Ultrasound Evaluation of the Entheses in Daily Clinical Practice during Tumor Necrosis Factor-α Blocking Therapy in Patients with Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To assess structural and inflammatory ultrasound (US) lesions of entheses in ankylosing spondylitis (AS) patients with active disease and to evaluate inflammatory lesions after 6 months of tumor necrosis factor (TNF-α) blocking therapy, in daily clinical practice.

Methods. Consecutive patients with AS were clinically evaluated and underwent US examination of 9 bilateral entheses before and after 6 months of TNF-α blocking therapy. US examination included the following as inflammatory lesions: bone erosions/cortical irregularities, enthesophytes, calcifications as structural lesions; adjacent bursitis, effusion, increased tendon hypoechogenicity or thickness; and positive power Doppler (PD) signal.

Results. At baseline, 105 (95%) of 111 included patients showed US abnormalities. Structural lesions were seen in 74 patients (67%) and inflammatory lesions in 88 (79%). Enthesophytes and positive PD signal were the most prevalent structural and inflammatory lesions, respectively. Most lesions were found at the lower extremities. Additionally, inflammatory lesions occurred at the lateral epicondyle of the elbow. Patients with structural lesions at baseline were significantly older, had longer disease duration, higher modified Stoke AS Spine score, and higher C-reactive protein. Individually, there was a great diversity in changes of inflammatory entheseal lesions during treatment, but on the group level no significant decrease was found.

Conclusion. This prospective observational cohort study in daily clinical practice shows a high prevalence of structural and inflammatory US lesions in AS patients with longstanding and active disease. Positive PD signal was the most common inflammatory feature. No significant change in inflammatory US lesions was found after 6 months of TNF-α blocking therapy. (J Rheumatol First Release March 15 2017; doi:10.3899/jrheum.160584)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS SPONDYLOARTHROPATHIES ULTRASONOGRAPHY
ENTHESITIS TUMOR NECROSIS FACTOR-α

Within the family of spondyloarthropathies (SpA), ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that mainly affects the spine and sacroiliac joints. Inflammatory involvement of entheses, so-called enthesitis, is one of the characteristic extraspinal manifestations of AS. Clinical symptoms of enthesitis are pain, stiffness, and tenderness, with or without local soft tissue swelling at the entheseal site. Reported prevalence rates of enthesitis are high in axial SpA (axSpA) and vary from 40% to more than 70%[1,2].

Clinical examination of enthesitis may reveal local tenderness by palpation, sometimes accompanied by swelling of the entheseal site. To evaluate entheseal involvement in clinical SpA studies, different enthesitis indexes have been developed such as the Maastricht AS Enthesitis Score (MASES)[3] and the Spondyloarthritis Research Consortium

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of Canada Enthesitis Index[4]. Although these indexes are easy to perform, there may be discrepancies in "true" enthesitis and enthesitis assessed with these clinical enthesitis indices. It can be difficult to distinguish enthesitis from entheseal pain without inflammation by clinical examination. Currently, no gold standard is available to calibrate the presence of enthesitis. Probably, the most reliable method to demonstrate "true" enthesitis is histopathological examination of the entheses at the insertion. However, obtaining entheseal biopsies in clinical practice is hampered by practical and ethical problems due to the burden of this intervention for the patient. Therefore, alternative methods to assess enthesitis are investigated, including musculoskeletal ultrasound (US).

Musculoskeletal US is a reliable and easy-to-perform dynamic imaging technique that can visualize pathological changes such as enthesophytes, calcifications, or bone erosions in greyscale. These structural lesions can be present in more advanced disease. Applying the power Doppler mode (PD), an US technology to visualize blood flow, active inflammation at the entheseal site can be detected. Hypervascularization shown with PD is the main feature of active inflammation and can be found in early as well as advanced stages of the disease. PDUS could be an appropriate technology to monitor and evaluate the effect of treatment on enthesitis.

