Consistently Good Clinical Response in Patients with Early Axial Spondyloarthritis After 3 Years of Continuous Treatment with Etanercept: Longterm Data of the ESTHER Trial

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ABSTRACT. ***Objective.*** In patients with early active axial spondyloarthritis (axSpA) with a disease duration of < 5 years, the longterm efficacy of 3 years of continuous etanercept (ETN) treatment was assessed.

Methods. In a previously reported ESTHER trial, patients with axSpA were randomized to treatment with ETN (n = 40) versus sulfasalazine (SSZ; n = 36) in the first year. We analyzed the clinical, laboratory, and magnetic resonance imaging (MRI) response in the pooled dataset of patients (study population; n = 61), including patients with ankylosing spondylitis (AS, n = 31) and nonradiographic axSpA (nr-axSpA, n = 30) who were continuously treated with ETN for 3 consecutive years. Data were analyzed using the last observation carried forward and completer analysis.

Results. In the entire group of patients in the study population (n = 61), the mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) decreased from 5.7 (± 1.3) at baseline to 2.6 (± 2.4) at Year 3. The Ankylosing Spondylitis Disease Activity Score (ASDAS) decreased from 3.4 (± 0.8) to 1.5 (± 1.0). Also, mean values for MRI spine and sacroiliac joint scores showed a significant decrease. Response rates in the nr-axSpA group were similar and at least as good compared to the AS group for all outcome measures. When comparing remission stages, we found that ASDAS inactive disease correlated better with C-reactive protein and MRI remission than with Assessment of SpondyloArthritis international Society partial remission.

Conclusion. There was a consistent and sustained clinical response in patients with early axSpA treated with ETN over 3 years. ClinicalTrials.gov registration number NCT00844142. (First Release July 15 2014; J Rheumatol 2014;41:2034–40; doi:10.3899/jrheum.140056)

Key Indexing Terms:

ANKYLOSING SPONDYLITIS — NONRADIOGRAPHIC AXIAL SPONDYLOARTHRITIS
MAGNETIC RESONANCE IMAGING — ETANERCEPT
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Patients with axial spondyloarthritis (axSpA) can be classified as nonradiographic axSpA (nr-axSpA) or radiographic axSpA, also termed ankylosing spondylitis (AS), according to the Assessment of SpondyloArthritis International Society (ASAS) classification criteria[1]. For patients with early axSpA who do not respond to treatment with nonsteroidal antiinflammatory drugs, tumor necrosis factor (TNF)-α inhibitors (or TNF blockers) have had proven, good short-term efficacy in controlled clinical trials [adalimumab, infliximab, etanercept (ETN), and just recently, certolizumab][2,3,4,5,6]. Further, one study indicated that treatment with the TNF blocker adalimumab in nr-axSpA shows a stable response for up to 2 years of treatment[6]. However, in contrast to longstanding established AS[7,8], longterm efficacy data for 3 years or longer are missing so far in early axSpA.

In the ESTHER trial, the longterm efficacy was assessed

of ETN in patients with early axSpA with a disease duration of < 5 years and evidence of active inflammation on whole-body magnetic resonance imaging (wb-MRI) in the spine and/or sacroiliac (SI) joints at baseline[2]. We report on the effects of continuous treatment over 3 years with ETN in patients with axSpA, also comparing patients with AS and nr-axSpA.

MATERIALS AND METHODS

In the previously reported ESTHER trial, 76 patients with axSpA were either treated with ETN (n = 40) or sulfasalazine (SSZ; n = 36) in the first year[2].

The inclusion criteria have been described before in detail[2], but all patients retrospectively fulfilled the ASAS classification criteria for axSpA and had evidence of active inflammation in the SI joints and/or the spine[1]. For further analysis, patients were divided into nr-axSpA and AS, applying the radiographic SI joint score according to the modified New York criteria[9]. Treatment was temporarily discontinued in 17 patients (n = 13 from the ETN group vs n = 4 from the SSZ group) who reached study remission at Week 48, and treatment with ETN was started in case of a flare (n = 13)[10]. Twenty-two patients from the initial ETN group continued ETN treatment without interruption and 26 patients from the initial SSZ group switched treatment directly to ETN at Week 48 (Figure 1)[10]. Four patients were excluded from the study who were in continuous drug-free remission in Year 2[10].

