Whole-body Magnetic Resonance Imaging in Axial Spondyloarthritis: Reduction of Sacroiliac, Spinal, and Entheseal Inflammation in a Placebo-controlled Trial of Adalimumab

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ABSTRACT. ***Objective.*** To investigate whether adalimumab (ADA) reduces whole-body (WB-) magnetic resonance imaging (MRI) indices for inflammation in the entheses, peripheral joints, sacroiliac joints, spine, and the entire body in patients with axial spondyloarthritis (axSpA).

Methods. An investigator-initiated, randomized, placebo-controlled, double-blinded 48-week followup trial included 49 patients with axSpA, who had Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4.0 despite treatment with nonsteroidal antiinflammatory drugs and a clinical indication for tumor necrosis factor inhibitor treatment. Patients were randomized to subcutaneous ADA 40 mg or placebo every other week for 6 weeks; thereafter, all patients received ADA. Conventional MRI and WBMRI were performed at weeks 0, 6, 24, and 48. The primary WBMRI endpoint was the proportion of patients with an improvement in WBMRI total inflammation index above the smallest detectable change (SDC) at Week 6.

Results. The primary WBMRI endpoint (improvement of SDC > 2.3) was met in 11 (44%) patients in the ADA group and 3 (13%) patients in the placebo group (p = 0.025, Fisher's exact test). The primary conventional MRI endpoint, the minimally important change in Spondyloarthritis Research Consortium of Canada Spine MRI Inflammation Index at Week 6, was achieved by 9 (36%) patients in the ADA group and 4 (17%) patients in the placebo group (p = 0.20). The primary clinical endpoint, BASDAI reduction > 50% or 2.0 at Week 24, was attained by 32 (65%) patients.

Conclusion. ADA provided significant reductions in WBMRI indices of peripheral, axial, and whole-body inflammation in patients with axSpA. WBMRI is promising for objective assessment and monitoring of peripheral and axial disease activity in future clinical trials. (First Release February 15 2018; J Rheumatol 2018;45:621–9; doi:10.3899/jrheum.170408)

Key Indexing Terms:
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Patients with axial spondyloarthritis (axSpA) have various patterns of involvement of sacroiliac joints (SIJ), spine, and peripheral joints and entheses that can be visualized on magnetic resonance imaging (MRI). Therefore, MRI can provide an objective measure of the inflammatory activity in different parts of the body. MRI scoring methods have been developed to assess inflammation in SIJ and the spine[1,2], and MRI axial inflammation decreases during anti-tumor necrosis factor (TNF) treatment[3,4,5].

Whole-body (WB-) MRI potentially allows assessment of the entire musculoskeletal system in 1 scan and may thus provide an objective assessment of the inflammatory activity of the whole patient[6,7,8]. MRI inflammatory lesions outside the axial skeleton improve during anti-TNF treatment[9,10]. Therefore, it is of considerable interest how WBMRI indices perform as outcome measures in a randomized clinical trial setting.

The aim was to investigate whether WBMRI indices of inflammation in both axial and peripheral joints and entheses are reduced by adalimumab (ADA) in patients with axSpA.

MATERIALS AND METHODS

Study design. This was a randomized, double-blind, placebo-controlled, investigator-initiated trial conducted at 5 rheumatology outpatient clinics in Denmark from February 2010 to March 2014. Patients were assigned to ADA 40 mg or placebo SC every other week for 6 weeks by site-wise randomization in blocks of 2:2. From Week 6 onward, patients in both groups received ADA. At Week 24, clinical responders [decrease in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 50% or 2.0] continued ADA while nonresponders were allowed treatment with other drugs following local treatment guidelines. AbbVie provided study medicine for the first 24 weeks of the study. Patients and all study personnel were blinded to treatment allocation. The study was approved by the Danish Health Authority and the Regional Ethics Committees in the Capital Region of Denmark (ethics approval number H1-2013-118). All patients gave written informed consent. (ClinicalTrials.gov, NCT01029847.)

Inclusion and exclusion criteria. Eligible patients were adults aged 18–85 years who fulfilled the Assessment of Spondyloarthritis international Society (ASAS) criteria for axSpA[11], had sacroiliitis as assessed by radiography or MRI, BASDAI ≥ 4.0 despite treatment with nonsteroidal antiinflammatory drugs, and clinical indication for anti-TNF treatment.

Exclusion criteria were glucocorticoid administration within 4 weeks before inclusion, drug or alcohol abuse, contraindications to MRI or anti-TNF treatment, or otherwise being unable to fulfill the investigational program owing to physical or psychological causes. Conventional disease-modifying antirheumatic drugs were allowed if dosage had been stable for 4 weeks before inclusion.

Study procedures and outcome measures. Clinical examination, patient-reported outcomes, adverse events, and blood and urine samples were collected at baseline and at weeks 2, 6, 8, 12, 18, 24, 36, and 48. The C-reactive protein assay had a lower detection limit of 0.3 mg/l (Sentinel Diagnostics).

