

Title

Whole-body magnetic resonance imaging inflammation in peripheral joints and entheses in axial spondyloarthritis: Distribution and changes during adalimumab treatment

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Short running head

Whole-body MRI inflammation

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Abstract

Objective

To investigate the distribution of whole-body MRI (WBMRI) inflammatory lesions of peripheral joints and entheses, their response to adalimumab treatment and agreement with clinical measures of disease activity in patients with axial spondyloarthritis.

Methods

Explorative analysis of an investigator-initiated randomized controlled trial of adalimumab. WBMRI was performed at weeks 0, 6, 24 and 48. Detailed analyses of WBMRI lesions in peripheral joints and entheses were performed, including agreement with clinical measures of disease activity.

Results

WBMRI inflammatory lesions were most frequently observed in the acromioclavicular, metatarsophalangeal and wrist joints (>10% of joints), and at the greater trochanter, calcaneal insertion of the Achilles tendon, and ischial tuberosity (>15% of entheses). Inflammation resolved in $\geq 2/3$ of involved sternoclavicular, metacarpophalangeal, 1st carpometacarpal, hip and tarsometatarsal joints, pubic symphyses and medial femoral condyles. In contrast, inflammation resolved in $\leq 1/6$ of involved acromioclavicular joints, knee joints and supraspinatus tendon insertions at humerus. Tenderness of joints and entheses agreed poorly with whole-body MRI inflammation (kappas <0.40). Joint tenderness resolved more frequently in “MRI-positive” than “MRI-negative” joints (8/13, 62%, vs. 9/34, 26%) after 6 weeks active treatment.

Conclusion

Inflammatory lesions of peripheral joints and entheses in patients with predominantly axial spondyloarthritis, and changes therein, can be mapped using WBMRI, and it may contribute to differentiate between inflammatory and non-inflammatory joint tenderness.

Trial registration: ClinicalTrials, NCT01029847. Registered 10 December 2009,

<https://clinicaltrials.gov/ct2/show/study/NCT01029847>.

Introduction

Spondyloarthritis (SpA) is a group of diseases with shared genetics and clinical manifestations.(1) Peripheral arthritis and enthesitis are frequent disease manifestations and are included in the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial and peripheral SpA.(2-3) Classical clinical signs of inflammation at peripheral joint and entheses, e.g. swelling, may be apparent, but the patient-reported pain and tenderness often does not correlate with clinical signs of inflammation. Tenderness in patients with SpA may be of inflammatory or non-inflammatory origin.(4-5)

Whole-body magnetic resonance imaging (WBMRI) is a new modality in musculoskeletal imaging that may visualize inflammatory changes in multiple peripheral joints and entheses at the same time, and has gained interest for the detection of arthritis and enthesitis and for objectively monitoring changes during treatment.(6-10) In previous WBMRI studies of patients with SpA, the joints of the anterior chest wall, the calcaneal insertion of the Achilles tendon and plantar fascia, iliac crest, greater femoral trochanter and ischial tuberosity have been found to be frequently involved.(6-8,11-13) These studies had rather small sample sizes, were cross-sectional, or included only patients with ankylosing spondylitis, and the distribution of peripheral MRI manifestations in a broader group of patients with axial SpA (axSpA) is therefore still largely unknown. It is of interest how inflammatory lesions change during an effective anti-inflammatory therapy, as this provides information on the validity of the MRI findings. Moreover, WBMRI may also be of value to distinguish pain associated with inflammation versus pain not associated with inflammation in joints and entheses.

The objective of this study was to investigate patients with axSpA for the distribution of inflammatory lesions of peripheral joints and entheses and their response to adalimumab treatment by WBMRI. Moreover, we aimed to investigate the agreement between WBMRI findings and clinical joint tenderness and swelling, enthesal tenderness, and other clinical measures of disease activity.