We analyzed the clinical, laboratory, and MRI response in the pooled dataset of those 61 patients who were continuously treated with ETN for 3 consecutive years (study population). Thus, for patients from the original SSZ group, study data from years 2 to 4 were used (the same for patients who flared after study drug discontinuation during Year 2 of the trial). For patients from the original ETN group who did not reach remission at Week 48, data from years 1, 2, and 3 were used.

Altogether, 42 patients completed 3 years of continuous ETN treatment (Figure 1). In 41 of them, wb-MRI were available and were scored for active inflammation (osteitis) in the SI joint quadrants and spine vertebral units by 2 blinded radiologists, according to a described protocol[2,10].

Written consent was obtained from all patients according to the Declaration of Helsinki (updated 2008) and the study was approved by a local ethics committee (Landesamt für Gesundheit und Soziales, Geschäftsstelle der Ethikkommission Berlin; ZS EK 14 EA4/100/05). This trial was registered in www.clinicaltrials.gov under the registration number NCT00844142. The EudraCT number is 2005-002320-34.

Statistical analysis. All patients in the study population (n = 61) were included in the primary analysis. Last observation carried forward (LOCF) analysis was applied to impute missing data. Linear mixed models were applied to investigate whether there was a change in the outcome measure

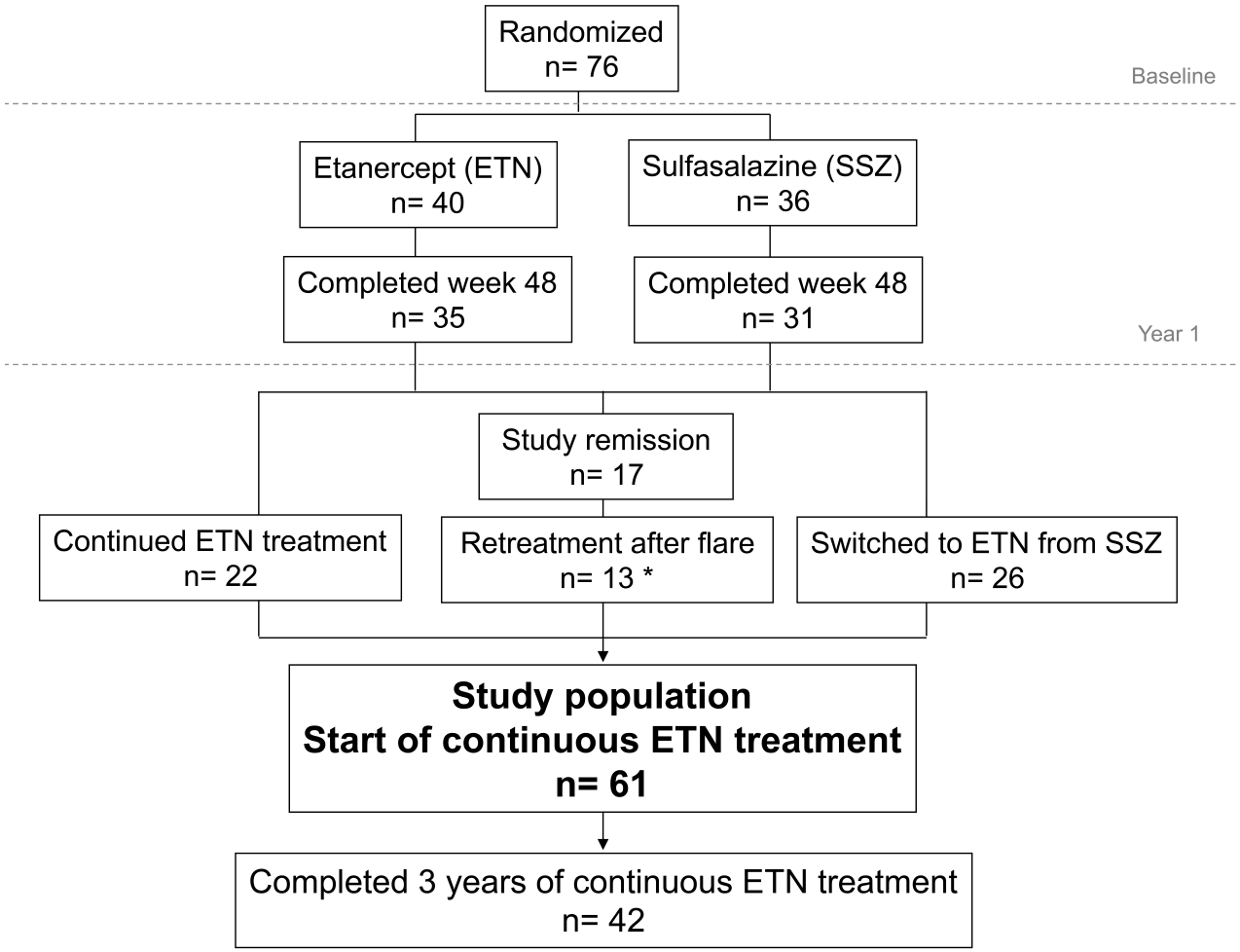

Figure 1. Flowchart describing treatment arms of the 61 patients in the study population who were continuously treated with etanercept (ETN). *Of the 17 patients in study remission, 4 (3 from the former ETN treatment arm and 1 from the former sulfasalazine treatment arm) were withdrawn from the study because of the ongoing remission[10]. SSZ: sulfasalazine.

