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CONCISE REPORT

Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial

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ABSTRACT

Objective We assessed whether there is a difference to etanercept (ETA) treatment in patients with ankylosing spondylitis (AS) compared with non-radiographic axial SpA (nr-axSpA) patients with a disease duration <5 years.

Method AS (n=20) and nr-axSpA (n=20) patients who were treated with ETA for 1 year were compared for differences in baseline data and treatment effect. Clinical, laboratory and MRI of sacroiliac joints (SI-joints) and spine were analysed.

Results At baseline, there were no significant differences between the 20 AS and the 20 nr-axSpA patients regarding age, disease duration, gender, HLA-B27 and clinical disease activity in terms of Bath AS Disease Activity Index (BASDAI), C-reactive protein and MRI SI-joint and spine scores in the AS compared with the nr-axSpA group. After 1 year of treatment with ETA the treatment effect was similarly good in AS and nr-axSpA (reduction of BASDAI by 3.3 (95% CI 2.2 to 3.8) vs 3.6 (95% CI 2.8 to 4.4) and reduction of AS Disease Activity Score by 1.8 (95% CI 1.5 to 2.2) vs 1.8 (95% CI 1.5 to 2.1), respectively).

Conclusions The response rate to TNF-blockers does not differ between AS and nr-axSpA if the baseline data regarding symptom duration and disease activity are similar for the two groups.

Regarding response rates to tumour necrosis factor α (TNF α)-blocker therapy, several studies have shown that nr-axSpA patients respond at least as good as, or even better than, AS patients. However, these findings are only based on comparing different studies not comparing these groups inside the same trial.^{5–7}

We recently reported about a good efficacy of etanercept (ETA) treatment in axial SpA patients treated with the TNF-blocker ETA over 1 year in comparison with treatment with sulfasalazine.⁵ One important criterion for inclusion into the study was symptom duration not exceeding 5 years, independently of whether the patients already had radiographic sacroiliitis or not, plus subchondral bone marrow oedema on MRI. In the current analysis, we took advantage of the fact that the patients had radiographic and nr-axSpA in about 50% each allowing a direct comparison of the response between the two groups in the same study.

PATIENTS AND METHODS

Study design

Patients with early axial SpA with a disease duration of <5 years, and with active inflammation on whole-body MRI (wb-MRI) in the spine and/or sacroiliac joints (SI-joints) at baseline were treated with ETA (n=40) or sulfasalazine (n=36) over 48 weeks.⁵ For this analysis, we analysed the ETA patient population (n=40) from year 1 (20 AS vs 20 nr-axSpA patients).

Outcome parameters

The following efficacy parameters were calculated: response of the ASAS response criteria for 40% improvement in disease activity (ASAS40),⁸ ASAS criteria for partial remission,⁹ Bath AS Disease Activity Index criteria for 50% improvement (BASDAI50), AS Disease Activity Score (ASDAS) for inactive disease, ASDAS clinically important change and ASDAS major improvement.¹⁰ Other clinical and laboratory outcome assessments included the BASDAI, Bath AS Functional Index (BASFI), patient's and physician's global assessments of disease activity and CRP.^{5 11}

INTRODUCTION

The recently published Assessment of SpondyloArthritis International Society (ASAS) classification on axial spondyloarthritis (SpA) includes patients with ankylosing spondylitis (AS) who have sacroiliitis on conventional radiographs according to the modified New York criteria,¹ and patients with non-radiographic axial SpA (nr-axSpA) without definite sacroiliitis on x-rays.² A similar level of clinical disease activity has been shown on AS patients compared with nr-axSpA patients, as measured by the Bath AS Disease Activity Index (BASDAI) or patient pain.^{3 4} However, it has been reported that nr-axSpA patients might have lower C-reactive protein (CRP)-levels,^{3 4} and less MRI-inflammation in the spine.⁴



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MRI

Wb-MRIs, short-time inversion recovery (STIR) and T1 images, were performed at weeks 0, 24 and 48 on a 1.5 T scanner (Avanto TIM, Siemens, Germany), as previously described.^{5 12 13} STIR sequences of wb-MRIs were scored for active inflammation according to a recently described protocol⁵ using the STIR sequences by two radiologists (KGH, CA), blinded for treatment arm and MRI time point.

Statistics

Statistical analysis was performed according to the intention-to-treat principle. To compare the outcome parameters between AS and nr-axSpA patients after adjustment for baseline, a mixed-model approach was applied. This statistical method allows the inclusion of dropouts (n=3) in the analysis. The Blyth-Still-Casella method was used to calculate 95% CIs of response rates.