Severe enthesitis may lead to disability, especially in case of resistance to therapy. It can be treated by reducing biomechanical stress in combination with nonsteroidal anti-inflammatory drugs (NSAID). In case of insufficient effect, additional local US-guided corticosteroid injections at the involved entheseal site can be considered. Further, tumor necrosis factor–α (TNF-α) blocking therapy is available for axSpA patients with persistent high disease activity despite NSAID and conventional treatment[5]. Clinical effectiveness of TNF-α blocking therapy on enthesitis has been investigated in axSpA and peripheral SpA. However, those studies were heterogeneous regarding the evaluated entheses, scoring methods used, and followup time[6,7,8].

Therefore, the 2 main objectives of our present study were to determine the prevalence of structural and inflammatory US lesions of the entheses in AS patients with active disease and to evaluate changes in inflammatory US lesions after 6 months of TNF-α blocking therapy in daily clinical practice.

MATERIALS AND METHODS

Patients. Between November 2004 and October 2008, consecutive outpatients with AS who started TNF-α blocking therapy at the Medical Center Leeuwarden (MCL) were included in this study. All patients participated in the Groningen Leeuwarden AS (GLAS) cohort, a prospective longitudinal observational cohort study with followup visits according to a fixed protocol[9]. All patients were over 18 years of age, fulfilled the modified New York criteria for AS, and started TNF-α blocking therapy because of active disease [Bath AS Disease Activity Index (BASDAI) ≥ 4 and/or expert opinion] according to the Assessment of SpondyloArthritis international Society (ASAS) consensus statement[10].

Patients were clinically evaluated and underwent complete US examination at baseline (before starting TNF-α blocking therapy) and after 6 months of treatment. Clinical evaluation of enthesitis was performed with the MASES (range 0–13; Supplementary Figure 1, available with the online version of this article)[3]. Disease activity was assessed with the BASDAI and the AS Disease Activity Score (ASDAS). Further, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. Physical functioning was assessed with the Bath AS Functional Index (BASFI) and quality of life with the AS Quality of Life (ASQoL) questionnaire[11,12]. Spinal radiographic damage was scored by 2 independent and trained readers blinded to patient characteristics using the modified Stoke AS Spine Score (mSASSS)[13].

The GLAS cohort was approved by the local ethics committees of the MCL and the University Medical Center Groningen (TPO 364). All patients provided written informed consent according to the Declaration of Helsinki.

US protocol. US examinations of the entheses in brightness (B) mode and PD mode were performed by 2 rheumatologists (GAWB, ENG) who are experts in the field of ultrasonography. The US examiners were blinded to clinical data such as the disease status of the patient and previous results of the US examination. US examinations at baseline and 6 months were performed by the same investigator. Patients were instructed to discontinue the use of NSAID a week before US examination, both at baseline and after 6 months, because of the potential effect on enthesitis.

An Esaote Technos MPX US machine (Esaote) was used, with 2 transducers including a linear array 7.5-15 MHz and a 3.5-5 MHz convex transducer. All entheses were scanned with the linear array transducer, except the greater trochanter of the femur because it is more deeply seated in most patients. US examination was done according to a specific scanning protocol easily applicable in daily clinical practice. The following 9 entheseal sites were scanned bilaterally in 2 orthogonal planes: plantar fascia, Achilles tendon, patellar ligament on the patellar apex and the tibial tuberosity, quadriceps femoris, pes anserine, greater trochanter of the femur, common extensor and flexor tendon on the lateral and medial epicondyle of the elbow (Supplementary Figure 1, available with the online version of this article). In B mode, the following abnormalities were scored: bone erosions/cortical irregularities, enthesophytes, calcifications, adjacent bursitis, effusion, increased hypoechogenicity, and increased thickness of tendon. In addition, the entheses were scanned for increased vascularization in PD mode. Special caution was taken for the recognition of normal nutrient vessels entering the entheseal bone. The settings for US were Doppler frequency of 7.5 MHz, low wall filter, and pulse repetition frequency of 750 KHz. Gain was adjusted until background noise was removed.