between end of Year 1 and end of Year 3 of continuous treatment with ETN. Three timepoints (end of years 1, 2, and 3 of continuous ETN treatment) were compared in this analysis. Linear mixed models were also applied in the completer analysis (n = 42). P values below 0.05 were considered statistically significant.

RESULTS

Baseline characteristics. At baseline, 61% (37 out of 61) of the patients were male and 84% (51 out of 61) HLA-B27–positive in the total study population. Mean age was 33.2 years (± 8.2) and mean disease duration was 2.7 years (± 1.7). Fifty-one percent of patients belonged to the group with AS (n = 31) and 49% to the group with nr-axSpA (n = 30).

When comparing the 2 subgroups, AS and nr-axSpA, there was no difference in sex or mean age, but there was a difference in disease duration (3.3 vs 2.2 yrs, p = 0.011) and HLA-B27 positivity (93.5% vs 73.3%, p = 0.033).

Efficacy data for the whole group of axSpA. The results for different disease variables for the study group (n = 61), as well as for the completer group (n = 42), are shown in Figure 2 A and B. Although the response was expectedly better in the completer population, a stable and sustained response could also be observed in the LOCF population.

A status of Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease after 3 years of continuous ETN treatment was achieved by 41% in the study population (n = 61) versus 60% in the completer population, and ASAS partial remission by 30% versus 43%, respectively.

The mean MRI SI joint score was reduced from 7.1 (± 6.4) at baseline to 2.0 (± 2.2) at Year 2 and to 2.2 (± 2.5) at Year 3, while the mean MRI osteitis spine score decreased from 1.7 (± 3.4) at baseline to 0.7 (± 1.4) at Year 2 and to 0.9 (± 1.8) at Year 3 in the total group (AS and nr-axSpA).

Response rates were similar regardless of whether patients had received SSZ or ETN during the first year and regardless of whether patients were retreated after a flare (data not shown).