Physical examination included Bath Ankylosing Spondylitis Metrology Index and thorax expansion. There were 70/68 peripheral joints assessed for tenderness and swelling: temporomandibular, sternoclavicular and acromioclavicular joints, shoulder, elbow, wrist, first carpometacarpal, first to fifth metacarpophalangeal, all interphalangeal joints of the hands, hip (only assessed for tenderness), knee, ankle and tarsal joints, first to fifth metatarsophalangeal, first interphalangeal and second to fifth proximal interphalangeal joints of the feet. There were 33 entheses assessed for tenderness: first and seventh costosternal joints, anterior superior iliac spine, posterior superior iliac spine, iliac crest, ischial tuberosity, spinous process of L5, supraspinatus tendon insertion into humerus, medial and lateral epicondyles of humerus, greater femoral trochanter, medial femoral condyle, quadriceps tendon insertion into patella, patellar ligament insertion into patella, patellar ligament insertion into the tibial tuberosity, calcaneal (Achilles) tendon insertion into calcaneus, and plantar aponeurosis insertion into calcaneus.

MRI was performed at baseline before treatment initiation and at weeks 6, 24, and 48. Because dedicated SIJ sequences were not performed at Week 6, SIJ at Week 6 could only be assessed as part of the WBMRI images. Radiographs of the spine and SIJ were obtained at baseline and at Week 48.

MRI acquisition. WBMRI was performed in a Philips 3.0 Tesla scanner using 6 separate imaging stations with a whole-body quadrature coil: (1) coronal and sagittal images of cervical spine/shoulders; (2) coronal images of thoracic spine; (3) coronal images of lumbar spine and SIJ; (4) coronal images of hips and hands; (5) coronal images of knees; and (6) coronal and axial images of ankles and feet. Short-tau inversion recovery (STIR) sequences had slice thickness of 3 mm for hips and hands (resolution 1.2 × 1.2 mm), and 5 mm for all other stations (resolution 1.8 × 2.6 mm, repetition time 5257–16,832 ms, echo time 70–83, and inversion time 200 ms). Pre- and post-gadolinium (Gd) T1-weighted (T1W) spin-echo sequences without fat saturation had slice thickness of 3–5 mm (repetition time 733–1374 ms and echo time 7.6 ms, resolution 1.1 × 1.1 to 1.5 × 1.5 mm).

Conventional MRI of SIJ and spine was performed on the same scanner using appropriate surface coils and with a slice thickness of 4 mm. The spine was imaged in 3 parts by sagittal T1W spin-echo (repetition time 518 ms, echo time 8 ms) and STIR (repetition time 4990–8530, echo time 80, inversion time 120). The SIJ were imaged by semicoronal T1W spin-echo (repetition time 699, echo time 20) and STIR (repetition time 4818, echo time 60, inversion time 200).

Evaluation of WBMRI. All WBMRI images covering both the axial and peripheral musculoskeletal system were anonymized and read in chronological order by an experienced musculoskeletal radiologist (IE) who was blinded to conventional MRI images, radiography, and clinical data. Bone marrow edema (BME) was assessed on STIR sequences, with post-Gd T1W sequences used for reference only. Synovitis and entheseal soft tissue inflammation were assessed based on both STIR and post-Gd T1W sequences[12]. Forty-eight peripheral joints were scored at each side (right and left) for synovitis and BME: glenohumeral, acromioclavicular, sternoclavicular, wrist, carpometacarpal, first to fifth metacarpophalangeal joints, all interphalangeal joints of the hands, hip, knee, ankle, tarsometatarsal, and first metatarsophalangeal joints. Fourteen peripheral entheses, supraspinatus tendon insertion at humerus, iliac crest, ischial tuberosity, pubic symphysis, greater femoral trochanter, medial femoral condyle, and calcaneal Achilles tendon insertion were scored bilaterally for entheseal BME and entheseal soft tissue inflammation. BME and soft tissue inflammation in the immediate surroundings of the symphysis may represent either symphysitis or enthesitis. The pubic symphysis was scored separately for left and right side; inflammation more laterally on the inferior side of the pubic bones was not scored. The medial femoral condyle was scored for inflammation at the insertion of the collateral ligaments, not at the adductor tubercle; BME below the cartilage of the femorotibial joint was assigned to the knee joint. WBMRI images of SIJ were scored for BME in each of 4 quadrants (upper/lower part of iliac side and upper/lower part of sacral side) in the cartilaginous parts of the joints. The spine was scored for BME in each discovertebral unit from C2/C3 to L5/S1; spine scores were based on BME in the vertebral bodies, while inflammatory lesions in the posterior structures of the spine (e.g., facet joints and costotransverse joints) were not scored. The scoring system was 0 (absent), 1 (mild/moderate), or 2 (severe).

Eight sets of WBMRI images at baseline and at Week 24 were reanonymized and scored again in known chronology to assess intrarater reliability.

Evaluation of conventional MRI of spine and SIJ. All conventional MR images were read in chronological order and scored according to the Spondyloarthritis Research Consortium of Canada (SPARCC) Sacroiliac Joint MRI Inflammation Index and the SPARCC Spine MRI Inflammation Index[1,2] by an experienced axSpA reader (SJP), blinded to WBMRI, radiography, and clinical data.

