Flare in axial spondyloarthritis: investigation of meaningful changes in symptomatic outcome measures

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Abstract

Objective

To assess symptomatic outcomes associated with flare after discontinuation of non-steroidal anti-inflammatory drugs (NSAIDs) in axial spondyloarthritis (axSpA).

Methods

Patients with NSAID-refractory axSpA discontinued NSAIDs, restarted if symptoms recurred, and self-recorded Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). 75th percentiles were calculated for changes in BASDAI total and components from NSAID discontinuation to resumption.

Results

75th percentiles for absolute/relative changes: BASDAI total (0–10)=1.5/28%; fatigue=2.0/25%; spinal pain=2.0/33%; joint pain/swelling=2.0/50%; enthesitis=2.0/43%; morning stiffness=1.5/27%.

Conclusion

No single score threshold applied but absolute change ≥2 or relative change ≥30% indicated symptomatic deterioration for most BASDAI components.

Key words

axial spondyloarthritis, flare, NSAID, etanercept, ASAS, BASDAI

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Introduction

For many patients with axial spondyloarthritis (axSpA), the natural course of disease is episodic, with intermittent periods of worsening disease activity, or flares, followed by periods of partial or complete remission. Reliable recognition of disease flares is essential in daily practice and clinical trial settings, as exacerbation of symptoms despite ongoing therapy can signal the need for treatment modification. In previously conducted cyclooxygenase-2 inhibitor "flare design" trials, patients with radiographic axSpA were required to experience disease flare after interrupting their pre-study non-steroidal anti-inflammatory drug (NSAID) therapy to be eligible for randomisation (1-3). Ongoing "discontinuation trials" are evaluating the potential for flare occurrence after an effective treatment is discontinued or tapered in patients who had achieved an acceptable symptom state. Although these trials have employed similar flare criteria, consensus on a standardised definition of flare in axSpA has not yet been achieved. Moreover, the concept of flare is not mentioned in a recent review of the best tools for assessment of axSpA (4).

The SPARSE trial was a randomised, double-blind, placebo-controlled trial that assessed the effects of the anti-tumour necrosis factor (TNF) agent etanercept on NSAID-sparing and conventional clinical outcomes in axSpA. During screening, all patients with active disease despite optimal treatment with NSAIDs were requested to discontinue NSAID use, allowing an opportunity to evaluate the occurrence of flare. We examined the threshold of meaningful change in the Bath Ankylosing Disease Activity Index (BASDAI) score that was associated with flare necessitating NSAID resumption in the SPARSE population.

Methods

Methodology of the SPARSE study has previously been described (5). Only findings from the 2–6-week screening period were used for the *post hoc* flare analyses presented in this report.

The SPARSE study was conducted in accordance with principles set forth in the International Conference on Harmonisation guidelines for Good Clinical Practice and the Declaration of Helsinki. Institutional Review Board approval and patient informed consent were obtained prior to initiation of study activities. The trial is registered on ClinicalTrials.gov (NCT01298531).

Patients

Eligible patients had axSpA based on ASAS criteria (6), with active axial involvement defined by mini-BASDAI score (7) ≥4 and inadequate response to ≥2 NSAIDs taken at maximum tolerated dosage for a total combined duration of ≥1 month. NSAIDs were taken for ≥5 days per week at two-thirds of the maximum licensed dosage for 4 weeks before screening.

Definition of flare

At the screening visit, patients were requested to discontinue their pre-study NSAID and resume its use only if symptoms recurred. The patient's decision to restart NSAID therapy, after having discontinued it for ≥2 consecutive days during screening, was the external standard for the definition of flare. The day of flare was defined as the day on which the patient resumed NSAID therapy. Patients who restarted treatment self-recorded details of NSAID intake and disease activity (using the original BASDAI) in a daily diary.

