
Evaluation of whether extremely high enthesitis or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores suggest fibromyalgia and confound the anti-TNF response in early non-radiographic axial spondyloarthritis

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ABSTRACT

Objective. Differentiating between pain from spondyloarthritis (SpA) and pain from fibromyalgia is challenging. We evaluated patients with non-radiographic axial SpA (nr-axSpA) to determine the percentage of patients with extremely high enthesitis and/or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores, the relationship between extreme scores and depression, and the effect of extreme scores on treatment outcomes with etanercept.

Methods. Patients with nr-axSpA received double-blind etanercept 50 mg or placebo weekly and were divided into those who did vs did not have extreme scores at baseline. Extreme scores were defined as the highest quintile for enthesitis score (≥ 6), and/or scores ≥ 8 on three of five BASDAI items (excluding morning stiffness duration). Depression was assessed with the Hospital Anxiety and Depression Scale, depression subscale (HADS-D) and medication use. Week 12 outcomes included Assessment of SpondyloArthritis (ASAS) 40 and ASAS partial remission.

Results. At baseline, 35/213 (16.4%) patients met extreme enthesitis criteria, 31 (14.6%) met extreme BASDAI criteria, 12 (5.6%) met both, and 135 (63.4%) met neither. More patients with extreme scores than without met the HADS-D definition of depression: 35/68 (51.5%) vs. 27/118 (22.9%), $p < 0.0001$. For patients with vs. without extreme scores who received etanercept, no significant difference existed in week 12 ASAS 40: 13/41 (31.7%) vs. 21/60 (35.0%), respectively, or ASAS partial remission: 8/41 (19.5%) vs. 19/60 (31.7%).

Conclusion. Extreme enthesitis and/or BASDAI scores were associated with measurements of depression, but did not affect week 12 ASAS 40 or ASAS partial remission.

Introduction

Many signs and symptoms of spondyloarthritis (SpA) and fibromyalgia are similar, and they sometimes coexist (1-4). Differentiating between pain from SpA, particularly polyenthesitis, and pain from fibromyalgia can be challenging (5). In clinical practice, a fibromyalgia score (e.g. several tender areas in the body) often assists in its diagnosis (6, 7). The enthesitis score used in SpA has been criticised owing to its lack of correlation with objective measures of enthesitis, such as magnetic resonance imaging (MRI), and because it overlaps with the fibromyalgia score (3). Some rheumatologists believe an extremely high enthesitis and/or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score (8, 9) may suggest fibromyalgia. Since depression is common in fibromyalgia (10), these extreme scores may also be associated with depression.

The EMBARK study evaluated etanercept for treating non-radiographic axial SpA (nr-axSpA) (11, 12). The enthesitis score and several patient-reported measurements (i.e. pain, stiffness, fatigue) were collected. This *post hoc* analysis evaluated whether extreme scores in patients with nr-axSpA may suggest the presence of fibromyalgia. The objectives were to: (1) estimate the percentage of patients with extreme enthesitis and/or BASDAI scores at baseline; (2) determine whether any differences exist in the baseline characteristics of these patients; (3) investigate whether depression is more common in these patients; and (4) evaluate the effect of baseline extreme scores on 12-week treatment outcomes with etanercept.

Materials and methods

Patients

Detailed study methods have been reported previously (11, 12). Briefly, all

patients met the Assessment of Spondyloarthritis International Society (ASAS) axSpA criteria without fulfilling the modified New York criteria for radiographic axSpA. The study was conducted according to the International Conference on Harmonisation Guidelines for Good Clinical Practice and the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants and the study was approved by an institutional review board or independent ethics committee at each participating centre.

Study design

In the 12-week, randomised, double-blind period, patients received 50 mg etanercept once weekly or placebo. For this analysis, patients were divided into those who did *versus* did not have extreme scores at baseline. Extreme scores were defined as: the highest quintile for enthesitis score (≥ 6), and/or scores ≥ 8 on three of five BASDAI items: (1) fatigue, (2) spinal pain, (3) peripheral arthritis, (4) enthesitis and (5) intensity of morning stiffness. Duration of morning stiffness was excluded. The percentage of patients achieving ASAS 40 and ASAS partial remission at 12 weeks was determined.