Definitions of WBMRI indices. WBMRI peripheral joint inflammation index was defined as the sum of scores for synovitis and BME for the abovementioned peripheral joints. WBMRI enthesis inflammation index was defined as the sum of scores for entheseal BME and entheseal soft tissue inflammation for the abovementioned entheses. WBMRI axial BME index was defined as the sum of scores for spine and SIJ BME. WBMRI total BME index was defined as the sum of scores for BME from peripheral joints, entheses, spine, and SIJ. WBMRI total inflammation index was defined as the sum of scores for synovitis, BME, and soft tissue inflammation from peripheral joints and entheses, spine, and SIJ (the primary WBMRI outcome measure).

Endpoints. The primary WBMRI outcome measure was improvement in WBMRI total inflammation index above smallest detectable change (SDC) at Week 6. The primary conventional MRI outcome measure was SPARCC Spine MRI Inflammation Index minimally important change (improvement ≥ 5) at Week 6[13]. The primary clinical endpoint used for assessment of treatment response during the trial was improvement in BASDAI of ≥ 50% or ≥ 2.0 at Week 24. Secondary endpoints included ASAS partial remission, ASAS20, ASAS40, and ASAS5/6 responses, and changes in WBMRI indices.

Statistical analysis. Intention-to-treat analysis with nonresponder imputation of missing data was used for binary outcomes. Missing data for continuous outcomes were imputed with last observation carried forward. Two patients had no dedicated conventional SIJ scans at baseline, and the first available SIJ scores were used as the baseline scores. Standardized response mean (SRM) was calculated as the overall mean change score divided by SD of this change score, while Guyatts responsiveness index (GRI) was calculated as the mean change score in the ADA group divided by SD of the change score in the placebo group at Week 6; values ≥ 0.8 were judged to represent high responsiveness[14].

The 95% CI for risk difference (difference between the proportions of patients with the outcome of interest) were calculated with continuity correction because of the small sample size. The statistical analyses included Fisher's exact test, Mann-Whitney U test, Wilcoxon signed-rank test, and Pearson correlation. ANCOVA analysis with group allocation and baseline WBMRI total inflammation score as covariates and change in WBMRI total inflammation score as outcome was performed as a posthoc secondary analysis to take differences in baseline values into account. Also, logistic regression with WBMRI total inflammation responder status at Week 6 as outcome and baseline WBMRI total inflammation score and group allocation as covariates was performed as posthoc secondary analysis. Similar analyses were performed for SPARCC Spine Inflammation Index.

Intrarater reliability was calculated using a 2-way random effects model, ICC(3,1), based on absolute agreement. ICC ≥ 0.6 were considered to represent good reliability, and ≥ 0.8 very good reliability. SDC was calculated from baseline to Week 24 as $1.96 \times (SD_{\text{difference in change scores}})/\sqrt{2}$, where SD is the standard deviation of the differences in change score between 2 separate scorings performed by the same reader (IE)[15]. All statistical analyses were performed using R version 3.4.0.

RESULTS

Study participants. Fifty patients were included from February 2010 to March 2013 (Figure 1). The intention-to-treat analyses were based on 49 patients because all data from 1 patient were unavailable as a result of an administrative error.

Baseline characteristics were similar among the randomization groups, except that the ADA group had more men, longer symptom duration (Table 1), higher baseline WBMRI peripheral joint inflammation, WBMRI enthesis inflammation, and WBMRI total inflammation indices (Table 2). Ten patients discontinued the study (Figure 1). Four patients stopped ADA because of adverse events; during the trial, 1 serious adverse event judged as probably not causally related to ADA was observed.

Primary imaging endpoints. At Week 6, the WBMRI total inflammation index had decreased in 11 (44%) patients in the ADA group and 3 (13%) patients in the placebo group; risk difference was 32% (95% CI 4%–59%, p = 0.025; Figure 2 and Figure 3). The primary conventional MRI endpoint of SPARCC Spine MRI Index minimally important change at Week 6 was met by 9 (36%) of the patients treated with ADA and 4 (17%) of the patients treated with placebo; risk difference was 19% (95% CI –9% to 47%, p = 0.20).

Intrarater reliability was very good or good for most WBMRI indices (Table 3). SDC ranged from 1.0 to 2.7 for the different WBMRI indices. SDC for the WBMRI total inflammation index was 2.3. In posthoc secondary analysis using logistic regression adjusted for baseline WBMRI total inflammation index, the difference between groups in total inflammation index responders was still significant (p = 0.048). SPARCC Spine minimally important change was also not significant when adjusted for baseline SPARCC Spine (p = 0.16).

Clinical endpoints at weeks 6, 24, and 48. The clinical endpoint of reduction in BASDAI of 50% or 2.0 at Week 6 was met by 13 (52%) patients in the ADA group and 3 (13%) in the placebo group (p = 0.005). Thereafter, all patients received ADA, and at Week 24 this endpoint was met by 18 (72%) patients in the ADA group and 14 (58%) in the placebo group (p = 0.38). Among the 32 patients who were clinical responders at Week 24, there were 27 (84%) who were still clinical responders at Week 48. Two clinical nonresponders at Week 24 were judged by the treating physician as having improved significantly and continued ADA; both were clinical responders at Week 48. Six clinical nonresponders at Week 24 were switched to etanercept; 2 of these were clinical responders at Week 48. A total of 31 (63%) patients were clinical responders at Week 48.

