Comparison of Clinical Examination versus Whole-body Magnetic Resonance Imaging of Enthesitis in Patients with Early Axial Spondyloarthritis during 3 Years of Continuous Etanercept Treatment

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ABSTRACT. ***Objective.*** To compare clinical examination versus whole-body magnetic resonance imaging (WB-MRI) of enthesitis in patients with early axial spondyloarthritis during 3 years of continuous etanercept (ETN) treatment.

Methods. Forty-one patients underwent clinical and WB-MRI examinations for enthesitis at baseline and after 2 and 3 years of treatment. Twenty-one sites were assessed in 4 anatomic regions — anterior chest wall, pelvis, knee, and foot.

Results. Clinical examination at baseline detected enthesitis in 57% of the patients (85 lesions, mean 2.1 lesions, SD 2.9), most of them in the pelvis (42 lesions in 17 patients) and anterior chest wall (19 lesions in 10 patients). The proportion of patients with clinically detected enthesitis decreased to 19% at Year 2 (mean 0.5, SD 1.5) and 14% at Year 3 (mean 0.7, SD 1.8). WB-MRI detected enthesitis at baseline in 21% of patients (22 lesions, mean 0.5 lesions, SD 1.1), also most frequently in the pelvis (12 lesions) and anterior chest wall (7 lesions). MRI-positive enthesitis decreased to 13% at Year 2 (mean 0.2 lesions, SD 0.5) and 14% at Year 3 (mean 0.2 lesions, SD 0.5). There was positive correlation of clinical and MRI findings at baseline at the anterior chest wall ($p = 0.001$) and the pelvis ($p = 0.0001$). No correlation was found at the knee and foot at baseline and for all regions at followup.

Conclusion. Both clinical examination and WB-MRI show a decrease in enthesitis after 2 and 3 years of ETN treatment, but correlation was limited to the pelvis and anterior chest wall at baseline.

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Key Indexing Terms:

MAGNETIC RESONANCE IMAGING | WHOLE-BODY MRI | ENTHESITIS
SPONDYLOARTHRITIS | TNF-α BLOCKER | CLINICAL TRIAL

Axial spondyloarthritis (axSpA) is a chronic rheumatic inflammatory disease that mainly affects the sacroiliac joints (SIJ) and the spine[1], but patients may also present with asymmetrical arthritis and enthesitis in peripheral locations[2,3]. Enthesitis is an important primary manifestation of SpA that can seriously degrade quality of life[4,5].

Magnetic resonance imaging (MRI) enables a more sensitive assessment of both inflammatory and structural SpA lesions than radiographic imaging[1,6]. Whole-body MRI (WB-MRI) has been studied by several research groups[7,8,9] and has been shown to be especially useful for detecting early inflammation and structural damage in different locations of the axial skeleton[9,10,11,12], and also in peripheral joints and entheses[9,12,13,14]. Further, its value as a tool for assessing disease activity and monitoring treatment effects has been studied[15,16,17]. Tumor necrosis factor (TNF) blockers have been shown to effectively reduce signs of peripheral and axial enthesitis[15,18,19]; however, published studies have been performed by investigators using different clinical methods for assessment of enthesitis[20]. MRI might be a better tool for identifying enthesitis in locations affected by SpA.

The aim of our prospective analysis was to compare the

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detection of enthesitis by clinical examination versus WB-MRI at baseline and during 3-year followup in the ESTHER (Enbrel Sulfasalazine Early Axial Spondyloarthritis) trial, which included patients with early axSpA with a disease duration of < 5 years and 3 years of continuous etanercept (ETN) treatment.

MATERIALS AND METHODS

From the previously reported ESTHER trial, we analyzed the pooled data of 42 patients with axSpA who received 3 years of continuous ETN treatment (25 mg given twice weekly subcutaneously), as previously described[21]. All patients were clinically evaluated at baseline and again after 2 and 3 years of treatment. WB-MRI was performed and evaluated in 41 patients for all 3 timepoints. One patient refused MRI because of claustrophobia. Written informed consent was obtained from all patients according to the Declaration of Helsinki (updated 2008), and our study was approved by the local ethics committee (Landesamt für Gesundheit und Soziales, Geschäftsstelle der Ethikkommission Berlin; ZS EK 14 EA4/100/05).