RESULTS

There were no significant differences between the 20 AS and 20 nr-axSpA patients treated with ETA in the first year (table 1) in terms of baseline parameters. Disease duration, mean MRI scores and the frequency of HLA-B27 were non-significantly higher in the AS group, but CRP was higher in the nr-axSpA group (table 1).

The response rate for the nr-axSpA and AS groups were very similar without significant differences (table 2). Similarly, there was no difference in the change of activity parameters, such as BASDAI, ASDAS, CRP and MRI scores, or in the change of the BASFI (figure 1) after adjustment for baseline values.

There was only a small, though non-significant, advantage in favour of the nr-axSpA group in some of the outcome variables, such as BASDAI50 (75% vs 50%), ASAS partial remission (60% vs 40%) or ASDAS clinically important improvement (75% vs 55%) (table 2).

DISCUSSION

This is the first comparison of the efficacy of a TNF α -inhibitor in patients with AS compared with patients with nr-axSpA in the same study. Importantly, the baseline characteristics were similar in the two groups. The results clearly show that there

is no difference in the response rate between the two groups if, especially, symptom duration, CRP-level and extent of bony MRI-inflammation are similar at baseline. If at all, there was even a small but non-significant difference in favour of the nr-axSpA patients. It has indeed been shown before that short symptom duration, elevated CRP and MRI-positivity are the best predictors of a good response to TNF-blockers both in AS patients^{14 15} and nr-axSpA patients.^{6 16} If only patients were included into TNF-blocker trials with short symptom duration and a positive MRI, as was the case in the infliximab⁷ and ETA trial,⁵ the response rate was clearly better than in trials without enrichment for these factors,^{6 16–18} confirming that these parameters are really relevant for a good response.

The clinical trials performed so far in the field of early axial SpA did not offer the opportunity to evaluate whether AS versus nr-axSpA patients respond differently to TNF α -inhibition. The first clinical trial in axial SpA only included nr-axSpA patients.⁶ In another axSpA study, all 40 patients showed active inflammation in the SIJ on MRI, among these patients, x-rays were available only in 34 patients, 11.8% (4/34) of whom fulfilled the modified New York criteria.⁷ The most recent study also included only patients with nr-axSpA.¹⁶

The current analysis was a posthoc analysis, and the study was originally not designed to address the question whether there is a different treatment response between the two groups. This can be seen as a limitation of the current investigation, although the number of patients and the baseline data were similar in the two groups.

The data presented here underline the concept of axial SpA being the same disease with different stages, and nicely demonstrate that the presence or absence of radiographic sacroillitis is not important if the other baseline parameters are similar. Thus, even if nr-axSpA patients on the group level show somehow less objective signs of inflammation^{3 4} as measured by CRP and/or MRI-inflammation compared with AS patients, the response rate to TNF-blockade seems to be similar if the treated patients have similar CRP-score and MRI-score levels.

Table 2 BASDAI, ASAS and ASDAS response rates in patients with ankylosing spondylitis (AS) compared with patients with non-radiographic axial spondyloarthritis (nr-axSpA) after 1 year of treatment with etanercept

Parameter at week 48	ETA, AS, (n=20)	ETA, nr-axSpA (n=20)
BASDAI20, % (95% CI)	80 (59 to 93)	85 (65 to 96)
BASDAI50, % (95% CI)	55 (34 to 75)	75 (54 to 90)
ASAS40, % (95% CI)	75 (54 to 90)	65 (43 to 83)
ASAS partial remission, % (95% CI)	40 (21 to 62)	60 (38 to 79)
ASDAS clinically important improvement, %*	55 (34 to 75)	75 (54 to 90)
ASDAS major improvement, %†	30 (14 to 52)	25 (10 to 46)
ASDAS inactive disease (<1.3), % (95% CI)	40 (21 to 62)	40 (21 to 62)

Results shown as percentage (%) and 95% CI. No statistical differences between patients with AS versus nr-axSpA were found for any of the parameters (p>0.05).

*ASDAS clinically important improvement: change of ASDAS between baseline and follow-up ≥ 1.1 .

†ASAS major improvement: change of ASDAS between baseline and follow-up ≥ 2.0 .

AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; ASAS40/partial remission, response of the Assessment of SpondyloArthritis international society (ASAS) criteria for 40% improvement in disease activity; ASAS criteria for partial remission; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASDAI20/50, Bath Ankylosing Spondylitis Disease Activity Index criteria for 20% and 50% improvement at week 48; CRP, C-reactive protein; ETA, etanercept; n, number of patients; nr-axSpA, nonradiographic axial spondyloarthritis.

