrew from the study (1 lost to followup in the placebo to etanercept group and 2 for withdrawn consent [1 in each arm]).

ASAS-NSAID score calculation. Such calculation was possible with no missing data as soon as the patients completed the planned visits. Of note, 1 patient was treated with lornoxicam and 1 patient was treated with nabumetone (i.e., NSAIDs not listed in the ASAS-NSAID score original publication). For these patients, the ASAS-NSAID score was calculated according to the recommended maximum dose.

ASAS-NSAID score change during the trial. Table 1 shows the observed changes in NSAID intake. During the 12 weeks preceding baseline, the NSAID intake was similar between the 2 groups. During the first period (randomized placebo-controlled trial, during which the patients were asked to maintain their NSAID intake whatever the level of their symptoms), there was no significant difference between the 2 groups. However, the placebo intratreatment group interperiod (week [W] 12 to W0 versus W0 to W−12) showed a statistically significant increase in the ASAS-NSAID score, but not in the etanercept group. During the open-label extension, there was an intragroup (i.e., etanercept to etanercept and placebo to etanercept) statistical difference when comparing the 2 consecutive periods (i.e., W24 to W12 versus W12 to W0).

Sensitivity to change. Table 2 shows the changes in both the conventional outcome measures and the ASAS-NSAID score between the start of therapy (W12) and the end of followup (W24) in the group of patients starting etanercept at W12 (i.e., the placebo to etanercept group).

Discussion

To our knowledge, this study was the first to evaluate the metrologic properties of the recently recommended ASAS-NSAID score measuring the magnitude of NSAID intake during clinical studies. This study demonstrated the feasibility of such outcome measures and also suggested that the ASAS-NSAID score might serve as a quality control measure in studies where a stable dose of NSAIDs is required during the study period. The ASAS-NSAID score may also serve as an outcome measure to evaluate the treatment effect of other therapies such as TNF blockers.

In the literature, to our knowledge, only a single study has used an NSAID score to evaluate the sparing effect of another treatment in AS (i.e., a double-blind placebo-controlled trial evaluating the short-term symptomatic efficacy of sulfasalazine in axial AS [14]). More recently, the ASAS recommended an NSAID score taking into account the specific dose and percentage of days of NSAID intake during a period of interest. This present study confirms the feasibility of the ASAS-NSAID score, as no missing data were observed as soon as the patients showed up at the planned visit.

However, it should be recognized that 2 patients were taking an NSAID (i.e., lornoxicam and nabumetone) for which no equivalent ASAS dose was provided. This information should prompt the ASAS members to regularly update the ASAS-NSAID equivalent score. In this study, the groups were comparable at baseline in terms of the ASAS-NSAID score and the NSAID intake was stable dur-

Table 2. Sensitivity to change of different conventional outcome measures as well as the ASAS-NSAID score during the 12-week period after starting etanercept in the group of 38 patients who had previously received placebo*

Parameter	Start of therapy (W12)	Final visit (W24)	Change (W24 to W12)	SRM
ASAS-NSAID score				−0.56
Mean ± SD	83 ± 57	59 ± 56	−24 ± 43	
Median (IQR)	100 (50–100)	54 (0–100)	0 (−41 to 0)	
Min–max	0–233	0–200	−150 to 28	
BASDAI				−0.74
Mean ± SD	44 ± 20	31 ± 24	−14 ± 19	
Median (IQR)	46 (32–58)	27 (9–47)	−14 (−26 to −1)	
Min–max	1–82	0–96	−45 to 19	
BASFI				−0.79
Mean ± SD	47 ± 22	36 ± 24	−11 ± 14	
Median (IQR)	47 (33–59)	28 (19–50)	−8 (−18 to −2)	
Min–max	7–96	0–97	−38 to 10	
BASMI				−0.38
Mean ± SD	5.5 ± 1.4	5.2 ± 1.6	−0.3 ± 0.8	
Median (IQR)	5.8 (4.4–6.6)	5.4 (3.8–6.4)	−0.4 (−0.8 to 0.0)	
Min–max	2.0–8.0	2.0–7.8	−2.0 to 2.2	
ASDAS-CRP				−1.20
Mean ± SD	3.1 ± 1.0	2.0 ± 1.1	−1.2 ± 1.0	
Median (IQR)	3.1 (2.5–3.6)	1.8 (0.9–3.0)	−1.2 (−1.7 to −0.5)	
Min–max	0.7–5.1	0.0–4.6	−3.3 to 0.7	

* ASAS = Assessment of SpondyloArthritis international Society; NSAID = nonsteroidal antiinflammatory drug; W = week; SRM = standardized response mean (mean changes/SDs of the changes); IQR = interquartile range; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score–C-reactive protein.

ing the double-blind placebo-controlled part of the study. However, a potential limitation of this present study was its focus on NSAID-refractory patients (i.e., patients eligible for TNF blockers). Such a required inclusion criterion might have restricted the range of possible ASAS-NSAID scores and, thereafter, might limit the conclusions of this post hoc analysis.

The ASAS-NSAID score could also help to control the quality of a clinical trial conducted in this field. For example, the ASAS-NSAID score evaluates the similarity between treatment group patients at baseline. Moreover, in trials evaluating therapies other than NSAIDs but authorizing concomitant NSAID intake, the ASAS-NSAID score could evaluate stable use of NSAID therapy during the trial.

Moreover, the ASAS-NSAID score could also be used as an outcome measure in a trial aimed at evaluating the NSAID-sparing effect of therapies. This was not the objective of this present study. However, in the open-label phase of the study, there was no particular recommendation concerning the NSAID intake, meaning that the patients were allowed to use NSAID therapy as needed or on a scheduled frequency. In this way, the data observed in this study may reflect current daily practice. One could consider that such a treatment effect might be of a higher magnitude if the patients were systematically advised to taper or stop NSAID therapy as soon as their symptomatic condition improved after initiation of another therapy such as TNF blockers. Prospective randomized controlled trials should be conducted to confirm this hypothesis. Finally, the data obtained in this trial may encourage all of the researchers to include the data necessary to calculate the ASAS-NSAID score in any study in the field of spondylarthritis.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Dougados had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Dougados, Szanto, Combe, Logeart.

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Analysis and interpretation of data. Dougados, Combe, Leblanc, Logeart.

ROLE OF THE STUDY SPONSOR

This trial has been conducted with Pfizer France as the sponsor. The authors have proposed such post hoc analysis and the sponsor has accepted that the authors have full access to the full database in order to conduct such post hoc analysis. Pfizer France had no role in the study design, data collection, data analysis, and writing of the manuscript, as well as the approval of the content of the submitted manuscript. Publication of this article was not contingent on the approval of Pfizer France.

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