Materials and Methods

Study design

The ASIM study comprised 49 patients that fulfilled the ASAS criteria for axSpA, had sacroiliitis as assessed by radiography and/or MRI, and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4.0 despite treatment with non-steroidal anti-inflammatory drugs. The study was a randomized, double-blind, placebo-controlled trial of adalimumab 40 mg or placebo subcutaneously (sc.) every other week (e.o.w.) for 6 weeks, followed by adalimumab 40 mg sc. e.o.w. from week 6 to week 48 in both treatment groups. At Week 24, clinical responders (decrease in BASDAI of 50% or 2.0) continued adalimumab while non-responders were allowed treatment with other drugs following local treatment guidelines. The inclusion and exclusion criteria, study procedures, and main results for clinical outcomes and WBMRI indices of inflammation have been reported previously.⁽¹⁴⁾ The study was approved by the Regional Committee on Health Research Ethics, Region Hovedstaden, Denmark, approval number: H1-2013-118. Trial registration: ClinicalTrials, NCT01029847. All participants provided written consent.

WBMRI acquisition

WBMRI was performed at baseline and at weeks 6, 24 and 48 on 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 including the sternoclavicular joints, 2) coronal images of thoracic spine, 3) coronal images of lumbar spine, sacroiliac joints and pelvis including the hips, 4) coronal images of hips and hands, 5) coronal images of knees, and 6) coronal and axial images of ankles and feet.⁽¹⁴⁾ Short tau inversion recovery (STIR), T1-weighted spin-echo (T1W) and T1-weighted spin-echo post-gadolinium (post-Gd-T1W) sequences were obtained.⁽¹⁴⁾

WBMRI scoring

An experienced musculoskeletal radiologist (I.E.) evaluated all images in known chronology blinded to radiography and clinical data. Reading images with known chronology was done to increase precision and feasibility, given the complexity of assessing WBMRI images at 4 timepoints in unknown order, knowing that it may introduce a risk of bias in changes over time. Osteitis was assessed on STIR sequences with post-Gd-T1W sequences used for reference only, while synovitis and enthesal soft tissue inflammation were assessed based on both these sequences.

Fifty-six peripheral joints: glenohumeral, acromioclavicular, sternoclavicular, wrist, carpometacarpal, metacarpophalangeal, hand interphalangeal joints, hip, knee, ankle, tarsometatarsal and metatarsophalangeal joints were scored separately for synovitis and osteitis on a semiquantitative scale (0 = absent / 1 = mild to moderate / 2 = severe). Joints were also assessed for the presence/absence of erosion.

Fifteen peripheral enthesal sites: supraspinatus tendon insertion at humerus, iliac crest, ischial tuberosity, pubic symphysis, greater femoral trochanter, insertion of the collateral ligament at the medial femoral condyle, calcaneal Achilles tendon insertion, and the 5th lumbar spinous process were scored separately for enthesal osteitis and soft tissue inflammation (0 = absent / 1 = mild to moderate / 2 = severe). The ischial tuberosity comprises the area where the hamstring muscles insert, and the greater femoral trochanters comprise the area where the gluteus medius inserts, but adjacent structures, when inflamed, might also cause increased signal in the bone marrow and soft tissue at these sites.

A previously developed WBMRI Enthesis Inflammation Index (range 0-60) that sums osteitis and soft-tissue inflammation scores of entheses into a patient-level index and a WBMRI Peripheral Joint Inflammation Index (range 0-184) that sums osteitis and synovitis scores of all individual joints were applied for correlation and cluster analysis with other variables.(14)

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Baseline and week 24 images of 8 patients were scored twice to assess intra-rater reliability. The costosternal joints and interphalangeal joints of the feet were only assessable in <10% of the patients and were excluded from the analysis.

Clinical examination

Patients had SJC-68 (swollen joint count of 68 joints) and TJC-70 (tender joint count of 70 joints) performed and the conventional SJC-44 and TJC-44 were also derived.(15) All enthesal sites in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index and Leeds Enthesitis Index (LEI) were assessed for tenderness.(16-18) A tender enthesis count of 33 entheses (TEC-33) based on all the entheses included in MASES, SPARCC and Leeds enthesitis indices was constructed.(14)

Statistical analyses

For the main analyses, WBMRI data at the lesion level were handled as binary (osteitis present/absent, synovitis present/absent, soft tissue inflammation present/absent) because most of the positive scores, 722 of 765 (94%), were scored as 1 (“mild or moderate”) and only few, 43 (6%), were scored as 2 (“severe”). As an additional analysis, “MRI positive” joints were defined as any signs of osteitis and/or synovitis (i.e. score ≥ 1), while “MRI positive” entheses were defined as any signs of osteitis and/or soft tissue inflammation (i.e. score ≥ 1).