Inclusion and exclusion criteria. Retrospectively, all patients fulfilled the recently published Assessment of SpondyloArthritis international Society classification criteria for axSpA[22]. All patients had to have a history of less than 5 years of chronic low back pain and a positive MRI for active inflammation of the spine and/or the SIJ at the beginning of our study. Other inclusion criteria are described elsewhere[15].

Clinical assessment. Clinical and laboratory outcome assessment was performed in all patients at 3 different timepoints: baseline, after 2 years, and after 3 years of treatment[23]. Assessment included the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index[24], Bath Ankylosing Spondylitis Metrology Index on an 11-point answer scale[25], a swollen joint count with 64 joints, patient's and physician's global assessments of disease activity, and C-reactive protein (CRP)[23]. Enthesitis was evaluated using a modified Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)[4] at the following 17 locations for each timepoint (Figure 1), subdivided into 4 anatomical regions: Region 1, anterior chest wall — first and seventh costosternal joints (4 locations per patient); Region 2, pelvis — iliac crest, anterior, and posterior superior iliac spine, spinous process of L5 (7 locations per patient); Region 3, knee — medial and lateral femoral condyles (4 locations per patient); and Region 4, foot — proximal insertion of the Achilles tendon (2 locations per patient). Every study center was equipped with a dedicated study team consisting of rheumatologists and trained and qualified study nurses. Clinical examination of enthesitis were performed by the same assessors specialized in SpA. To assess enthesitis, the investigator applied pressure over the investigated entheses. The patients' response to firm palpation was used to assess the absence or presence of enthesitis, which was scored dichotomously.

Whole-body MRI. WB-MRI was performed on a 1.5 Tesla scanner (Avanto, Siemens). Coronal T1-weighted fast spin echo (FSE) sequences (T1W) and short-tau inversion recovery (STIR) sequences were acquired, including the head, neck, chest with chest wall, abdomen, pelvis, and lower extremities.

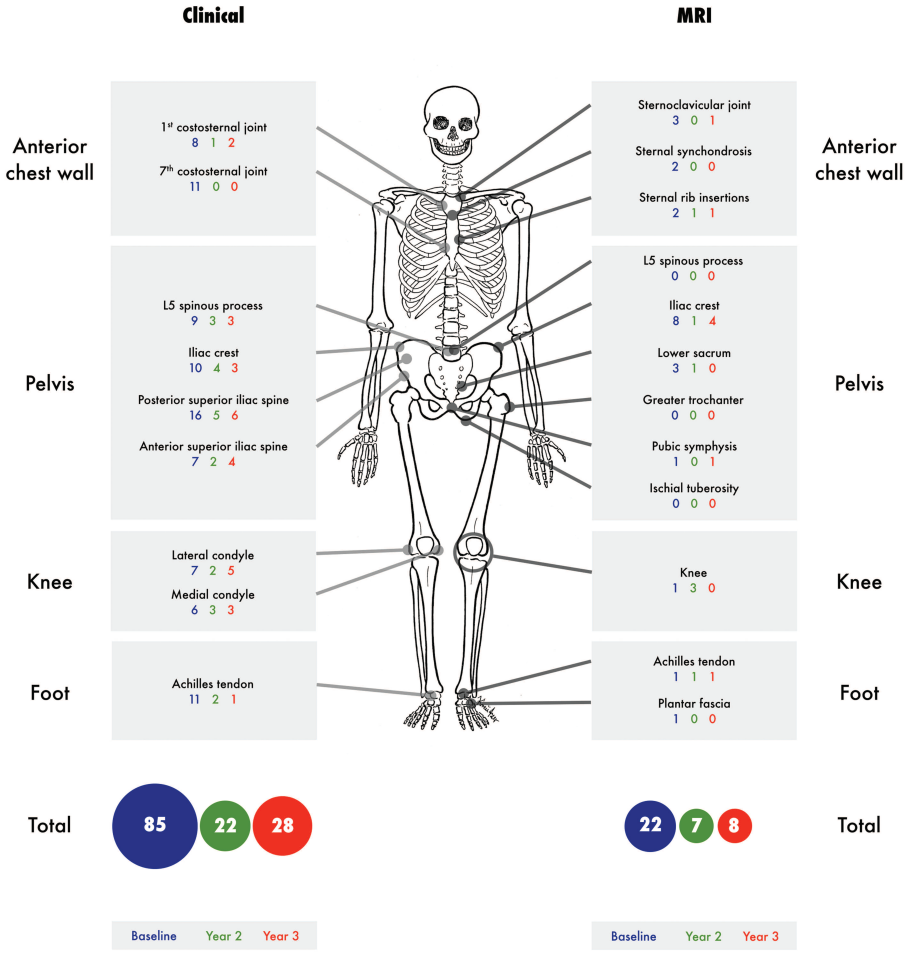

Figure 1. Lesion count of clinical assessment and WB-MRI. WB-MRI: whole-body magnetic resonance imaging.