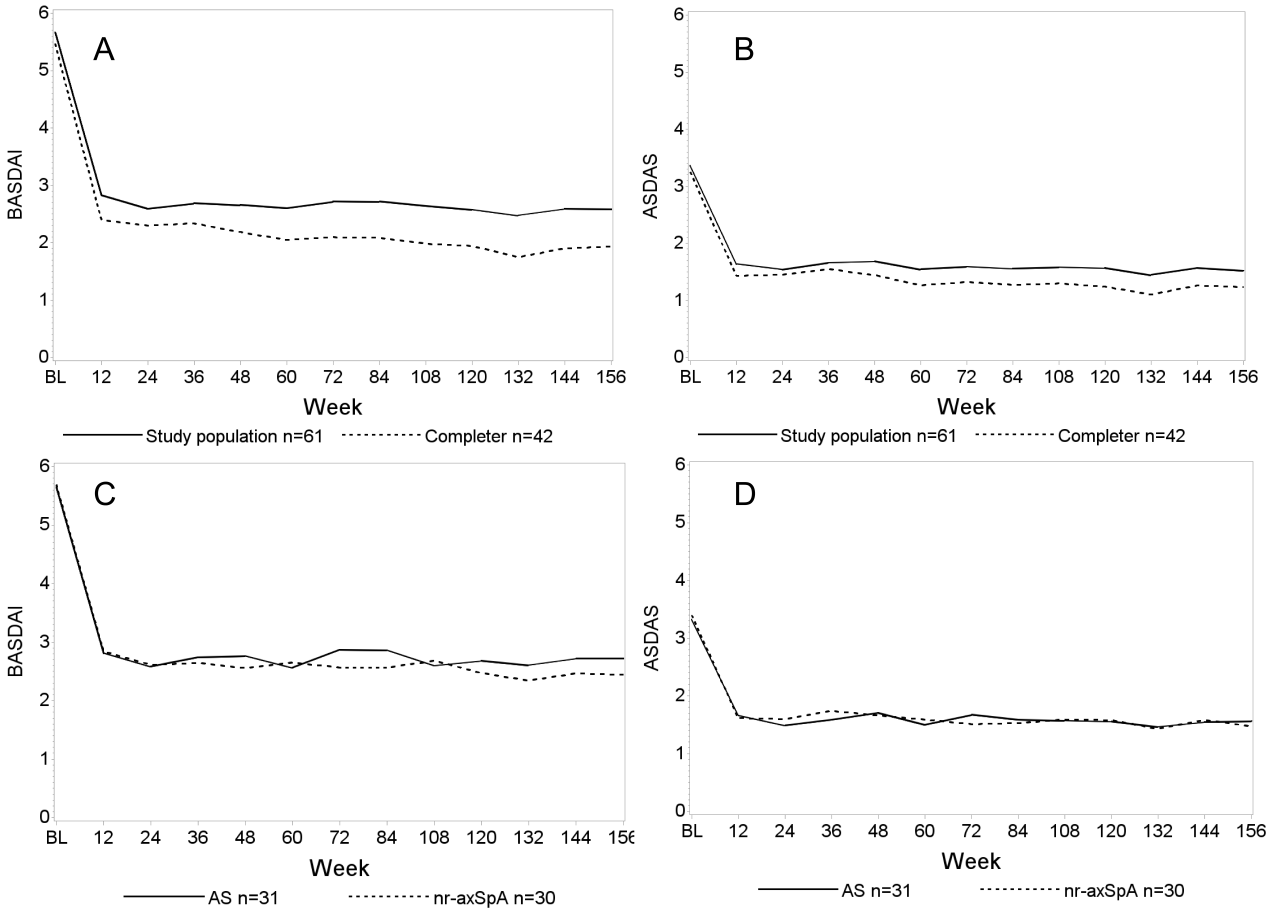

Figure 2. (A) Bath Ankylosing Spondylitis Disease Activity Score (BASDAI) and (B) Ankylosing Spondylitis Disease Activity Score (ASDAS) values in the study population (n = 61) versus the completer population (n = 42) during 3 years of continuous treatment with etanercept. (C) BASDAI and (D) ASDAS values in the study population in the 2 subgroups of patients with ankylosing spondylitis (AS, n = 31) versus nonradiographic axial spondyloarthritis (nr-axSpA, n = 30).

Efficacy data in AS versus nr-axSpA. When the study population data were analyzed in the subgroups of AS (n = 31) and nr-axSpA (n = 30), the response rates at years 2 and 3 were similar in both groups. This is shown in detail for the clinical variables, MRI scores, and CRP levels in Table 1 and Figures 2C and 2D. For example, the BASDAI decreased from 5.6 (± 1.3) at baseline to 2.7 (± 2.5) at Year 3 in the AS group and from 5.7 (± 1.2) at baseline to 2.4 (± 2.3) at Year 3 in the nr-axSpA group. There was even a trend toward a slightly better response for some of the outcome variables in nr-axSpA, as compared to patients with AS (Table 1).

Remission analysis. We further addressed the question of how many patients achieved different kinds of remission at Year 3 in the whole group (AS and nr-axSpA) and analyzed the overlap between the different remission variables. For this purpose, we analyzed the patients who were continuously treated with ETN for 3 years and for whom the whole sets of MRI from baseline, Year 2, and Year 3 were available (41 out of 42 patients).

Figure 3 shows the numbers of patients after 3 years of continuous ETN treatment who reached ASAS partial remission [n = 18 out of 41 (43.9%)], ASDAS inactive disease [n = 25 out of 41 (61.0%)], a CRP value below 5 mg/l [n = 35 out of 41 (85.4%)], or who became free of active inflammatory lesions both in the spine and the SI joints according to at least 1 of the 2 scorers [n = 14 out of 41 (34.1%)].