Primary endpoints

The change from screening in BASDAI score (8) and the percentage change in BASDAI score were the primary endpoints used to identify the threshold of meaningful change. The BASDAI (8) comprises 6 questions, *i.e.* fatigue (Question 1), spinal pain (Question 2), joint pain/swelling (Question 3), enthesitis (Question 4), and morning stiffness (Questions 5 and 6), answered on a 0–10 scale, with higher scores denoting worse disease activity. The BASDAI was selected for analysis because it is completely patient-oriented and is one of the most widely used tools for the measurement of disease activity in patients with axSpA (8, 9).

Statistical analysis

Continuous baseline demographic and disease characteristics were summarised using descriptive statistics for the subset of patients who experienced flare and had diary data. Summary statistics, including the mean [±standard deviation (SD)] and median, were calculated for absolute and relative changes in BASDAI total and component scores from the screening visit to the day when NSAID intake was resumed. Patients with a score of 0 at screening were excluded from calculation of relative change.

To determine a threshold based on the BASDAI for defining flare, the 75th percentile of the distribution of change in the BASDAI total and component scores from screening to flare was examined in the subset of patients who experienced flare and had diary data. Corresponding 95% confidence intervals (CI) were also calculated.

Table I. Baseline demographics and disease characteristics.

Baseline characteristics	Total (n=32*)
Age, y	40.0 (11.0)
Female, n (%)	16 (50.0)
White, n (%)	32 (100.0)
Disease characteristic	
Duration since axSpA diagnosis, y	4.6 (5.3)
Family history of SpA, n (%)	5 (15.6)
Positive pelvic x-ray, n (%)	16 (50.0)
HLA-B27 positive, n (%)	18 (56.3)
MRI sacroiliitis positive, n (%)	13 (40.6)
ASAS imaging/clinical arm, n (%)	21 (65.6)/7 (21.9)
Abnormal CRP level†, n (%)	10 (31.3)
NSAID intake	
ASAS-NSAID score‡	83.4 (32.2)

ASAS: Assessment of SpondyloArthritis international Society; axSpA: axial spondyloarthritis; CRP: C-reactive protein; HLA-B27: human leukocyte antigen B27; MRI: magnetic resonance imaging; NSAID: non-steroidal anti-inflammatory drug; SpA: spondyloarthritis.
Data are mean (standard deviation), unless otherwise specified.
*Findings are from the subset of patients who experienced flare after discontinuing NSAID therapy and had appropriate follow-up diary data. †Abnormal C-reactive protein = >1.25 x the upper limit of normal (4.9 mg/l). ‡Last observation carried forward, with imputation, intention to treat population. NSAID score was calculated during the week prior to the baseline visit.

Table II. Changes in BASDAI total and component scores from screening visit to NSAID restart (*i.e.* flare).

BASDAI measure: Question No.	Mean ± standard deviation (median)		
		Change from screening to flare	
	Screening	Absolute	Percentage*
Total score: Q1 + 2 + 3 + 4 + (5 + 6) / 2)	5.8 ± 1.2 (5.8)	0.7 ± 1.2 (0.8)	13 ± 21 (14)
Fatigue: Q1	6.7 ± 1.6 (7.0)	0.9 ± 1.9 (1.0)	23 ± 54 (13)
Spinal pain: Q2	6.6 ± 1.5 (7.0)	0.8 ± 1.6 (1.0)	16 ± 27 (14)
Joint pain: Q3	4.3 ± 2.8 (5.0)	0.1 ± 2.5 (0.0)	16 ± 80 (0)
Enthesitis: Q4	5.0 ± 2.3 (5.0)	0.9 ± 2.5 (1.0)	43 ± 129 (17)
Morning stiffness†: (Q5 + Q6) / 2	6.5 ± 1.7 (6.5)	0.6 ± 1.3 (0.5)	12 ± 23 (7)

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; NSAID: non-steroidal anti-inflammatory drug; Q: question.
*Patients with a score of 0 at screening were not included in the calculation of the percentage change. †Average of scores for intensity and duration of morning stiffness questions.