Elbows, hands, and toes were not imaged because of coil limitations. The detailed WB-MRI protocol has been described previously[10,15,26]. All WB-MRI examinations have been acquired within 14 days after the clinical assessment.

Definitions of enthesitis. Enthesitis was diagnosed when there was high signal intensity on STIR images with a corresponding signal loss on T1W images within the bone marrow [bone marrow edema (BME)] or the surrounding soft tissue (soft tissue edema). The following 21 locations were evaluated, subdivided into 4 regions (Figure 1): Region 1, anterior chest wall — tendon insertions and joint capsule insertions at the sternoclavicular joints, sternal synchondrosis, and costosternal junctions (5 locations); Region 2, pelvis — tendon and ligament insertions at the iliac crest, ischial tuberosity, lower border of the sacrum (the insertion site of the sacrococcygeal ligament), spinous process of L5, greater femoral trochanter, and pubic symphysis (10 locations); Region 3, knee — femoral condyles of the knees (2 locations); and Region 4, foot — insertion sites of the Achilles tendon and the plantar fascia (4 locations). The resulting maximum possible lesion count was 861 for each timepoint.

Of note, entheseal lesions (osteitis and soft tissue involvement) at the humerus and acromion were not evaluated because field inhomogeneity artifacts frequently obscured that region in our patients and reliable analysis was deemed difficult.

Scoring of WB-MRI. Reading sessions took place at a PACS (Picture Archiving and Communication Systems) workstation using 2 high-resolution monitors. Scoring was performed with the help of the open source digital imaging and communications in medicine (DICOM) viewer software OsiriX (Pixmeo SARL). Patient identification data as well as timepoint were blinded. Enthesitis assessment on WB-MRI was performed by 2 experienced musculoskeletal radiologists (CA, 12 yrs of experience, and KGH, 15 yrs of experience) in a consensus approach. Enthesitis on WB-MRI was scored dichotomously (present/absent). For a positive lesion, both expert readers needed to agree on the finding. Discrepancies were solved by a short discussion of the lesion.

Statistical analysis. All 41 patients for whom clinical and MRI assessment of enthesitis at baseline, Year 2, and Year 3 were available were included in the primary analysis. Continuous variables were tested using the Wilcoxon signed-rank test, and dichotomous variables were tested using Fisher's exact test. Differences between timepoints were analyzed using the nonparametric Brunner test. Correlation of clinical and MRI outcomes was calculated using Spearman rho (ρ).

P values below 0.05 were considered to be statistically significant. Standardized response means (SRM) were calculated as the difference between 2 measurement points divided by the SD for the difference[27]. According to Cohen, the thresholds for interpreting effect sizes are 0–0.2 (no effect), 0.2–0.5 (small effect), 0.5–0.8 (moderate effect), and > 0.8 (large effect)[28]. These thresholds are also guidelines to interpret results of SRM. No missing data imputation has been performed because all primary data were available.

RESULTS

Demographic and clinical data of the 41 patients included in our analysis are presented in Table 1 and Table 2 separately for patients with ankylosing spondylitis (AS) and nonradiographic axSpA (nr-axSpA). The patients had a median age of 32.8 years, 28 patients (68%) were men, and 80% were positive for HLA-B27. The median symptom duration was 2.6 years for all patients with 3.2 years in the AS group compared with 2.1 years in patients with nr-axSpA. All patients had active disease at baseline as shown by elevated values for BASDAI (≥ 4) and MRI showing active inflammatory lesions in the SIJ or spine.

Clinical assessment of enthesitis. At baseline, 57% of patients (n = 24) showed clinical signs of enthesitis (total of 85 out of 697 possible lesions). The mean clinical enthesitis score was 2.1 (SD 2.9) out of 17 possible scoring points. The results are presented in Figure 1.