Secondary imaging endpoints. The WBMRI enthesis inflammation index decreased significantly in the ADA group (mean change –0.9) compared with the placebo group (+0.4) at Week 6 (Table 2). In the ADA group, WBMRI enthesis BME index and enthesis soft tissue inflammation index both decreased at Week 6, while they were largely unchanged in the placebo group.

WBMRI axial BME index. WBMRI total BME index and total inflammation index decreased significantly at Week 6 in the ADA group, as well as at weeks 24 and 48 in both groups in comparison to baseline. At Week 6, changes in

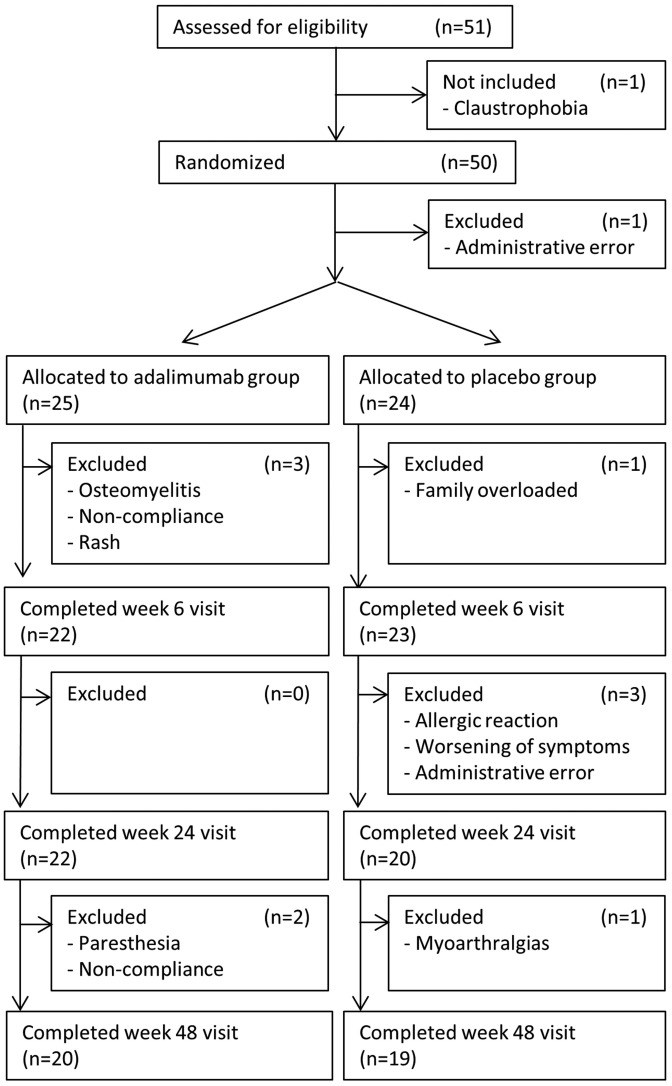

Figure 1. Patient disposition. Two of the patients in the adalimumab group who were excluded between baseline and Week 6 had MRI performed at Week 6, but no clinical visit. Two of the patients in the placebo group who were excluded between Week 6 and Week 24 had MRI performed at Week 24, but no clinical visit. Thus, the total number of patients with MRI scans performed were 49, 47, 44, and 39, respectively, at weeks 0, 6, 24, and 48. MRI: magnetic resonance imaging.

these indices differed significantly between groups. No significant changes were observed in WBMRI peripheral joint synovitis index or peripheral joint BME index.

In posthoc secondary analysis, WBMRI total inflammation index at Week 6 improved significantly in the ADA group compared to the placebo group when adjusted for baseline WBMRI total inflammation index ($p = 0.011$). Change in SPARCC Spine was significant at Week 6 in ANCOVA analysis with adjustment for baseline SPARCC Spine ($p = 0.013$). Overall, the SPARCC SIJ minimally important change (≥ 2.5) at Week 24 was attained by 19 (39%) patients.

Other secondary endpoints. At Week 6, ASAS partial remission was reached by 5 (20%) patients in the ADA group and none in the placebo group ($p = 0.05$). Moreover, ASAS20 was reached by 13 (52%) patients in the ADA group and 4 (17%) patients in the placebo group ($p = 0.02$); ASAS40 was reached by 12 (48%) in the ADA group and 1 (4%) in the placebo group ($p = 0.001$); and ASAS5/6 was reached by 13 (52%) patients in the ADA group and 1 (4%) patient in the placebo group ($p < 0.001$).

Responsiveness and construct validity of WBMRI indices. Responsiveness as assessed by GRI at Week 6 was good for

Table 1. Baseline characteristics. Values are mean ± SD or n (%) unless otherwise specified.