Depression at baseline was defined using two methods: (1) the Hospital Anxiety and Depression Scale, depression subscale (HADS-D); scores ≥ 8 suggested at least mild depression and ≥ 11 suggested at least moderate depression (13); and (2) use of an antidepressant, muscle relaxant, anxiolytic or opioid.

Statistical analyses

Patients in the modified intent-to-treat population with BASDAI and enthesitis scores at baseline were included. *P*-values for baseline demographics and disease characteristics were calculated using one-way analysis of variance or Fisher's exact test (two-tail) with extreme *versus* non-extreme subgroup as a factor ("met ≥ 1 of the 2 criteria" *versus* "met neither of the 2 criteria"). Efficacy analyses utilised observed case with no imputation for missing post-baseline data. *P*-values comparing extreme and non-extreme scores and

Table I. Baseline disease characteristics according to whether or not patients met criteria for extreme scores.

	Met ≥ 1 of 2 criteria n=78 Mean (SD)	Met neither criteria n=135 Mean (SD)	<i>p</i> -value*
BASDAI, 0–10	7.2 (1.4)	5.3 (1.7)	<0.0001
BASFI, 0–10 cm VAS	5.5 (2.2)	3.2 (2.2)	<0.0001
ASDAS-CRP	3.5 (0.9)	2.7 (0.9)	<0.0001
PGA, 0–10	6.2 (1.8)	4.9 (1.9)	<0.0001
SGA, 0–10	7.1 (1.8)	5.0 (2.1)	<0.0001
HADS-D, 0–21	7.3 (4.4)	4.8 (3.5)	<0.0001
HADS-anxiety, 0–21	8.0 (4.6)	5.9 (3.4)	0.0004
	Met ≥ 1 of 2 criteria n=72 n/N (%)	Met neither criteria n=120 n/N (%)	<i>p</i> -value†
Depression status at baseline			
HADS-D ≥ 11 , n=30	20/68 (29.4)	10/118 (8.5)	0.0002
HADS-D ≥ 11 and/or taking an antidepressant, n=42	28/70 (40.0)	14/120 (11.7)	<0.0001
HADS-D ≥ 11 and/or taking an antidepressant or other medication, n=63	35/72 (48.6)	28/120 (23.3)	0.0003
HADS-D ≥ 8 , n=62	35/68 (51.5)	27/118 (22.9)	<0.0001
HADS-D ≥ 8 and/or taking an antidepressant, n=71	41/70 (58.6)	30/120 (25.0)	<0.0001
HADS-D ≥ 8 and/or taking an antidepressant or other medication, n=91	48/72 (66.7)	43/120 (35.8)	<0.0001
Taking an antidepressant, n=18	13/72 (18.1)	5/120 (4.2)	0.0014
Taking other medication, n=30	14/72 (19.4)	16/120 (13.3)	NS
Taking an antidepressant and/or other medication, n=41	21/72 (29.2)	20/120 (16.7)	0.041

Modified intent-to-treat population with BASDAI and enthesitis scores. Other medications include muscle relaxants, anxiolytics, and opioids. Patients were considered to have extreme scores if their enthesitis score at baseline was in the top quintile and/or they met criteria for three of five baseline BASDAI items ≥ 8 .

* One-way analysis of variance with treatment as factor.

† Cochran-Mantel-Haenszel test.

ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score based on C-reactive protein; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; HADS-D: Hospital Anxiety and Depression Scale-depression subscale; NS: non-significant; PGA: physician global assessment of disease activity; SGA: subject global assessment of disease activity; VAS: visual analogue scale.

comparing etanercept and placebo for ASAS 40 and ASAS partial remission were calculated using the Cochran-Mantel-Haenszel test. The impact of extreme scores on treatment effect was determined by calculating the interaction *p*-value from logistic models of week 12 ASAS 40 and ASAS partial remission, with treatment, extreme/non-extreme categories and their interaction as factors in the models.