The anterior chest wall (Region 1) was affected in 24% of patients (n = 10). The pelvic region (Region 2) was the most frequently affected body region in terms of enthesitis with 40% of affected patients (n = 17). Here, the posterior superior iliac spine was the most commonly affected location (total of 16 lesions in all patients). Enthesitis was less frequent in Regions 3 (knee) and 4 (foot), with 14% of patients each showing evidence of enthesitis in these locations.

Continuous ETN treatment led to a reduction in the percentage of patients with clinical evidence of enthesitis, starting from 57% of all patients (n = 24) with only 19% of patients after 2 years (n = 8) and 14% of patients after 3 years

Table 1. Baseline characteristics of the 41 study patients. P values were calculated using the Wilcoxon signed-rank test for continuous variables and Fisher's exact test for dichotomous variables. Values are n (%) unless otherwise specified.

Characteristics	AS	nr-axSpA	All Patients	p
Patients, n	17	24	41	
Male	12 (71)	16 (67)	28 (68)	1.00
Age, yrs, mean (± SD)	30.9 (6.6)	34.1 (8.8)	32.8 (8.1)	0.26
Disease duration, back pain duration, yrs, mean (± SD)	3.2 (1.7)	2.1 (1.4)	2.6 (1.6)	0.04
HLA-B27–positive	16 (94)	17 (71)	33 (80)	0.11
BASDAI, 0–10, mean (SD)	5.5 (1.3)	5.5 (1.1)	5.5 (1.2)	0.94
BASMI, 0–10, mean (SD)	1.2 (1.3)	1.6 (1.4)	1.4 (1.4)	0.29
CRP, mg/l, mean (SD)	12.4 (16.8)	8.4 (11.2)	10 (13.7)	0.67
Patients with raised CRP (> 5 mg/l)	10 (63)	11 (46)	21 (53)	0.35
Presence of clinical enthesitis	11 (65)	13 (54)	24 (59)	0.54
Presence of MRI enthesitis	5 (29)	4 (17)	9 (22)	0.45

AS: ankylosing spondylitis; nr-axSpA: nonradiographic axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; MRI: magnetic resonance imaging.

Table 2. Clinical data and WB-MRI findings of the 41 study patients. Values are mean (SD) unless otherwise specified.

Variables	Baseline	Yr 2	Yr 3
Enthesitis score, clinical, 0–17	2.1 (2.9)	0.5 (1.5)	0.7 (1.8)
Enthesitis score, MRI, 0–17	0.5 (1.1)	0.2 (0.5)	0.2 (0.5)
BASDAI, 0–10	5.5 (1.2)	1.9 (1.6)	1.9 (1.5)
BASDAI fourth question ≥ 4, n (%)	24 (59)	7 (17)	7 (17)
SJC, 0–64	1.9 (3.9)	0.1 (0.6)	0.03 (0.2)
CRP, mg/l	10.0 (13.7)	3.2 (5.0)	2.9 (5.5)

WB-MRI: whole-body magnetic resonance imaging; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASDAI fourth question: "How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?"; SJC: swollen joint count; CRP: C-reactive protein.

(n = 6). The number of enthesitis lesions decreased from 85 at baseline to 22 at Year 2 and 28 at Year 3.

WB-MRI assessment of enthesitis. Enthesitis was detected less commonly by WB-MRI than by clinical assessment. WB-MRI identified enthesitis in 21% of patients (n = 9; total of 22 out of 861 possible lesions) with a mean of 0.5 (SD 1.1) lesions per patient at baseline. Detailed results are depicted in Figure 1.

Seven enthesitis lesions were detected by MRI in Region 1 (anterior chest wall), 12 lesions in Region 2 (pelvis), 1 lesion in Region 3 (knee), and 2 lesions in Region 4 (foot). Imaging examples are presented in Figure 2 and Figure 3.

After 2 years of continuous treatment with ETN, enthesitis detected by MRI decreased to 7 lesions in 5 patients (13%) with a mean of 0.2 lesions (SD 0.5) per patient, and remained low with 8 lesions in 6 patients (14%) after 3 years of treatment (mean 0.15 lesions, SD 0.43; Figure 1).

Comparison of clinical and WB-MRI findings. At baseline, findings of enthesitis were much more frequent in clinical assessment (57% of patients, 85 lesions) than in the evaluation of the MR images (21% of patients, 22 lesions). According to Cohen thresholds of effect size values, small to moderate effects of ETN treatment on enthesitis could be detected both by clinical assessment and MRI on a global scale. Both methods showed a similar decline of inflammation with an SRM of 0.55 for clinical findings and 0.34 for MRI after 2 years of ETN treatment, and 0.47 (clinical) and 0.28 (MRI) after 3 years of treatment.