All abnormalities in B and PD mode were scored as absence (0) or presence (1). Bone erosions/cortical irregularities, enthesophytes, and calcifications were considered structural lesions. Adjacent bursitis, effusion, increased hypoechogenicity, increased thickness, and positive PD were considered inflammatory lesions.

Statistical analysis. Prevalence rates were expressed as number of patients or lesions (%). Further, normally distributed data were reported as mean ± SD and non-normally distributed data as median (range).

Independent samples t test, Mann-Whitney U test, chi-square test, and Fisher's exact test were used to compare patient characteristics. Wilcoxon signed-rank test was used to evaluate the change in clinical and laboratory variables from baseline to 6 months. Generalized estimating equations (GEE) were used to evaluate the change in inflammatory US lesions from baseline to 6 months. This model takes into account the within-patient correlation of the 9 bilateral entheses. The exchangeable correlation matrix was used. Spearman's correlation coefficient was used to investigate changes from baseline to 6 months in clinical, laboratory, and US variables. Statistical analysis was performed using PASW Statistics 22 (SPSS).

RESULTS

In total, 111 consecutive patients with AS underwent US examination before starting TNF-α blocking therapy. The

mean age of all patients was 42.9 years (SD ± 10.9), 71% were male, median symptom duration was 15 years (range 2–49), 81% were HLA-B27–positive, mean BASDAI was 6.0 (± 1.57), and 77% had ≥ 1 tender enthesis according to clinical examination (Table 1).

Of these 111 patients, 85 (77%) had a second US examination after 6 months. Baseline characteristics, including disease activity, were comparable between patients with and without the 6-month US examination, except for symptom duration and time since diagnosis (17 vs 8 yrs, $p < 0.001$; and 9 vs 3 yrs, $p < 0.005$, respectively).

Prevalence of US lesions before start of TNF-α blocking therapy. At baseline, 105 of 111 patients (95%) showed US abnormalities. Structural lesions were seen in 74 patients (67%), inflammatory lesions in 88 patients (79%), and both structural and inflammatory lesions were seen in 57 patients (51%).

Patients with structural lesions were significantly older than patients without structural lesions at baseline (44.4 vs 39.8 yrs, $p = 0.036$), had longer time since diagnosis (9 vs 3.5 yrs, $p = 0.033$), higher mSASSS (12.9 vs 6.9, $p = 0.007$), and higher CRP levels (16 vs 11, $p = 0.022$). No significant differences in patient characteristics were found between patients with and without inflammatory lesions at baseline (Supplementary Table 1, available with the online version of this article).

Table 1. Characteristics of the AS patients at baseline (n = 111). Values are presented as mean ± SD or median (range) unless otherwise indicated.

Characteristics	n =111
Male, n (%)	79 (71)
Age, yrs	42.9 ± 10.9
Duration of symptoms, yrs	15 (2–49)
Time since diagnosis, yrs	7 (0–37)
HLA-B27+, n (%)	90 (81)
History of psoriasis, n (%)	9 (8)
History of IBD, n (%)	11 (10)
History of uveitis, n (%)	31 (28)
History of peripheral arthritis, n (%)	36 (32)
mSASSS score, range 0–72	9.9 (0–72)
MASES, range 0–13	2 (0–12)
MASES ≥ 1, n (%)	85 (77)
BASDAI, range 0–10	6.0 (0.8–9.2)
BASDAI ≥ 4, n (%)	100 (90)
$ASDAS_{crp}$	3.8 (1.7–5.9)
$ASDAS_{crp}$ ≥ 2.1, n (%)	108 (97)
CRP, mg/l	15 (2–99)
CRP ≥ 5, n (%)	93 (84)
ESR, mm/h	22 (2–90)
BASFI, range 0–10	6.2 (0.5–9.7)
ASQoL, range 0–18	10 (1–18)

AS: ankylosing spondylitis; IBD: inflammatory bowel disease; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life score.