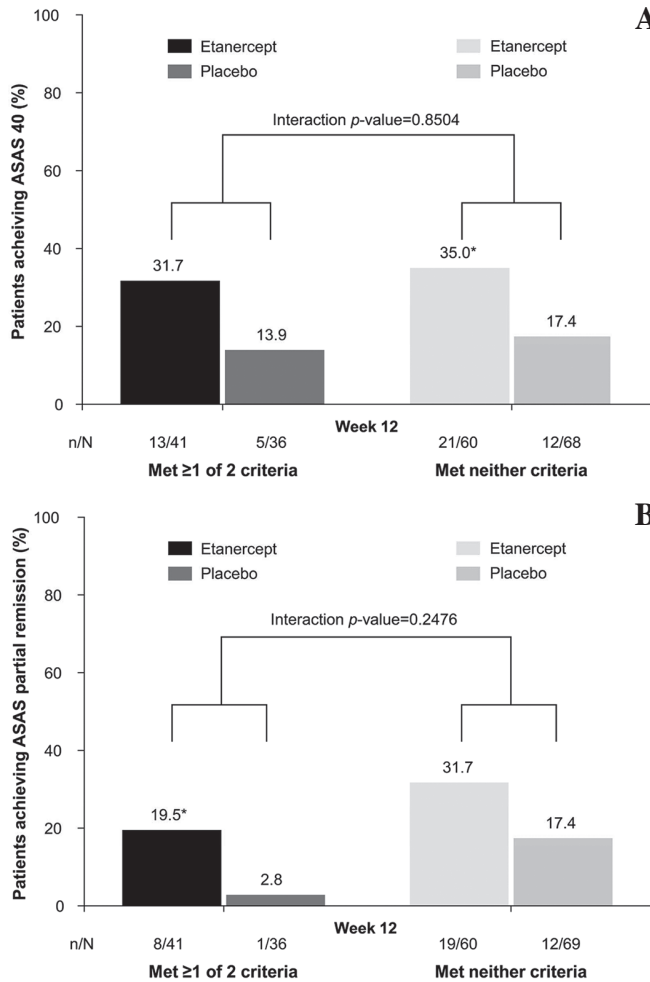
Results

Patients

Baseline BASDAI and enthesitis scores were available for 213 patients. A total of 135 (63.4%) patients did not meet either criterion for extreme scores, and 78 (36.6%) patients met at least one criterion: 35 (16.4%) had extreme en-

thesitis scores, 31 (14.6%) met the extreme BASDAI criterion and 12 (5.6%) met both criteria. There were no significant differences between the groups with *versus* without extreme scores for mean [standard deviation (SD)] age: 32.9 (7.9) years *vs.* 31.3 (7.6) years, respectively; sex: 53.9% *vs.* 63.7% were male; or mean (SD) body mass index: 25.5 (5.0) kg/m² *vs.* 24.8 (4.3) kg/m². The only significant difference in demographics was in race; the group with extreme scores was 78.2% white, 11.5% Asian and 10.3% other, compared with 70.4% white, 28.2% Asian and 1.5% other for the group without extreme scores (*p*=0.0007).

The groups had no significant differences in these disease characteristics: mean (SD) C-reactive protein: 7.3 (9.2)



A **Fig. 1.** Proportion of patients achieving (A) ASAS 40 response and (B) ASAS partial remission at week 12, according to whether or not patients met criteria for extreme scores. Modified intent-to-treat population, observed case analysis. * $p < 0.05$, etanercept vs. placebo.

13.9=17.8% vs. 35.0-17.6=17.4% for patients with versus without extreme scores (interaction p -value=0.8504); achievement of ASAS partial remission was 19.5-2.8=16.7% vs. 31.7-17.4=14.3%, respectively (interaction p -value=0.2476; Fig. 1).

Discussion

There were several key findings in this analysis. First, 37% of the study population had extreme scores at baseline. Second, extreme scores were associated with two measurements of depression: the HADS-D scale and antidepressant use. Third, extreme scores did not interfere with anti-TNF treatment, although numerically fewer of these patients achieved ASAS 40 and ASAS partial remission.