Clinical and MRI results were also compared with the BASDAI and Ankylosing Spondylitis Disease Activity Score (ASDAS), which are designed to measure disease activity of patients with predominantly axial manifestations. We found a positive correlation between global BASDAI and clinical findings at years 2 and 3 (p = 0.004 and 0.02), but no correlation at baseline or with MRI for all 3 timepoints. No correlation was found for baseline and ASDAS-CRP for all timepoints.

Comparison of anatomical sites by region revealed a significant association of clinical assessment and WB-MRI in Region 1 (anterior chest wall; p = 0.001, Wilcoxon) and Region 2 (pelvis; p = 0.0001, Wilcoxon) at baseline. In Regions 3 (knee) and 4 (foot), no significant associations were found (Table 3). No positive correlation was found for any of the 4 regions at 2 years and 3 years.

DISCUSSION

Ours is the first comprehensive study to evaluate the course of enthesitis in 41 patients with active axSpA under ETN therapy. Enthesitis at baseline was detected more frequently by standardized clinical examination compared with WB-MRI (57% vs 21% of patients), with a predominance of lesions in the anterior chest wall and pelvis. Enthesitis was much less common in the lower extremities. An overall reduction of enthesitis after 2 and 3 years of therapy was evident both clinically and on WB-MRI. While positive correlation of both methods was found for the anterior chest wall and the pelvis at baseline, no correlation was demonstrated for locations in the lower extremity or at all locations taken together after ETN treatment.

The ESTHER trial was designed to study inflammation on the axial skeleton and the peripheral locations, and to compare ETN and sulfasalazine therapies. After 48 weeks of

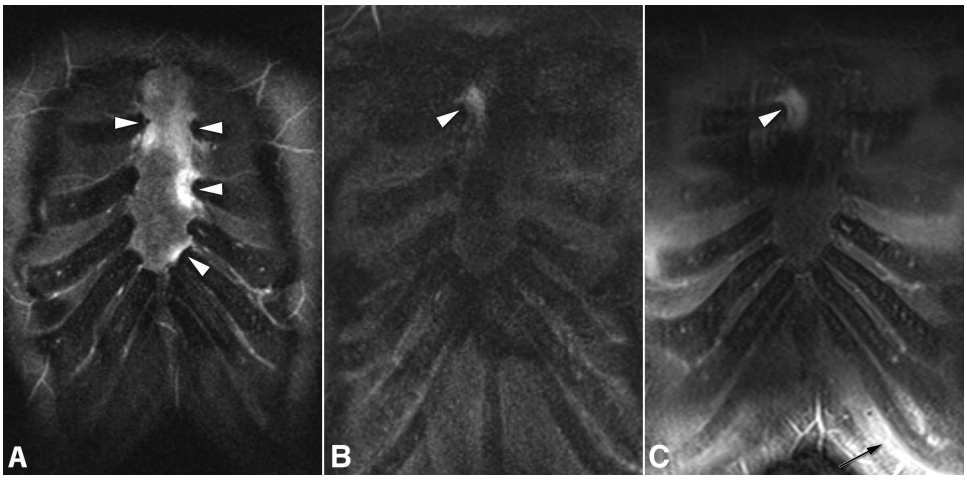

Figure 2. A. WB-MRI STIR images of the anterior chest wall in coronal orientation with BME at the third costosternal joint on the right as well as third, fourth, and sixth costosternal joint on the left (arrowheads) at baseline. B. After 2 years of ETN therapy, there is a marked decrease with only residual inflammation at the third costosternal joint on the right (arrowhead). C. After 3 years, this minor enthesitis persists (arrowhead). Slight rib perichondritis is now evident (black small arrow). Clinical investigation showed no evidence of enthesitis at the anterior chest wall at all 3 timepoints. WB-MRI: whole-body magnetic resonance imaging; STIR: short-tau inversion recovery; BME: bone marrow edema; ETN: etanercept.