Patients with only structural lesions had significantly longer time since diagnosis than patients with only inflammatory lesions (15 vs 7 years, $p < 0.05$). No relationship was found between the presence of structural and inflammatory lesions at baseline ($p = 0.408$).

Additionally, no significant differences in structural and inflammatory lesions were found between male and female patients (data not shown).

Structural US lesions. In total, 202 structural lesions were found in 74 patients, with an average of 2.7 per patient (Table 2). Enthesophyte was the most common structural lesion (65%). Most structural lesions were found at the lower extremities: 85 (42%) at the Achilles tendon, 37 (18%) at the quadriceps tendon, 28 (14%) at the greater trochanter of the hip, 21 (10%) at the patellar tendon, and 18 (9%) at the plantar fascia (Table 2).

Inflammatory US lesions. In total, 254 inflammatory lesions were found in 88 patients with an average of 2.9 per patient (Table 3). Positive PD and bursitis were the most prevalent inflammatory lesions (55% and 34%, respectively). Most inflammatory lesions were seen at the following entheseal sites: 59 (23%) at the pes anserine, 43 (17%) at the quadriceps tendon, 42 (16%) at the patellar tendon, and 39 (15%) at the lateral epicondyle of the elbow (Table 3).

The effect of TNF-α blocking therapy. As expected, significant decreases in disease activity (BASDAI, ASDAS, CRP, ESR), physical function (BASFI), and quality of life (ASQoL) were found after 6 months of TNF-α blocking therapy (Table 4). The clinical enthesitis index (MASES) decreased significantly from 2 (range 0–12) to 1 (range 0–9; $p < 0.001$).

Evaluation of the total number of inflammatory entheseal lesions at the group level showed an insignificant decrease from 210 lesions at baseline to 180 lesions after 6 months in 85 patients with a first and second US examination ($p = 0.20$). Evaluation at the individual entheseal sites showed that positive PD signal disappeared in 100 entheses, but it appeared in 79 entheses. A persisting positive PD signal was found in 25 entheses (Table 5).

GEE analysis revealed no significant change over time in inflammatory US lesions at both patient and lesion level ($p = 0.218$ and $p = 0.193$, respectively). Table 6 shows the diversity of changes in inflammatory lesions at the different entheses during TNF-α blocking therapy.

No significant correlations were found between the change in total number of inflammatory entheseal lesions and the change in MASES, BASDAI, ASDAS, CRP, ESR, BASFI, or ASQoL.

DISCUSSION

In our prospective observational cohort study, US lesions of entheses were found in 95% of patients with AS who had active and longstanding disease. This high prevalence of entheseal involvement is in accordance with a small

Table 2. Prevalence of structural abnormalities at the 9 bilateral entheses in patients with ankylosing spondylitis, at baseline (n = 111). Values are presented as no. patients and no. lesions.

	Total		Erosion/irregular		Osteophyte/enthesophyte		Calcification	
	Patients	Lesions	Patients	Lesions	Patients	Lesions	Patients	Lesions
Entheses total	74	202	29	47	42	131	18	24
Plantar fascia	13	18	2	3	12	15	0	0
Achilles tendon	47	85	8	10	40	67	7	8
Tibial tuberosity	2	3	1	2	0	0	1	1
Patellar tendon	12	21	9	14	3	3	3	4
Quadriceps tendon	22	37	3	4	17	27	5	6
Pes anserine	1	2	1	2	0	0	0	0
Greater trochanter (hip)	18	28	5	7	11	16	4	5
Medial epicondyle (elbow)	0	0	0	0	0	0	0	0
Lateral epicondyle (elbow)	6	8	5	5	2	3	0	0

Total no. included patients: 111; no. examined entheses per patient: 18; no. possible structural lesions per enthesis: 3.