Results

Patients

Of 128 screened patients, 91 (71%) had a BASDAI available at the screening visit. Of these 91 patients, 45 (49%) discontinued NSAID therapy for ≥2 consecutive days and all experienced flare and resumed NSAID use. Of these 45 patients, 32 (35% of the full sample) experienced flare and completed their diary on the day that they restarted NSAID use, and thus were analysed. Demographic and disease characteristics for these 32 patients are shown in Table I.

BASDAI changes from screening to flare

In patients who experienced symptom flare and restarted NSAIDs during the screening period, the mean increase (± SD) and the percentage increase (± SD) in BASDAI total score between the screening visit and the reported flare (calculated to identify the threshold of meaningful change) were 0.7 (±1.2) and 13% (21) (Table II). The mean (±SD) increases observed in BASDAI component scores ranged from 0.1 (± 2.5) for joint pain to 0.9 (±1.9/±2.5) for fatigue and enthesitis.

For individual patients who discontinued NSAIDs for ≥2 days and restarted upon flare, Figure 1A shows the cumulative distribution of the absolute changes and percentage changes in BASDAI score between screening and flare for the total score and for each symptom. The 75th percentiles are identified on each plot. The smooth curves show the normal distribution of these changes, whereas the stepped curves depict the distribution of changes in analysed patients. The stepped effect of the latter curves is relatively pronounced due to the small sample size. For most BASDAI variables, the curves flattened out above the 75th percentile cut-off.

The 75th percentiles (95% CIs) for absolute and relative changes in BASDAI score are summarised in Figure 1B. The 75th percentile for absolute change in BASDAI total score was 1.5 (95% CI 1.2–1.9), meaning that at the time a flare occurred, 75% of patients who flared had an absolute change in BASDAI total score of up to 1.5. The 75th percentile for absolute change in fatigue, spinal pain, joint pain/swelling, and enthesitis was 2.0 (95% CI 1.0–3.0; 2.0–2.0; 1.0–3.0; and 1.0–3.0, respectively); and for absolute change in morning stiffness, the 75th percentile was 1.5 (95% CI 1.0–2.5). At the time a flare occurred, 75% of patients had a relative change in BASDAI total score of up to 28% (95% CI 20–38), and relative changes