Agreement between WBMRI and tenderness as well as the intra-rater reliability of scoring WBMRI were assessed using Cohen’s kappa, with values >0.75 representing excellent agreement, values between 0.4 and 0.75 fair to good agreement, and values <0.4 poor agreement.(19) In a post-hoc analysis, to explore the disease characteristics of patients with discrepancies between WBMRI findings and clinical tenderness further, two subgroups were created: one subgroup of patients with ≥ 5 “MRI positive” joints or entheses that were not tender (n=11), and one subgroup of patients with ≥ 5 joints or entheses that were

tender but “MRI negative” (n=12). These cut-offs were chosen post-hoc to include about 1/5 of the patients in each subgroup.

Hierarchical cluster analysis of the WBMRI peripheral joint inflammation index and the WBMRI enthesis inflammation index along with other disease activity measures was performed. SPARCC Spine/SIJ Inflammation Index was derived by adding SPARCC Spine Inflammation Index and SPARCC SIJ Inflammation Index. C-reactive protein (CRP), TEC-33, TJC-70 and SPARCC Spine/SIJ Inflammation Index were log transformed to be approximately normally distributed, $\log(x + 1)$ was used to allow for zero values. Thereafter, all variables were scaled to a mean of 0 and a standard deviation of 1. Distances between measures were calculated using the Manhattan distance where the pairwise discrepancies in two measures across all patients are summed, and hierarchical cluster analysis was performed using “average” as aggregation method, where all values are simultaneously taken into account. To assess the uncertainty of the clustering procedure, the bootstrap probability for each cluster was computed using 10,000 bootstrap samples.(20)

Results

Distribution of peripheral arthritis as assessed by WBMRI and palpational tenderness

At baseline, 114 joints out of 2174 (5%) were “MRI positive” (osteitis and/or synovitis), 27 joints (1%) had osteitis, while 100 joints (4%) had synovitis, see **Table 1** and **Figure 1**. By clinical examination, 131 joints out of 3430 (4%) were tender and 8 (0.2%) were swollen. Five patients (10%) had ≥ 1 swollen joint, 26 patients (53%) had ≥ 1 tender joint and 35 patients (71%) had ≥ 1 “MRI positive” joint.

The most frequent “MRI positive” joints were the 1st MTP (38%), acromioclavicular (16%) and wrist joints (12%). The most frequent tender joints were the sternoclavicular (18%), 1st to 4th MTP (8-12%) and shoulder joints (9%). Erosions were most frequently observed in the acromioclavicular joints (9%) and 1st MTP joints (7%). Image examples are shown in **Supplementary Figure 1**.

Distribution of enthesitis as assessed by WBMRI and tenderness

At baseline, 597 entheses were assessed by WBMRI, 28 entheses (5%) were scored positive for osteitis, 45 entheses (8%) were scored positive for soft tissue inflammation, and, in total, 59 entheses (10%) were “MRI positive” (osteitis and/or soft tissue inflammation), see **Table 2** and **Figure 1**. In comparison, 327 out of 1617 entheses (20%) were tender on palpation. Forty patients (82%) had ≥ 1 tender enthesis and 28 patients (57%) had ≥ 1 enthesis with inflammation on MRI. Overall, 41 patients (84%) had ≥ 1 tender joint or enthesis, and 41 patients (84%) had ≥ 1 “MRI positive” joint or enthesis.

The most frequent “MRI positive” entheses were greater femoral trochanter (21%), calcaneal Achilles tendon insertion (17%) and ischial tuberosity (16%), whereas the most frequent tender enthesal sites were at the 1st and 7th costosternal junctions (35-43%), posterior superior iliac spine (38%) and greater femoral trochanter (35%). Image examples are shown in **Supplementary Figure 1**.