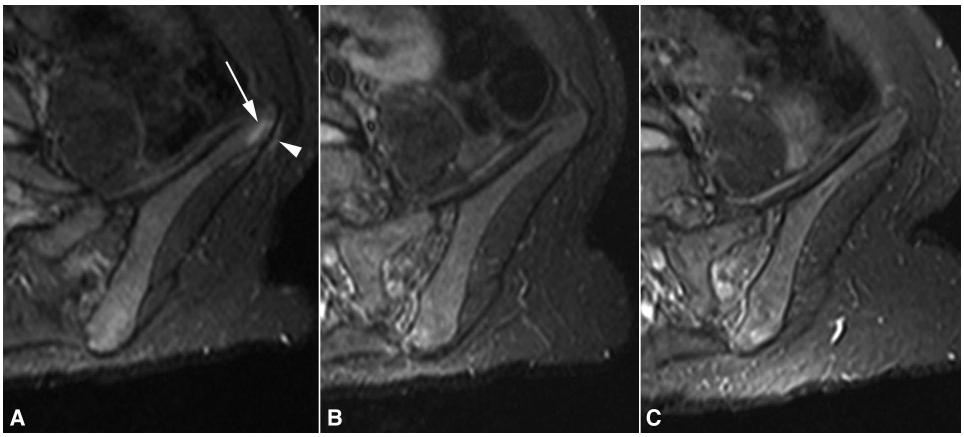

Figure 3. A. Whole-body MR STIR images of the pelvis in oblique coronal orientation demonstrating bone marrow edema (arrow) as well as slight soft tissue edema (arrowhead) at baseline, compatible with enthesitis at the crest of the iliac bone. After (B) 2 years and after (C) 3 years, there is complete resolution of this enthesitis. Clinical investigation revealed enthesitis at baseline, but not after 2 and 3 years. MR: magnetic resonance; STIR: short-tau inversion recovery.

Table 3. Lesion count and longterm response after 2 and 3 years of continuous etanercept treatment in patients with early axial spondyloarthritis.

Variables	Baseline	Yr 2	Yr 3
Clinical			
Lesion count	85	22	28
Mean	2.07	0.54	0.68
SD	2.89	1.48	1.84
SRM	N/A	0.56	0.47
MRI			
Lesion count	22	7	8
Mean	0.54	0.17	0.20
SD	1.10	0.50	0.51
SRM	N/A	0.43	0.34

SRM: standardized response mean; MRI: magnetic resonance imaging; N/A: not applicable.

therapy, both groups showed a similar positive effect on enthesitis; however, this positive effect was achieved already in Week 24 with ETN[15]. Earlier clinical trials performed with the use of WB-MRI did not analyze enthesitis in patients with very early SpA. Only 1 study investigated peripheral entheseal inflammation in patients with AS receiving TNF-α blocking therapy. However, only 10 patients were followed for over 1 year and only patients with established disease were included[17], and the investigators did not perform a detailed analysis of enthesitis in different body regions or correlate MRI with clinical findings.

An advantage of WB-MRI is that the imaging volume includes the anterior chest wall, which was 1 of the most common sites of enthesitis in our cohort. WB-MRI at baseline identified 7 enthesitic lesions at the sternoclavicular joints, sternal synchondrosis, and sternal rib insertions, while the clinical examination revealed 19 lesions in the anterior chest wall. A study by Weber, *et al* investigated clinical examination and MRI signs of inflammation at the anterior chest wall in patients with more established disease[11]. In our study, MRI detected more inflammatory lesions than clinical examination, but no significant association between the 2 methods could be established. It is not clear why MRI detected more enthesitic lesions than the clinical examination in the study by Weber, *et al,* while the opposite occurred in our study. The main difference between the 2 studies was the short disease duration in our study compared with the 11 years in the study by Weber, *et al*. When one only looks at the patients with nr-axSpA in the study by Weber, *et al*, the frequency of enthesitis lesions is low for both methods. Based on their findings, Weber, *et al* expressed doubt about the validity of including anterior chest wall tender points in an enthesitis score[11]. Ultrasonography (US) has also been used to investigate clinical involvement of the anterior chest wall. Recently, Verhoeven, *et al* demonstrated that, ultrasonographically, the anterior chest wall is frequently involved in SpA, but this does not necessarily reflect a simultaneous clinical involvement[29].

Indeed, inflammatory changes at the anterior chest wall are also known to be a diagnostic challenge for MRI because "inflammation-like" changes are also commonly found in healthy subjects[30]. However, our results indicate that entheses of the anterior chest wall are affected in a relevant percentage of patients with early axSpA, including both radiographic and nr-axSpA. Interestingly, the number of affected sites went down during TNF-α blocker therapy when MR images were scored for inflammatory lesions by readers blinded to timepoints, suggesting that the positive MRI findings were real.