The objective disease characteristics and medical history related to SpA were similar between the groups, suggesting the same phenotypic presentation of the disease. However, as expected, disease characteristics that include patient assessments were more severe in the group with extreme scores.

Additionally, a higher percentage of patients with extreme scores had depression according to both the HADS-D and antidepressant use. However, this observation must be interpreted with caution, since medication may be taken for many purposes.

A study limitation is that we did not utilize objective measurement tools for enthesitis, such as MRI. However, this is rarely performed in daily practice. Also, we did not collect fibromyalgia information according to specific, validated criteria. Therefore, we cannot confirm that patients with extreme scores have concomitant fibromyalgia. Rather, fibromyalgia may be considered in these cases, since the presence of fibromyalgia has been shown to impact patient-reported outcomes, including the pain visual analogue scale (14). Additionally, we did not collect efficacy data beyond 12 weeks. A recently published study reported a lower retention rate of anti-TNF therapy and a higher rate of switching between anti-TNF agents in patients with concomitant fibromyalgia and SpA (15). A strength of this analysis is that the data come from a prospec-

mg/L vs. 6.3 (11.3) mg/L for patients with versus without extreme scores, respectively; the percentage of patients with MRI(+) sacroiliitis: 82.1% vs. 80.0%, or arthritis: 42.3% vs. 54.1%, or enthesitis: 39.7% vs. 43%, respectively. Although objective disease characteristics and medical history were similar between the groups, disease characteristics containing patient assessments were more severe in the extreme group (Table I).

Depression at baseline

Depression data were available for 192 patients. Baseline mean scores on the HADS-D and the HADS-anxiety subscales were significantly higher (worse) for patients with versus without extreme scores, Table I. Additionally, more patients with extreme scores had depression at baseline, as measured by the HADS-D, and/or according to medication use. The exception was the group of patients taking mus-

cle relaxants, anxiolytics, or opioids; there was no significant difference in depression status according to extreme scores, Table I.

Clinical efficacy

A smaller proportion of patients with vs. without extreme scores achieved ASAS 40 at week 12; however, the difference was not significant: etanercept 13/41 (31.7%) vs. 21/60 (35.0%), respectively; placebo 5/36 (13.9%) vs. 12/68 (17.6%) (Fig. 1). Similarly, in the etanercept group, fewer patients with vs. without extreme scores achieved ASAS partial remission: 8/41 (19.5%) vs. 19/60 (31.7%), respectively, p =ns. In the placebo group, the difference was significant: 1/36 (2.8%) with vs. 12/69 (17.4%) without extreme scores achieved ASAS partial remission, p =0.032.

Treatment effect was not impacted; achievement of ASAS 40 in the etanercept minus the placebo group was 31.7-

tive, randomised, placebo-controlled study.

The potential for bias exists since the outcomes (ASAS 40 and ASAS partial remission) are comprised of measurements that defined the two groups at baseline. When predicting the results, two possible scenarios emerged. Since the patients with high baseline values have more room for improvement, they may be expected to demonstrate greater improvement, resulting in a comparatively higher ASAS 40 response rate. Conversely, extremely high baseline values may prevent the achievement of a low-disease activity state, as measured by ASAS partial remission.

We did not observe the expected results for ASAS 40 response; the patients without extreme scores achieved slightly greater response rates than the patients with extreme scores. Extreme scores may indeed inhibit achievement of low disease activity, as indicated by a notably lower percentage of these patients achieving ASAS partial remission. Interestingly, the treatment effect of etanercept did not differ according to baseline scores. This suggests that patients with high BASDAI or enthesitis scores should be evaluated for fibromyalgia; however, this does not rule out the diagnosis of SpA and anti-TNF treatment may be needed.

In summary, these results suggest that the presence of extreme scores should not rule out treatment with etanercept if the diagnosis is nr-axSpA. Extreme

BASDAI scores may indicate a potential concomitant depression or related condition, which may interfere with tools that evaluate SpA disease activity. These findings require confirmation by additional studies.

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