Table 3. Prevalence of inflammatory abnormalities at the 9 bilateral entheses in patients with ankylosing spondylitis, at baseline (n = 111). Values are presented as no. patients and no. lesions.

	Total		Bursitis		Effusion		Hypoechogenicity		Thickening		Positive PD	
	Pts.	Lesions	Pts.	Lesions	Pts.	Lesions	Pts.	Lesions	Pts.	Lesions	Pts.	Lesions
Entheses total	88	254	42	86	9	10	6	6	10	13	69	139
Plantar fascia	3	3	0	0	2	2	0	0	0	0	1	1
Achilles tendon	13	21	11	14	0	0	0	0	2	2	4	5
Tibial tuberosity	10	15	0	0	1	1	1	1	1	1	10	12
Patellar tendon	28	42	23	31	1	1	0	0	1	1	6	9
Quadriceps tendon	25	43	20	33	1	1	0	0	1	1	8	8
Pes anserine	34	59	2	2	2	3	1	1	3	4	31	49
Greater trochanter (hip)	12	19	4	5	0	0	0	0	1	2	8	12
Medial epicondyle (elbow)	11	13	1	1	1	1	0	0	0	0	10	11
Lateral epicondyle (elbow)	24	39	0	0	1	1	4	4	2	2	23	32

Total number of included patients: 111; number of examined entheses per patient: 18; number of possible structural lesions per enthesis: 3. PD: power Doppler.

Table 4. Clinical variables in patients with ankylosing spondylitis at baseline and after 6 months of TNF-α blocking therapy (n = 85). Values are presented as median (range).

Variables	Baseline	T = 6 mos	p
MASES, range 0–13	2 (0–12)	1 (0–9)	< 0.001
Tender entheses, range 0–28	4 (0–20)	2 (0–19)	< 0.001
BASDAI, range 0–10	5.8 (0.8–9.0)	2.6 (0.0–7.4)	< 0.001
ASDAScrp	3.8 (1.7–5.3)	1.8 (0.6–4.0)	< 0.001
CRP, mg/l	15 (2–99)	3 (2–38)	< 0.001
ESR, mm/h	22 (2–90)	7 (2–71)	< 0.001
BASFI, range 0–10	6.3 (1.7–9.7)	3.2 (0.0–9.3)	< 0.001
ASQoL, range 0–18	11 (1–17)	5 (0–17)	< 0.001

TNF-α: tumor necrosis factor-α; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life score.

cross-sectional study of 36 AS patients with less active disease (median BASDAI 4.5) and also longstanding disease (> 10 yrs), in which a prevalence rate of 97% was reported[14]. A larger cross-sectional study of 197 patients with SpA, of which 135 were diagnosed with AS and similar disease activity and also longstanding disease (mean 10 yrs) showed 91% greyscale or PD lesions[8]. Additionally, they reported 47% intraentheseal and up to 58% in perientheseal US lesions.

As expected in longstanding disease, a large proportion of our patients had structural US lesions of the entheses (67%). A new finding is that structural lesions at baseline were associated with more advanced and active disease such as older age, longer disease duration, more spinal radiographic damage, and higher CRP. The prevalence of inflammatory lesions was also high (79%). Positive PD was the most prevalent inflammatory lesion (55%) and frequently seen at the pes anserine of the knee (35%). The knee joint has

Table 5. Change in positive PD signal at 9 bilateral entheses (right and left) in patients with ankylosing spondylitis before and after 6 months of TNF-α blocking therapy (n = 85). Values are presented as no. lesions.