Table 1 Baseline demographics between patients with ankylosing spondylitis (AS) and patients with non-radiographic axial spondyloarthritis (nr-axSpA)

Parameter	ETA, AS (n=20)	ETA, nr-axSpA (n=20)
Age in years, mean (\pm SD)	33.8 (\pm 8.2)	33.3 (\pm 9.1)
Disease duration in years, mean (\pm SD)	2.7 (\pm 1.6)	2.6 (\pm 1.8)
Male, %	60	55
HLA-B27+, %	90	80
BASDAI (0–10), mean (\pm SD)	5.5 (\pm 1.4)	5.6 (\pm 1.3)
CRP (<5 mg/l), mean (\pm SD)	9.4 (\pm 9.9)	14.4 (\pm 15.7)
ASDAS (0– ∞), mean (\pm SD)	3.2 (\pm 0.7)	3.6 (\pm 0.9)
BASFI (0–10), mean (\pm SD)	4.2 (\pm 2.2)	4.5 (\pm 2.4)
MRI spine score (0–69), mean (\pm SD)	3.4 (\pm 4.3)	1.3 (\pm 1.9)
MRI SI-joint score (0–24), mean (\pm SD)	8.6 (\pm 6.8)	7.1 (\pm 5.9)

No statistical differences between patients with AS versus nr-axSpA were found for any of the parameters (p>0.05).

AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ETA, etanercept; nr-axSpA, nonradiographic axial spondyloarthritis; .

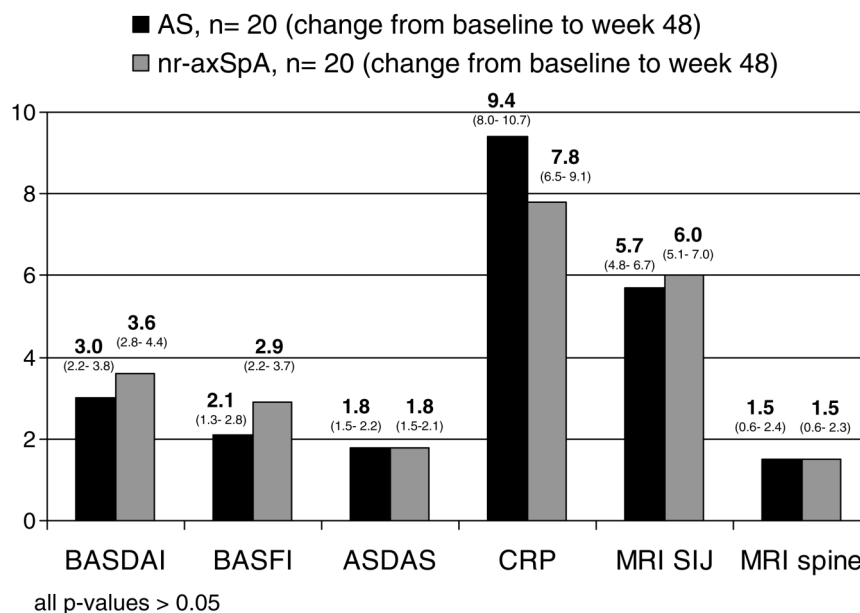


Figure 1 Comparison of mean differences (and corresponding 95% CIs) between patients with ankylosing spondylitis (n=20) and patients with non-radiographic axial spondyloarthritis (nr-axSpA) (n=20) for BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), BASFI (Bath Ankylosing Spondylitis Functional Index), ASDAS (Ankylosing Spondylitis Disease Activity Score), C-reactive protein (CRP, mg/l), MRI spine (active inflammation on MRI of the spine) and MRI SI-joints scores (active inflammation on MRI of the sacroiliac joints) after 1 year of treatment with etanercept.⁵

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Contributors IHS: study design, patient care, data management, data interpretation, preparation of manuscript. AWW: statistical analysis, interpretation of trial data. KGH: blinded reading of MRIs, interpretation of trial data. HH: study design, interpretation of trial data. CA: blinded reading of MRIs, interpretation of trial data. DP: patient care, interpretation of trial data. JL: statistical analysis, interpretation of trial data. EL: project management, interpretation of trial data. BF: study design, interpretation of trial data. MR: study design, interpretation of trial data. JS: study design, sponsor of trial, preparation of manuscript, interpretation of trial data.

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Competing interests IS, HH, DP: Pfizer/Wyeth Pharmaceuticals, Merck Sharp Dohme/Schering Plough, Abbott Immunology Pharmaceuticals: consulting fees or other remuneration. MR and JS: Pfizer/Wyeth Pharmaceuticals, Merck Sharp Dohme/Schering Plough, Abbott Immunology Pharmaceuticals, UCB: consulting fees or other remuneration. BF: former employee of Pfizer/Wyeth. EF: employee of Pfizer. AW, KGH, CA, JL: none.

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