Interestingly, patients who became free of active inflammatory lesions both in the spine and the SI joints, or who had ASDAS inactive disease, were nearly all CRP-negative, as shown in Figure 3A, but 16 out of 25 patients (64%) with inactive ASDAS were not in MRI remission.

As shown in Figure 3B, ASAS partial remission showed less overlap with the remission status of objective measures of inflammation, such as CRP and MRI compared to ASDAS inactive disease: 4 out of 18 patients (22%) in ASAS remission were not in CRP remission and 13 out of 18 (72%) were not in MRI remission.

Dropouts. There was a total dropout rate of 32 out of 76 (42.1%) at Year 4 (Week 216). The 4 patients who reached the end of Year 2 in ongoing remission[10] were not counted. Until Year 2 (week 108), 17 out of 76 (22.4%) dropped out of the study. The exact reasons for the dropouts in the first 2 study years have been reported[2,10]. The reasons for dropouts in years 3 and 4 (weeks 108–216) were inefficacy of ETN in 6 cases, wish for pregnancy in 3 cases, wish for alternative nonpharmacological treatment options in 1 case, and psychiatric problems/noncompliance in 1 patient; most of the other cases were lost to followup.

Adverse events (AE). During years 3 and 4 (weeks 108–216), a total of 256 AE were observed. Of those, 41.8% were infections of the upper respiratory tract (mostly mild).

In years 3 and 4, 3 new serious AE occurred. One occurred in a male patient who developed sarcoidosis and was hospitalized for diagnostic investigations. The study drug was discontinued in this patient because a relationship with ETN treatment was regarded as possible. Two more patients were hospitalized, 1 for tonsillectomy and 1 for disc problems. These 2 serious AE were regarded not to be related to study drug. No cases of malignancy, opportunistic infections, or tuberculosis were observed.

Table 1. Longterm efficacy of 3 years of continuous etanercept treatment in patients with early axial spondyloarthritis (axSpA). Data at baseline after 1, 2, and 3 years of treatment with etanercept. Data shown based on study population (n = 61). Data shown for the study population based on the last observation carried forward method as mean values (SD) unless otherwise stated.

Variables	AS, n = 31				nr-axSpA, n = 30				p*	p**
	BL	Year 1	Year 2	Year 3	BL	Year 1	Year 2	Year 3		
BASDAI, 0–10, mean (SD)	5.6 (1.3)	2.8 (2.1)	2.6 (2.5)	2.7 (2.5)	5.7 (1.2)	2.6 (2.3)	2.7 (2.4)	2.4 (2.3)	0.87	0.89
BASFI, 0–10, mean (SD)	4.5 (2.1)	2.3 (2.1)	2.3 (2.4)	2.3 (2.3)	4.3 (2.0)	1.8 (1.9)	1.8 (1.9)	1.7 (1.9)	0.71	0.98
ASDAS, 0–∞, mean (SD)	3.3 (0.7)	1.7 (0.8)	1.6 (1)	1.6 (1)	3.4 (0.8)	1.7 (1.1)	1.6 (1.2)	1.5 (1)	0.14	0.65
BASMI, 0–10, mean (SD)	1.8 (1.7)	2 (1.9)	2 (1.8)	2.1 (1.7)	1.6 (1.5)	1.3 (1.5)	1.2 (1.5)	1.1 (1.5)	0.71	0.77
Joint count, 0–64, mean (SD)	1.1 (1.6)	0 (0)	0.1 (0.4)	0.1 (0.4)	2.4 (4.5)	0.2 (0.6)	0.2 (0.9)	0.1 (0.6)	0.56	0.85
Enthesitis score, 0–17, mean (SD)	4.1 (4.3)	1.9 (3.8)	1.5 (3.5)	1.5 (3.5)	3.7 (3.5)	1.4 (3.7)	1.5 (3.6)	1.7 (3.8)	0.64	0.44
CRP, mean mg/l (SD)	11 (13.4)	3.8 (4.5)	3.9 (5.6)	3 (4.1)	9.9 (13.8)	5.3 (11.3)	4.6 (10.9)	5 (11.8)	0.67	0.90
MRI spine score, 0–69, mean (SD)***	2.3 (4.3)	NA	0.6 (0.8)	0.9 (1.2)	1.3 (2.5)	NA	0.8 (1.7)	1 (2.2)	0.11	0.28
MRI SI joint score, 0–24, mean (SD)***	8.5 (7.4)	NA	3 (2.7)	2.5 (2.9)	6.2 (5.5)	NA	1.4 (1.5)	2 (2.3)	0.64	0.29
ASAS partial remission (%)	NA	29%	39%	26%	NA	40%	40%	33%	NA	NA
ASDAS inactive disease (%)	NA	32%	35%	32%	NA	40%	40%	50%	NA	NA
ASDAS major improvement (%)	NA	29%	32%	26%	NA	40%	33%	37%	NA	NA