Characteristics	Adalimumab, n = 25	Placebo, n = 24
Age, yrs	39.9 ± 10.8	35.1 ± 7.8
Male	15 (60)	10 (42)
BMI	25.0 ± 4.2	24.4 ± 3.7
Symptom duration, yrs	13.8 ± 13.4	10.4 ± 7.1
Time since diagnosis, yrs	4.6 ± 10.2	2.3 ± 3.5
Positive for HLA-B27	17 (68)	19 (79)
Previous disorders		
Psoriasis	0 (0)	2 (8)
IBD	1 (4)	2 (8)
Uveitis	3 (12)	7 (29)
Radiographic AS[1]	13 (52)	15 (63)
hsCRP, median (range)	4.2 (≤ 0.3–38)	3.2 (≤ 0.3–74)
BASDAI	6.3 (1.2)	6.4 (1.5)
BASFI	5.2 (1.9)	5.0 (2.1)
BASMI	2.6 (2.0)	2.8 (2.0)
ASDAS	3.5 (0.7)	3.5 (0.9)
Pain score	68 (19)	65 (19)
PtGA	70 (18.1)	68 (18.9)
PGA	58 (22)	62 (23)
SPARCC MRI Spine Inflammation Index	13.3 (17)	10.7 (16)
SPARCC MRI SIJ Inflammation Index	7.7 (9.2)	11.1 (14)
mSASSS, median (range)	2 (0–61)	0 (0–53)

[1]Fulfill radiographic part of the modified New York criteria for AS. AS: ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BMI: body mass index; IBD: inflammatory bowel disease; hsCRP: high-sensitivity C-reactive protein; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; PtGA: patient's global assessment; PGA: physician's global assessment; SPARCC: Spondyloarthritis Research Consortium of Canada; MRI: magnetic resonance imaging; SIJ: sacroiliac joints.

WBMRI enthesis BME, axial BME index, total BME index, and total inflammation index, while the other indices had lower responsiveness. A similar pattern was seen with SRM at weeks 6, 24, and 48, where the 2 most composite indices, WBMRI total BME index and total inflammation index, had good or moderate responsiveness in the range of 0.65 to 0.86, while the individual components had somewhat lower responsiveness (Table 3). At baseline, the Pearson correlation coefficient between WBMRI SIJ score and SPARCC SIJ MRI Index was 0.75, while the correlation between WBMRI spine score and SPARCC Spine MRI Index was 0.80.

DISCUSSION

Our present study, using WBMRI indices in a randomized controlled trial setting, documents the effect of TNF inhibitor therapy on the objective inflammatory load in patients with axSpA. A beneficial effect of ADA compared to placebo was seen already at Week 6 both for axial BME, peripheral entheseal inflammation, and total whole-body inflammation. Our study confirms the known antiinflammatory axial effect of ADA, but the effect of TNF inhibitor therapy on WBMRI inflammation indices has, to our knowledge, not previously been shown. The intrarater reliability of WBMRI assessments was generally good, especially for the most comprehensive indices (total BME index and total inflammation index) and the method offers significant potential as a measure of the total inflammatory burden in patients with arthritis.

Interestingly, peripheral enthesitis represented a significant part of the WBMRI total inflammation index, even though the patients were selected by the presence of sacroiliitis by imaging. The WBMRI enthesis inflammation index decreased significantly more in the ADA group compared to the placebo group at Week 6. The frequent finding of MRI enthesitis is in line with anatomical investigations that point to the synovio-entheseal complex as the initial site of inflammation in SpA[16,17], and for many years, it has indeed been known that MRI may visualize enthesitis and a range of other causes of regional pain[18,19,20,21].

The SDC was relatively low (2.2–2.3) for WBMRI total inflammation index and total BME index. MRI scans were read in known chronology; if they were read in random order, SDC would possibly be somewhat larger. The highest ICC among the WBMRI indices were found for the WBMRI total inflammation index (status score 0.93, change score 0.85) and total BME index (status score 0.96, change score 0.91), and these composite scores had overall good responsiveness. Overall, this suggests that further work on WBMRI as a sensitive objective outcome measure is justified and that the WBMRI total inflammation index, total BME index, and enthesis inflammation index seem to be most promising. The indices should be validated in independent cohorts.

Slice thickness was 3–5 mm of the STIR sequences, which, because of partial volumen averaging, makes it hard to confidently judge the anatomical location of small high-signal areas in small structures and at tissue boundaries. Improved resolution may allow for better ICC as well as greater sensitivity, but longer scan time was judged unfeasible.

We chose simple addition of scores to obtain the indices, well aware that other weightings of the scores may lead to higher correlations with patient-reported outcomes. Future studies may explore different ways of weighting scores according to the size or functional importance of the affected anatomical structures.

The ABILITY-1 trial demonstrated the efficacy of ADA in patients with nonradiographic axSpA[4]. Compared with the ADA arm of the ABILITY-1 trial at Week 12, the composite endpoints such as ASAS40 and Ankylosing Spondylitis Disease Activity Score major improvement were reached by a larger proportion of patients already at Week 6 in the ADA arm of our present trial. Our baseline scores for SPARCC Spine MRI Index and SPARCC SIJ MRI Index were about twice as high as in ABILITY-1, and because MRI inflammation is a known predictor for treatment response to TNF

Table 2. WBMRI indices by group allocation.