Clinical indices of enthesitis, tender and swollen joints

At week 6, TJC-70 decreased significantly more in the adalimumab group compared to the placebo group. No significant changes in SJC-68 were observed over time. MASES, LEI and SPARCC enthesitis indices and TEC-33 all decreased numerically during treatment, but the between-group difference in change at Week 6 did not reach statistical significance, see **Supplementary Table 1**.

Agreement between WBMRI arthritis/enthesitis and clinical tenderness

The agreement between WBMRI enthesitis and tenderness of the individual joints, agreement was poor with kappa values site by site < 0.4 , except for 3rd-5th metatarsophalangeal joints (kappa for these joints ranged 0.6 to 1.0, but the majority were judged not assessable by MRI). Among 2139 joints in total at baseline, 17/1965 were concordantly positive/negative, 60 were tender but “MRI negative”, and 97 were “MRI positive” but not tender (kappa 0.14). Also with regards to the entheses, agreement between WBMRI and tenderness was poor with kappa values site by site < 0.4 . Among 597 entheses in total at

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baseline, 19/388 were concordantly positive/negative, 104 were tender but “MRI negative”, and 37 were “MRI positive” but not tender (kappa 0.08).

When limiting the analysis to sites that were scored as “severe” by MRI at baseline, none of the 6 joints scored as “severe” by MRI were clinically tender or swollen, and only 2 of 9 entheses scored as “severe” by MRI (the left and right ischial tuberosity in a single patient) were clinically tender.

Intra-rater reliability of WBMRI at the joint and enthesis level

Intra-rater agreement at the joint level was fair to good, with kappa 0.46 and percentage exact agreement 96%. Similar results were found for entheses, with kappa 0.59 and percentage exact agreement 93%.

Patients with major discordance between MRI inflammation and clinical tenderness

Patients with ≥ 5 sites with tenderness that were “MRI negative” were more often women, had shorter disease duration and more frequently non-radiographic axSpA, with less spinal inflammation and new bone formation, and tended to have more fatigue, see **Table 3**. In contrast, patients with ≥ 5 “MRI positive” sites but no tenderness tended to be men, had longer disease duration and more frequently radiographic axSpA, i.e. ankylosing spondylitis, more spinal inflammation and new bone formation, and tended to have less fatigue.

Correlation between MRI inflammation and other disease activity measures

WBMRI Enthesis Inflammation Index and WBMRI Peripheral Joint Inflammation Index correlated with each other ($\rho=0.37$, $p=0.008$). WBMRI Enthesis Inflammation Index correlated with SPARCC Spine MRI Inflammation Index ($\rho=0.32$, $p=0.03$). The WBMRI Enthesis Inflammation Index tended to correlate weakly with CRP ($\rho=0.20$, $p=0.15$), while the WBMRI Peripheral Joint Inflammation Index did not correlate with CRP ($\rho=0.00$, $p=0.99$). There was no correlation between the WBMRI Enthesis Inflammation Index and TEC-33 ($\rho=0.03$, $p=0.81$), and no correlation between the WBMRI Peripheral Joint Inflammation Index and TJC-70 ($\rho=-0.09$, $p=0.56$). Similar results were found when the analysis

was limited to the 13 entheses and 56 joints that were assessed both clinically and by MRI. TEC-33 correlated most closely with TJC-70 ($\rho=0.64$, $p<0.001$), fatigue ($\rho=0.36$, $p=0.01$) and pain ($\rho=0.32$, $p=0.02$).

Hierarchical cluster analysis of measures of disease activity

Using hierarchical cluster analysis in an exploratory post-hoc analysis showed that objective measures of disease activity, i.e. WBMRI indices of inflammation of peripheral joints and entheses, inflammation of the axial skeleton (SPARCC Spine/SIJ) on conventional MRI, CRP and SJC-68 formed one cluster, while the patient-reported measures of disease activity, including pain, fatigue and palpational tenderness seemed to form another separate cluster, see **Figure 2**.