* Mixed model to assess whether there is change in time between years 1, 2, and 3. ** Mixed model to assess whether the 2 groups differ in their change in time between years 1, 2, and 3. *** MRI data shown for completers of whom complete sets of MRI were available at baseline, Year 2, and Year 3 of continuous etanercept treatment; these were n = 17 patients with AS and n = 24 patients with nr-axSpA. BL: baseline; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASMI: Bath Ankylosing Spondylitis Mobility Index; CRP: C-reactive protein; MRI: magnetic resonance imaging; SI joint: sacroiliac joint; ASAS: Assessment of SpondyloArthritis international Society; NA: not applicable; nr-axSpA: nonradiographic SpA.

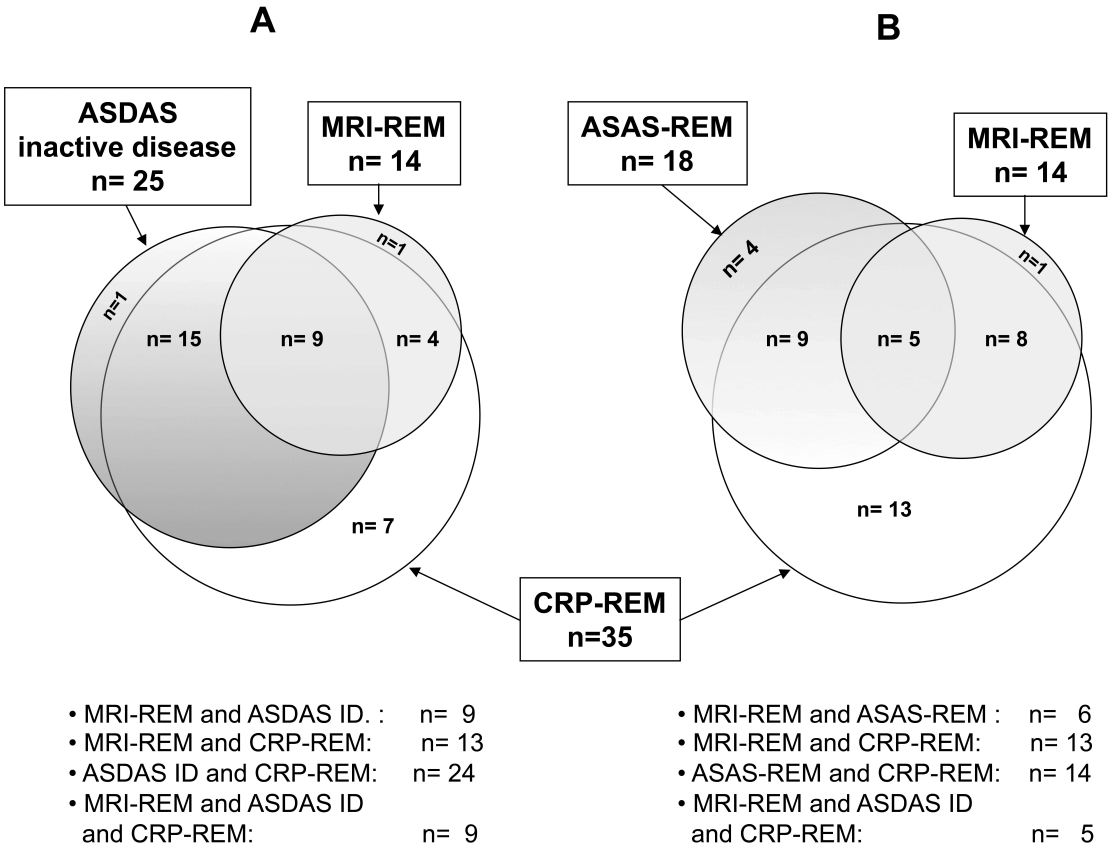

Figure 3. Numbers of patients in Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (ASDAS ID), in ASAS partial remission, with CRP < 5 mg/l (CRP-REM), and who did not have any active inflammatory lesion in the spine and the sacroiliac joints according to at least 1 of the 2 scorers (MRI-REM). Remission data at the end of 3 years (Week 156) of continuous etanercept treatment are shown.