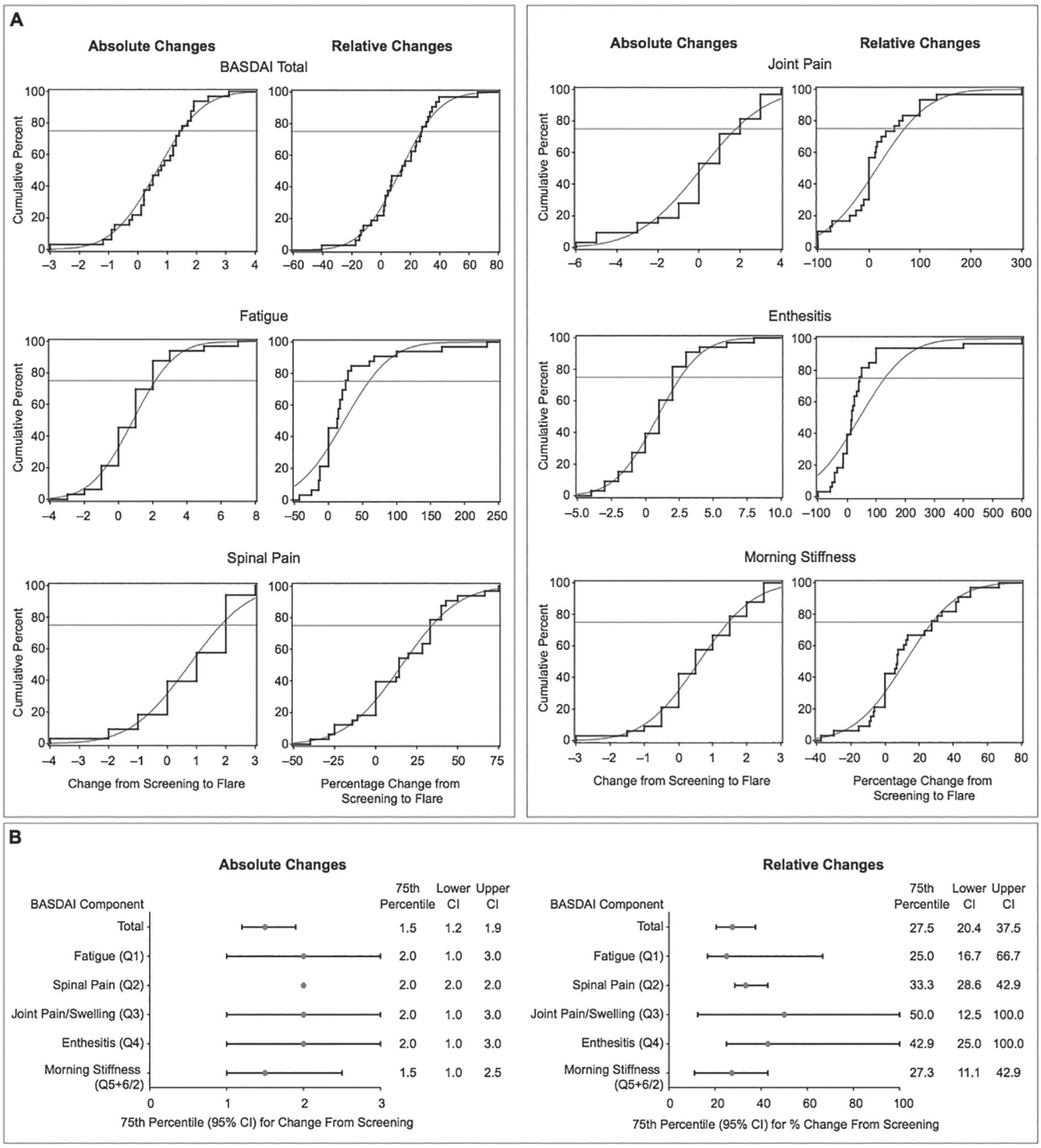

Fig. 1. A. The 75th percentile of the distribution of absolute and relative changes in BASDAI total and component scores from screening to flare. Smooth curves depict normal distribution; stepped curves depict findings for analysed patients. **B**: The 75th percentile (95% CI) for absolute and relative changes in BASDAI total and component scores from screening to flare. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CI: confidence interval.

in individual BASDAI components that ranged from 25% or lower (95% CI 17–67) for fatigue to 50% or lower (95% CI 13–100) for joint pain/swelling.

Discussion

In these analyses, a single threshold for defining flares in axSpA did not appear to be applicable to all the clinical outcome measures evaluated. However, the findings suggest that an absolute change ≥2 (on a scale of 0–10) or a relative change ≥30% may indicate a meaningful symptomatic deterioration for most BASDAI components. A lower absolute change of 1.5 was associated with worsening for total BASDAI, potentially because the combined score provides consistent information on individual questions, resulting in a lower cut-off. Such values could

be of interest because they could be used in the future as study endpoints to evaluate the percentage of patients who flare during the study (*e.g.* a flare could be defined as worsening of ≥1.5 in BASDAI). However, because all patients enrolled in the present study had active disease (mean total BASDAI, 5.8) at screening, findings from this study are not comparable to those from discontinuation studies, in which flare occurrence is evaluated after patients achieve remission or an acceptable symptom state.

The strengths of these analyses include use of the external standard for flare, *i.e.* patient's decision to resume NSAID therapy due to symptom recurrence, which is considered clinically relevant. In addition, this trial permitted optimal evaluation of changes in BASDAI. The findings reported in the SPARSE trial were similar to those previously reported in studies using different methodologies (10, 11). The small sample size was a limitation, and analyses were based on findings from a single study. The context is also important to consider. As patients had active disease at screening, and were asked to stop their NSAIDs, they may have anticipated a flare and may have restarted NSAID therapy upon experiencing only minimal worsening of symptoms. The results may also have been influenced by patients' expectation bias, *i.e.* anti-TNF therapy expected upon flare. Unexpectedly, the values observed for the BASDAI variables at the 75th percentile did not coincide with the values seen at the flattening of the distribution curves (Fig. 1). Although these findings may be explained by the small sample size, they may indicate that the most relevant thresholds for flare were not the values at the 75th percentiles in this population but the values at the observed flattening of the curves, which were higher for most variables.