Findings of enthesitis were most common in the pelvis, which is in concordance with a recent study of Poggenborg, e*t al* in patients with axSpA and psoriatic arthritis (PsA)[12]. These authors also reported a high rate of enthesitis detected by MRI in the lower extremities. Our findings do not confirm this report because knee and foot enthesitis were rather uncommon on MRI in our patient population. However,

comparison of results in patients with SpA with healthy subjects in the study by Poggenborg, *et al* reveals that some areas lacked specificity, namely the greater femoral trochanter, medial femoral condyle, and Achilles tendon insertion, where a large proportion of healthy subjects also had pathological findings[31]. Half of these patients had PsA, a disease potentially more frequently associated with enthesitis, and the patients with axSpA included had a rather long mean disease duration of 16 years, which might explain this difference. In a study by Weckbach, *et al*[9], enthesitis was found more frequently using WB-MRI than with clinical assessment in patients with PsA. In this study of patients of PsA with established disease, the WB-MRI protocol included contrast-enhanced sequences, while we and other investigators[11,12] used only STIR sequences to identify enthesitis. In the study by Weckbach, *et al*, 13% of pathological findings, among them especially subtle enthesitis lesions, were only detected after contrast medium administration[9]. This is in line with the recent results reported by Klang, *et al* investigating the involvement of contrast medium injection for evaluation of pelvic entheses using conventional MRI[32]. Klang, *et al* found improved intraobserver reliability, as well as better sensitivity and specificity for contrast-enhanced MRI. Our MRI protocol included T1 FSE and STIR images with no additional contrast-enhanced sequences because it is usually sufficient to image the spine and SIJ in the setting of a clinical trial[33,34].

To the best of our knowledge, ours is the first study that investigated the course of enthesitis under continuous TNF-α blocker therapy using clinical examination and WB-MRI. With both assessment methods, lesion counts were found to have decreased after 2 years of treatment and remained stable until the end of the observation period after 3 years of treatment; however, no correlation on a lesion-by-lesion basis was demonstrated. Nevertheless, most other investigators also report discrepancy between clinical examination and imaging in the assessment of enthesitis, including investigators using US[29,35,36,37]. Interestingly, both clinical examination and WB-MRI proved sensitive to change in our cohort, although clinical examination revealed slightly higher SRM values. Currently, there is no true gold standard for clinical investigation of enthesitis[38]. However, clinical examination is usually not blinded, while MR images may be easily scored without knowledge of the clinical status or the timepoint, as in our study. Thus, our results — along with the data from other groups — suggest that an imaging method should be preferred when enthesitis in SpA is investigated because of the great variability of clinically defined enthesitis. Except for a study of the knee joint[37], there are no studies comparing US and MRI for the investigation of enthesitis directly. However, US is not able to detect BME, depends on the skill of the investigator, and the investigation is very difficult to blind. Therefore, we think that MRI is the better imaging method for the assessment of enthesitis as a manifestation of SpA, although the longterm consequences of enthesitis on MRI in the absence of any clinical findings remains to be determined.

While our study was well planned prospectively, it has some limitations. First, the modified MASES was used for standardized clinical assessment of enthesitis, although it did not evaluate exactly the same locations as those defined in the evaluation scheme of WB-MRI. This approach allowed us to include entheseal locations that are difficult to access clinically, and by the definition of 4 regions we tried to correct for location mismatch. The imaging protocol of our study included coronal whole-body sequences with 5-mm slice thickness to evaluate the majority of entheseal locations. This might have led to some underscoring of inflammation by WB-MRI compared with conventional MRI using slice thicknesses of 3–4 mm, which are usually recommended for imaging single-joint regions. The lack of contrast-enhanced sequences has been discussed above. Evidence has become available that the use of contrast agents improves sensitivity and specificity of MRI for routine workup of individual patients[32,39]. However, the group of Poggenborg, *et al* has pointed out that the use of contrast agents also involves a risk of false-positive findings[12].

Both clinical examination and WB-MRI show a resolution of enthesitis after 2 and 3 years of ETN treatment. However, the 2 methods correlated only for the pelvis and anterior chest wall at baseline.

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