		Disappearance of Positive PD Signal	Appearance of Positive PD Signal	Positive PD Signal at Both Timepoints
Plantar fascia	Left	—	—	—
	Right	—	—	—
Achilles tendon	Left	3	—	—
	Right	1	—	1
Tibial tuberosity	Left	2	3	2
	Right	6	6	—
Patellar tendon	Left	4	1	—
	Right	3	4	1
Quadriceps tendon	Left	—	2	1
	Right	4	3	1
Pes anserine	Left	14	19	10
	Right	17	21	3
Greater trochanter (hip)	Left	7	3	—
	Right	4	2	1
Medial epicondyle (elbow)	Left	6	3	—
	Right	5	2	—
Lateral epicondyle (elbow)	Left	12	4	3
	Right	12	6	2
Total		100	79	25

TNF-α: tumor necrosis factor-α; PD: power Doppler.

Table 6. Inflammatory lesions at the 9 bilateral entheses in patients with ankylosing spondylitis at baseline and after 6 months of TNF-α blocking therapy (n = 85). Values are presented as no. patients and no. lesions.

	Total		Bursitis		Effusion		Hypoechogenicity		Thickening		Positive PD	
	Pts. 0 m/6 m	Lesions 0 m/ 6 m	Pts. 0 m/6 m	Lesions 0 m/6 m	Pts. 0 m/6 m	Lesions 0 m/6 m	Pts. 0 m/6 m	Lesions 0 m/6 m	Pts. 0 m/6 m	Lesions 0 m/6 m	Pts. 0 m/6 m	Lesions 0 m/6 m
Entheses total	69/63	210/180	28/30	58/57	8/1	9/1	6/6	6/6	9/7	12/12	60/52	125/104
Plantar fascia	2/—	2/—	—/—	—/—	2/—	2/—	—/—	—/—	—/—	—/—	—/—	—/—
Achilles tendon	9/6	15/8	7/3	8/4	—/—	—/—	—/—	—/—	2/2	2/3	4/1	5/1
Tibial tuberosity	9/11	13/12	—/—	—/—	1/1	1/1	1/—	1/—	1/—	1/—	9/10	10/11
Patellar tendon	17/21	28/37	14/17	19/28	1/—	1/—	—/—	—/—	—/2	—/3	5/6	8/6
Quadriceps tendon	18/17	30/30	13/15	23/23	—/—	—/—	—/—	—/—	1/—	1/—	6/5	6/7
Pes anserine	31/35	54/61	2/2	2/2	2/—	3/—	1/3	1/3	2/2	4/3	28/34	44/53
Greater trochanter	12/6	19/6	4/—	5/—	—/—	—/—	—/—	—/—	1/—	2/—	8/6	12/6
Medial epicondyle	11/5	13/5	1/—	1/—	1/—	1/—	—/—	—/—	—/—	—/—	10/5	11/5
Lateral epicondyle	21/13	36/22	—/—	—/—	1/—	1/—	4/3	4/3	2/3	2/4	20/13	29/15

TNF-α: tumor necrosis factor-α; PD: power Doppler.

numerous entheseal sites and structures, which makes it harder to connect clinical symptoms to defined anatomical structures. This may lead to underestimation of pes anserine enthesitis. On the other hand, the presence of the inferior geniculate artery may be regarded as a pitfall, because the Doppler signal may be mistaken for inflammatory activity of the enthesis. The increase in positive PD at the pes anserine after 6 months of treatment may be explained by this pitfall.

To place the high prevalence of US lesions in AS into perspective, it is necessary to observe prevalence rates of US lesions in healthy controls. The limited publications show prevalence rates of morphostructural lesions between 0% and 29%[15,16,17,18]. Interestingly, a positive PD signal was never reported in healthy controls[15,16,17,18]. Therefore, positive PD appears to be a distinctive US feature to assess inflammation at the entheseal site in patients with SpA.