Although the results are not definitive, they are relevant given the increasing interest in the concept of flares in axSpA (12). Additional research, including larger patient populations and analyses across several clinical studies, is warranted to further explore the occurrence of flare in patients with axSpA. Moreover, studies based on other statistical models to define flare are also needed to provide additional insight into how clinicians can best identify this clinically important event.

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SPARSE study investigators

C. Benhamou, F. Berenbaum, P. Bertin, A. Cantagrel, B. Combe, E. Dernis, P. Dieude, L. Euller-Zieglar, B. Fautrel, P. Hilliquin, S. Lassoued, L. Marguerie, C. Miceli, M. Nguyen, B. Pallot-Prades, G. Razjbaum, T. Schaeverbeke, M. Soubrier, and O. Vittecoq.

References

1. DOUGADOS M, BÉHIER JM, JOLCHINE I *et al.*: Efficacy of celecoxib, a cyclooxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis: a six-week controlled study with comparison against placebo and against a conventional nonsteroidal antiinflammatory drug. *Arthritis Rheum* 2001; 44: 180-5.
2. VAN DER HEIJDE D, BARAF HS, RAMOS-REMUS C *et al.*: Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: results of a fifty-two-week, randomized, controlled study. *Arthritis Rheum* 2005; 52: 1205-15.
3. GOSSEC L, VAN DER HEIJDE D, MELIAN A *et al.*: Efficacy of cyclo-oxygenase-2 inhibition by etoricoxib and naproxen on the axial manifestations of ankylosing spondylitis in the presence of peripheral arthritis. *Ann Rheum Dis* 2005; 64: 1563-7.
4. BRAUN J, KILTZ U, BARALIAKOS X, VAN DER HEIJDE D: Optimisation of rheumatology assessments - the actual situation in axial spondyloarthritis including ankylosing spondylitis. *Clin Exp Rheumatol* 2014; 32: S-96-104.
5. DOUGADOS M, WOOD E, COMBE B *et al.*: Evaluation of the non-steroidal anti-inflammatory drug-sparing effect of etanercept in axial spondyloarthritis: results of the multicenter, randomized, double-blind, placebo-controlled SPARSE study. *Arthritis Res Ther* 2014; 16: 481.
6. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al.*: The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68: 777-83.
7. SONG IH, RUDWALEIT M, LISTING J, SIEPER J: Comparison of the Bath Ankylosing Spondylitis Disease Activity Index and a modified version of the index in assessing disease activity in patients with ankylosing spondylitis without peripheral manifestations. *Ann Rheum Dis* 2009; 68: 1701-7.
8. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
9. VAN DER HEIJDE D, SIEPER J, MAKSYMOWYCH WP *et al.*: 2010 update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011; 70: 905-8.
10. DOUGADOS M, BRAUN J, SZANTO S *et al.*: Efficacy of etanercept on rheumatic signs and pulmonary function tests in advanced ankylosing spondylitis: results of a randomised double-blind placebo-controlled study (SPINE). *Ann Rheum Dis* 2011; 70: 799-804.
11. BRAUN J, VAN DER HORST-BRUINSMA IE, HUANG F *et al.*: Clinical efficacy and safety of etanercept versus sulfasalazine in patients with ankylosing spondylitis: a randomized, double-blind trial. *Arthritis Rheum* 2011; 63: 1543-51.
12. GODFRIN-VALNET M, PUYRAVEAU M, PRATI C, WENDLING D: Flare in spondyloarthritis: Thresholds of disease activity variations. *Joint Bone Spine* 2015; 82: 192-5.