Resolution of tenderness and WBMRI lesions during treatment

TJC-70, TJC-44, MASES, SPARCC, LEI and TEC-33 improved numerically over time in both groups, but the between-group difference in change at Week 6, i.e. at the end of the placebo period, did not reach significance, except for TJC-70; however, this Week 6 between-group difference in change in TJC-70 was driven by an observed worsening in the placebo group more than actual improvement in the adalimumab group, see **Supplementary Table 1**.

At the lesion level, clinical tenderness of the individual joints/entheses resolved at Week 6 with similar frequencies in the adalimumab group (36%/42%) and the placebo group (52%/50%), whereas MRI inflammation of joints/entheses tended to resolve more often in the adalimumab group (31%/26%) than in the placebo group (10%/17%). In the adalimumab group, clinical tenderness of joints and entheses that were positive for baseline MRI inflammation tended to resolve more frequently, while in the placebo group, clinical tenderness of joints and entheses that were negative for baseline MRI inflammation tended to resolve more frequently, see **Table 4**. At week 6, tenderness of joints resolved more frequently when positive for inflammation by MRI (Fisher's Exact test, $p=0.041$), while no difference in the resolution of tenderness of entheses in relation to the presence or absence of MRI inflammation was observed.

Discussion

In this study of patients with predominantly axial spondyloarthritis, WBMRI documented inflammation of peripheral joints and/or entheses in most patients. Inflammatory lesions as assessed by WBMRI tended to disappear during treatment with adalimumab, which supports the validity of WBMRI as a potential method of measuring inflammation during follow-up of spondyloarthritis patients. Furthermore, a post-hoc sub-analysis showed that tender joints with MRI inflammation improved clinically during TNF inhibitor therapy more frequently than tender joints without MRI inflammation, which suggests that MRI may be able to differentiate inflammatory from other non-inflammatory causes of tenderness and pain in patients with SpA. To our knowledge, no studies have previously investigated whether WBMRI inflammation of peripheral joints and entheses predicts treatment response, while in axSpA MRI inflammation of the sacroiliac joints is known to predict treatment response to TNF inhibitor therapy.(21)

MRI inflammation present at baseline resolved most frequently ($\geq 50\%$ of lesions) in sternoclavicular, metacarpophalangeal, 1st carpometacarpal, hip and tarsometatarsal joints and at the pubic symphysis, medial femoral condyle and the calcaneal insertion of the Achilles tendon. Thus, MRI inflammation detected at these sites is likely to be truly related to an inflammatory disease such as SpA. In contrast, inflammation resolved in only few of the acromioclavicular joints and 1st metatarsophalangeal joints; these sites are known to be prone to osteoarthritis and the persisting inflammation that was observed may be unrelated to SpA. Only few of the osteitis lesions at the supraspinatus tendon insertions at humerus (14%) resolved, and because of the limited image resolution and only coronal images of the

shoulder, this may be hard to discriminate from fluid in bone erosions at this site of the shoulder in patients with axSpA;(22) discrimination between supraspinatus and infraspinatus tendon insertions may also be very difficult. A frequent involvement of the acromioclavicular and 1st MTP joints was not found in two other studies, but whether this reflects genuine differences between the patient cohorts or different image resolution or reader sensitivity is unclear.(11-12)

If WBMRI were to be used as an objective measure of SpA remission, sites prone to degenerative changes may need to be disregarded when assessing the peripheral inflammatory activity related to SpA. An option would be to assess each joint for osteoarthritis and disregard scores for inflammation of joints where osteoarthritis is judged present. However, WBMRI has poorer resolution compared to conventional dedicated MRI and is therefore not currently sufficient for assessment of damage, except for gross pathology, in small structures, e.g. finger or toe joints; newer MRI units and improved sequence types can provide better resolution.