WBMRI Indices	ADA, n = 25			Placebo, n = 24			Difference Between Groups in Change from Baseline, p[b]
	Mean	SD	Change from baseline, p[a]	Mean	SD	Change from baseline, p[a]	
Peripheral joint							
Synovitis index, range 0–92							
Baseline	2.7	2.6		1.3	1.8		
Wk 6	2.5	2.2	0.60	1.4	1.9	0.79	0.75
Wk 24	2.5	2.5	0.57	1.2	1.8	1.00	0.66
Wk 48	2.2	2.2	0.11	1.3	2.0	0.79	0.10
BME index, range 0–92							
Baseline	0.9	1.3		0.4	0.7		
Wk 6	0.8	1.3	0.59	0.5	0.7	0.35	0.18
Wk 24	0.6	0.9	0.12	0.3	0.6	0.23	0.70
Wk 48	0.6	0.8	0.11	0.4	0.6	0.77	0.36
Inflammation index, range 0–184							
Baseline	3.6	2.9		1.7	2.1		
Wk 6	3.3	2.7	0.57	1.9	2.3	0.43	0.50
Wk 24	3.1	2.6	0.23	1.5	2.0	0.89	0.41
Wk 48	2.8	2.3	0.10	1.7	2.1	0.65	0.12
Enthesis							
BME index, range 0–30							
Baseline	1.1	1.9		0.6	1.1		
Wk 6	0.7	1.4	0.054	0.7	1.3	1.00	0.015
Wk 24	0.6	1.1	0.11	0.5	1.1	0.79	0.35
Wk 48	0.6	1.0	0.12	0.5	1.1	0.71	0.81
Soft tissue inflammation index, range 0–30							
Baseline	1.4	1.7		0.6	0.8		
Wk 6	0.9	1.6	0.15	1.0	1.3	0.29	0.064
Wk 24	0.8	1.5	0.038	0.8	1.1	0.60	0.032
Wk 48	0.8	1.5	0.073	0.8	1.3	0.57	0.054
Inflammation index, range 0–60							
Baseline	2.5	2.9		1.3	1.5		
Wk 6	1.6	2.3	0.040	1.7	2.2	0.24	0.032
Wk 24	1.4	2.0	0.027	1.3	1.9	0.92	0.12
Wk 48	1.4	1.8	0.048	1.3	2.1	0.90	0.22
Axial BME index, range 0–62							
Baseline	2.5	3.8		3.0	3.2		
Wk 6	1.0	2.0	0.003	2.8	3.1	0.50	0.049
Wk 24	1.0	2.1	0.008	0.9	1.9	0.002	0.45
Wk 48	1.4	2.4	0.051	0.9	2.5	0.002	0.34
Total BME index, range 0–184							
Baseline	4.5	4.6		4.0	4.1		
Wk 6	2.5	3.5	0.001	4.0	4.0	0.88	0.001
Wk 24	2.3	2.8	0.001	1.8	2.3	0.002	0.90
Wk 48	2.6	3.0	0.007	1.8	3.2	0.001	0.89
Total inflammation index, range 0–306							
Baseline	8.6	6.3		5.9	5.7		
Wk 6	6.0	5.1	0.005	6.3	6.4	0.48	0.004
Wk 24	5.6	4.6	0.001	3.7	4.5	0.002	0.64
Wk 48	5.6	4.3	0.009	3.9	5.6	0.004	0.58

Patients in the placebo group started ADA at Week 6. At Week 24, 6 patients stopped ADA and were switched to etanercept. [a]Wilcoxon signed-rank test. [b]Mann-Whitney U test. WBMRI: whole-body magnetic resonance imaging; BME: bone marrow edema; ADA: adalimumab.

inhibitors in patients with axSpA[22], this difference may explain the higher clinical response rates in our study.

Based on the current data, WBMRI total inflammation index can discriminate between the treatment and placebo groups in a randomized controlled trial setting with a total of 50 patients with SpA randomized to the 2 treatment groups. Other properties are also important for an outcome measure to be potentially useful, such as face and content validity. The comprehensive WBMRI approach would seem to have an advantage rather than only assessing the SIJ and spine, particularly in patients with widespread disease located in many different anatomical structures. Regarding feasibility, the