We found a large individual diversity in inflammatory lesions over time, especially positive PD and bursitis, but no decrease in total numbers of inflammatory lesions after 6 months of TNF-α blocking therapy or any relationship with clinical outcome. In contrast, Naredo, *et al* did find a significant decrease in several predefined entheseal US scores after 6 months of TNF-α blocking therapy[8]. This inconsistency can be caused by differences in study populations (85 patients with AS vs 197 patients with SpA, of which 135 were AS) and US protocol (daily clinical practice vs standardized

approach). Wang, *et al* mentioned a significant improvement of Achilles enthesitis in 75 patients with AS after only 3 months of TNF-α blocking therapy; unfortunately, the exact results were not reported. In contrast with our study population, those patients were younger and had higher disease activity[19]. Recently, Song, *et al* demonstrated that a followup period of 1 or 2 years may be necessary to evaluate the effect of TNF-α blocking therapy on inflammatory entheseal lesions evaluated with MRI[20]. Overall, the minimum followup time needed to show an effect of TNF-α blocking therapy on inflammatory signs of enthesitis is not yet clear.

Unfortunately, no clear consensus is available on the exact US definition of enthesitis, neither on the location nor on the number of entheses to be examined with US in patients with SpA[8,21,22,23]. Several standardized quantitative scoring methods have been proposed. However, these various scoring methods include different entheseal sites and US techniques[21,22,23,24,25,26]. This leads to heterogeneous results, making the direct comparison of the several studies difficult and results hard to interpret. Therefore the Outcome Measures in Rheumatology (OMERACT) US working group published the definition of SpA-related enthesitis and the elementary lesions that should be included in US examination, based on a Delphi process[27]. Excellent agreement (93%) was reached on separating structural lesions from inflammatory lesions, as was also performed in our study. The selected lesions of this Delphi process show high comparability with the included US lesions of our study[27]. Additionally, we incorporated effusion and bursitis, which were present in 10% and 48% of patients with AS, respectively. The high prevalence of bursitis suggests that this may be of supplementary value.

To date, US studies of entheses in SpA have focused mainly on the lower limbs[6,21,22,28,29]. In our study, the lateral epicondyle of the elbow was also frequently involved (17%). Including the lateral epicondyle of the elbow in the US evaluation of the entheses should be considered for future SpA studies.

Our US study was embedded in a larger observational cohort study of patients with active disease before the start of TNF blocking agents in daily clinical practice. Therefore no control group was included in this US study, which is a limitation. Unfortunately, it is difficult to perform a randomized controlled trial on this subject because it is unethical to deprive patients with SpA who have active disease of a proven effective treatment.

Although both ultrasonographists trained extensively together prior to our study, and baseline and 6-month US examinations were performed by the same ultrasonographist, no formal interobserver and intraobserver reliability was obtained, and interpretation bias might be present. The 26 patients who did not have a second US examination had a shorter symptom duration and time since diagnosis than did the 85 patients who underwent US examination at both timepoints. This could have led to selection bias. However, no significant differences were found in the prevalence of structural and inflammatory lesions at baseline between patients with or without a second US examination.

The European League Against Rheumatology recommendations for the use of imaging in the diagnosis and management of SpA in clinical practice have been published[30]. Although these recommendations state that US provides additional information on peripheral disease activity, no clear advice can be given based on the results of US research. Regarding the results of our present study, routinely monitoring the effect of TNF-α blocking therapy on enthesitis after 6 months with US does not seem useful in daily clinical practice.

Our present study showed that structural and inflammatory US lesions were highly prevalent in AS patients with longstanding and active disease. Enthesophyte was the most prevalent structural lesion, and positive PD was the most frequently found feature of inflammation. Overall, there was no significant change in inflammatory entheseal US lesions after 6 months of TNF-α blocking therapy, with large individual variety of changes.

Until now, the absence of a clear US definition of enthesitis and description of location and number of entheses to be examined have led to heterogeneous study results. It is hoped that the outcome of the OMERACT Delphi process, the development of a clear US enthesitis definition, multiple followup visits, and longterm followup will help us to provide more robust data on entheseal involvement in SpA.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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