DISCUSSION

We found a consistent efficacy of ETN treatment on all assessments of clinical disease activity and on active inflammation on MRI of spine and SI joints in our followup study of patients with early axSpA, with a short mean disease duration of less than 3 years for patients who were treated continuously with ETN for 3 consecutive years. Further, ETN treatment was safe in the study population during the trial period.

Our data indicate that continuation of ETN for up to 3 years is successful regardless of whether treatment was temporarily interrupted or whether patients were treated with SSZ in Year 1. For this analysis, we decided to pool the data to achieve a homogeneous dataset of patients who were continuously treated with ETN over 3 years.

There has been ongoing discussion about the relevance of the nr-axSpA subgroup of axSpA and its longterm outcomes[11,12]. We have previously reported that patients with AS and nr-axSpA show a similar response after 1 year of ETN treatment[13]. We have shown that for every outcome variable, such as patient-reported outcomes, MRI, and CRP, the 2 subgroups show a similar longterm response if treated with ETN for 3 continuous years and if baseline measures for clinical activity and objective signs of inflammation such as CRP and MRI inflammation are similar, as was the case here[13].

Several publications reported on the efficacy of a continuous treatment with TNF blockers for a duration of 3 years or longer in established longstanding AS[7,8]. The dropout rates were between 38% and 51% in these trials after 3 years of active treatment and were thus comparable to that found in our study. Also, the clinical response was comparable to the one we found in our study[7,8,14], with even a trend for a somewhat better clinical response in our early axSpA cohort, for example, as measured by ASAS partial remission (in our trial achieved by 30% using LOCF and 43% using a completer analysis vs 21% and 28%, respectively)[7].

We also found a consistently good effect not only on patient-reported outcomes, but also on active inflammation on MRI on spine, SI joints, and entheses, a result similar to earlier AS studies[15,16].

Recently, treat-to-target recommendations have been

defined for SpA, including axSpA, by an international expert group[17]. The key treatment target should be clinical remission/inactive disease of musculoskeletal involvement, also taking extraarticular manifestations into consideration. Clinical remission/inactive disease was defined as the absence of clinical and laboratory evidence of significant inflammatory disease activity. According to these recommendations, other factors, such as axial inflammation on MRI, may also be considered when setting clinical targets. We report here for the first time, to our knowledge, the overlap of different remission variables in patients with axSpA treated with a TNF blocker. Ninety-six percent (24 out of 25) of all patients fulfilling the ASDAS inactive disease criteria were also in CRP remission (CRP-negative). This is unsurprising because the ASDAS is influenced by CRP. In contrast, 22% (4 out of 22) of those patients meeting the ASAS partial remission criteria were still CRP-positive, indicating that ASDAS inactive disease might be the preferred remission criterion in the context of the treat-to-target recommendations[17]. Indeed, both elevated CRP[18] and an elevated ASDAS[19] have been found to be correlated with radiographic progression in the spine of patients with AS, although it has still to be shown that normalization of these variables by treatment intervention can prevent such a progression. There is also limited data suggesting that MRI inflammation of SI joints[20,21] and of the spine[22,23,24] might be associated with radiographic progression. Here we show for the first time, to our knowledge, that a substantial proportion of patients both with ASDAS inactive disease [16 out of 25 (64%)] and ASAS partial remission [13 out of 18 (72%)] are not in MRI remission, based on an MRI analysis of SI joints and the whole spine. Thus, MRI remission might also turn out to be an important target. More data are needed here. It is also of interest whether persistent inflammation on MRI is associated with the occurrence of structural damage. Future research will show whether and how much persistent MRI inflammation matters and whether MRI inflammation should be included in future remission outcome measures.

In this longterm followup study, patients with early axSpA who received 3 years of continuous treatment with ETN showed sustained efficacy on patient-reported outcomes, laboratory values, and importantly, active inflammation on whole-body MRI. Also, there was a good safety profile in these patients. The longterm data for the nr-axSpA subgroup with MRI evidence of active inflammation are at least as good as in longstanding AS. These data underline the importance of early diagnosis and early effective treatment, and confirm the concept that axSpA includes both nr-axSpA and AS.

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