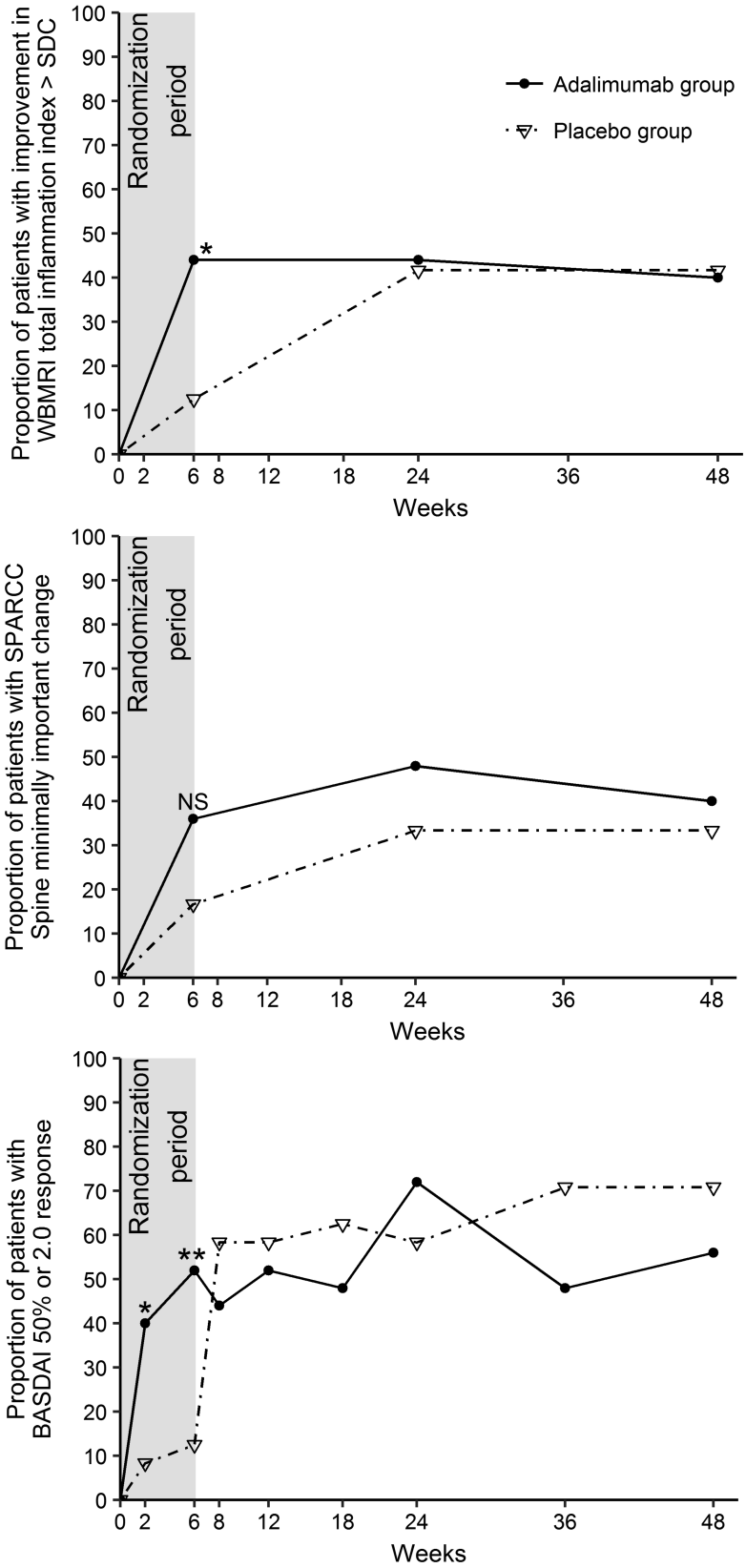

Figure 2. Improvement in WBMRI total inflammation index, SPARCC Spine minimally important change, and BASDAI 50% or 2.0 response by treatment group. SDC for WBMRI total inflammation index was 2.3. BASDAI 50% or 2.0 response was defined as a decrease in BASDAI of 50% or 2.0. P values for difference between groups at weeks 2 and 6 by Fisher's exact test. Patients in the placebo group started adalimumab (ADA) at Week 6. At Week 24, 6 patients stopped ADA and started etanercept. * P value in the range of 0.01–0.05; ** P value = 0.005. SDC: smallest detectable difference; WBMRI: whole-body magnetic resonance imaging; NS: not significant; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; SPARCC: Spondyloarthritis Research Consortium of Canada.

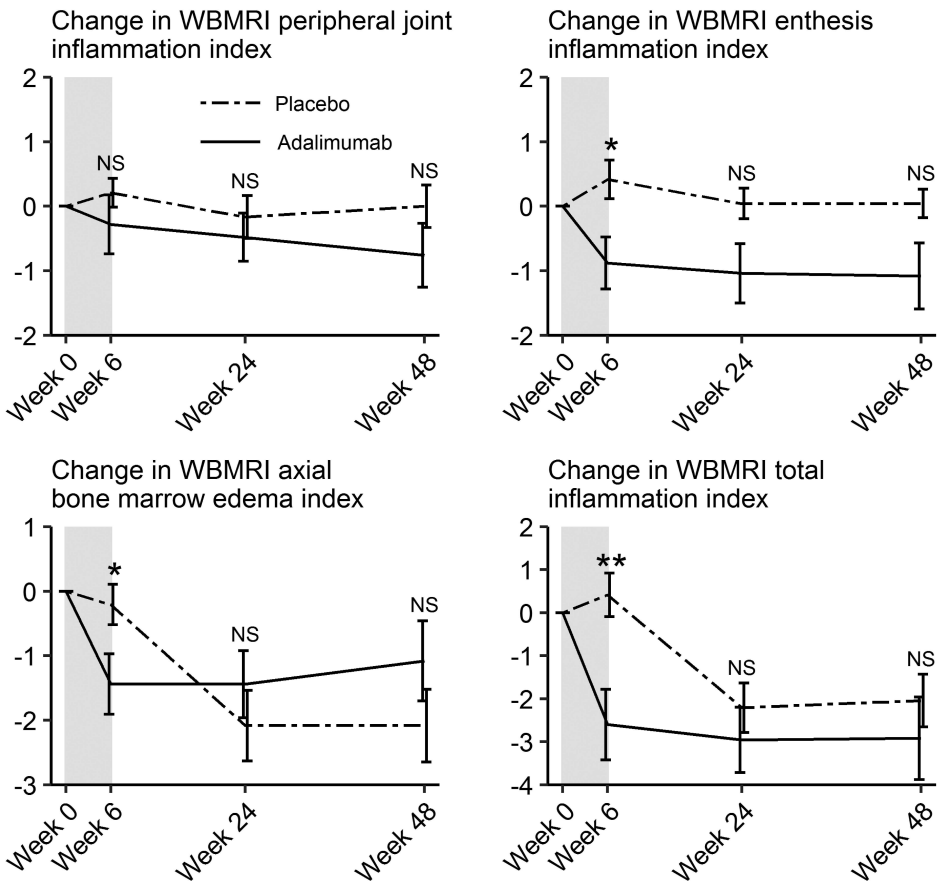

Figure 3. Mean change in WBMRI indices from baseline by treatment group. Lines show the mean change values and error bars show SEM of change values in each group. The shaded area indicates the randomization period; patients in the placebo group started adalimumab (ADA) at Week 6. At Week 24, 6 patients stopped ADA and started etanercept. P values were calculated by Mann-Whitney U tests. * P value in the range of 0.01-0.05; ** P value = 0.004. WBMRI: whole-body magnetic resonance imaging; SEM: standard error of the mean; NS: not significant.

more comprehensive WBMRI approach demands longer scan times, as well as image analysis and scoring, but novel MRI scanners and software with ensuing improvements in image quality and scan time, as well as the possible development of automated image analysis software, may improve the feasibility of this approach in the future. The sagittal scan planes used in our trial are not optimal for visualizing all subsets of peripheral joints and entheses; a consensus proposal for scan planes and pathology to be assessed using WBMRI has recently been published[23]. In our study, we chose to score entheses on WBMRI that are part of existing clinical enthesitis indices and that were judged to be possible to evaluate with the scan planes performed and the current image quality.

Our investigator-initiated trial shows that ADA reduces WBMRI indices of inflammation in both axial and peripheral joints and entheses, in parallel with improvements in conventional clinical measures of disease activity. To our knowledge, this study is the first to document significant improvements in axial and peripheral inflammatory disease activity assessed with WBMRI in a randomized, double-blind, placebo-controlled trial in patients with axSpA. Our present study encourages further development and validation of WBMRI indices as future outcome measures in peripheral SpA and axSpA.

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Table 3. Intrarater reliability, SDC, and responsiveness of WBMRI indices.

Variables	ICC, Status Score, Wk 0 (95% CI)	ICC, Change Score, wks 0–24 (95% CI)	SDC	GRI, Wk 6	SRM, Wk 6, ADA/PBO	SRM, Wk 24, Both Groups	SRM, Wk 48, Both Groups
No. patients	8	8	8	47	47	44	39
Peripheral joint indices							
Synovitis	0.45 (–0.42 to 0.86)	0.13 (–0.44 to 0.70)	1.3	0.16	0.08/–0.12	0.06	0.14
BME	0.43 (–0.33 to 0.85)	0.52 (–0.32 to 0.88)	1.0	0.43	0.15/–0.30	0.32	0.22
Inflammation	0.67 (–0.03 to 0.93)	0.25 (–0.47 to 0.78)	2.0	0.26	0.13/–0.19	0.19	0.22
Enthesis indices							
BME	0.71 (0.14–0.93)	0.86 (0.45–0.97)	1.4	1.10	0.45/–0.21	0.27	0.20
Soft tissue inflammation	0.34 (–0.34 to 0.81)	0.33 (–0.20 to 0.79)	1.6	0.34	0.33/–0.26	0.20	0.11
Inflammation	0.73 (0.08–0.94)	0.82 (0.37–0.96)	1.8	0.61	0.44/–0.29	0.29	0.19
Axial BME	0.91 (0.62–0.98)	0.67 (–0.06 to 0.92)	2.7	0.96	0.63/0.14	0.71	0.62
Total BME	0.96 (0.79–0.99)	0.91 (0.61–0.98)	2.2	1.32	0.82/0.03	0.86	0.72
Total inflammation	0.93 (0.69–0.99)	0.85 (0.37–0.97)	2.3	1.07	0.65/–0.17	0.83	0.70

SDC: smallest detectable change; WBMRI: whole-body magnetic resonance imaging; GRI: Guyatts responsiveness index; ADA: adalimumab; PBO: placebo; SRM: standardized response mean; BME: bone marrow edema.

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