The agreement between tenderness and objective signs of inflammation of peripheral joints and entheses as assessed by WBMRI was overall poor. Subtle areas with inflammation might be missed by MRI due to the rather coarse image resolution, and small joints of hands and feet were at the threshold of resolution with just one or two slices depicting a joint and partial volume averaging was a challenge. This may have limited the intra-rater agreement in this study and may contribute to the poor correlation between clinical and imaging findings. However, a poor correlation between MRI findings and clinical assessment of entheses has been found in several studies.(7-8,13,23) Therefore, we tried to look at possible explanations. In post-hoc analyses, we observed that the subgroup of patients with many tender joints and entheses were more frequently women with non-radiographic axSpA, while the subgroup of patients with many “MRI positive” sites were more frequently men fulfilling the radiographical criteria for ankylosing spondylitis. Similar differences between men and women have previously been reported in a large French cohort, where women had worse patient-reported outcomes despite less radiographic sacroiliitis and MRI inflammation of sacroiliac joints and spine.(24) Women tend to have non-radiographic disease and more often fulfil the diagnostic criteria for fibromyalgia,(4,25) and the lack of

good correlation between MRI inflammation and other measures of disease activity may thus in part reflect variations across the spectrum of axSpA.(26)

A disconnect between patient-reported and objective measures also emerged when disease measures were analysed in hierarchical cluster analysis. We identified a cluster of patient-reported measures, including palpational tenderness of joints and entheses, and a separate cluster of objective measures, including MRI, CRP and SJC. Joint and enthesal tenderness may or may not be related to active SpA at the tender sites, but the positive predictive value of tenderness was low when using MRI inflammation as standard reference (22% of joints with tenderness were “MRI positive”, while 15% of entheses with tenderness were “MRI positive”).

The relation of WBMRI inflammation to other objective measures of disease activity and the fact that joints responded better clinically when positive by MRI suggest that the method has credibility, despite the concerns mentioned above. However, the clinical relevance of subclinical MRI inflammation for the diagnosis and management of patients with axSpA is unknown, and the data on the prevalence of “WBMRI positive” joints and entheses in healthy subjects and subjects with degenerative changes across different age groups are also very limited. Thus, at this stage, WBMRI is not recommended for use in routine clinical practice in patients with axSpA but is of high interest for research purposes. The OMERACT MRI in Arthritis Working Group has recently recommended which scan planes to use for WBMRI image acquisition and assessment.(27) In the present study, it is a limitation that sagittal MRI images of ankles and knees were not performed, which meant that certain structures, e.g. the plantar fascia and patellar ligament could not be scored, and therefore this study does not provide data on these sites. WBMRI was scored by one experienced musculoskeletal radiologist and we acknowledge that an additional reader might have improved the overall robustness of the conclusions. An initiative regarding the refinement of a semiquantitative scoring system of WBMRI and testing its reliability among several readers at varying levels of experience is currently ongoing within the OMERACT MRI in Arthritis Working Group.

In conclusion, the distribution of inflammatory lesions was mapped using whole-body MRI of peripheral joints and entheses in 49 patients with predominantly axSpA. Joint and enthesal tenderness agreed poorly with WBMRI inflammation. Patients with many tender joints or entheses that were “MRI negative” were frequently women with non-radiographic axSpA, while patients with many “MRI positive” joints or entheses that were not tender were frequently men with ankylosing spondylitis. WBMRI seems to be a promising objective tool for assessing the distribution and changes over time in inflammation of peripheral joints and entheses and may separate inflammation of joints and entheses from tenderness of non-inflammatory origin.

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Authors' contributions

M.Ø, S.J.P and I.J.S. initiated the ASIM trial. I.E. evaluated the whole-body MRI images. I.J.S., B.J., O.R.M. and S.J.P. recruited and managed the patients who participated in the ASIM trial. J.M.M. and L.B. had responsibility for obtaining the MRI scans. S.K. performed statistical analyses and drafted the manuscript. All authors critically revised the manuscript.

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Figure legends

Figure 1. Percentage of joints and entheses that were “MRI positive” at baseline. A, supraspinatus tendon insertion at humerus; B, 5th lumbar spinous process; C, iliac crest; D, pubic symphysis; E, ischial

tuberosity; F, greater femoral trochanter; G, medial femoral condyle; H, calcaneal Achilles tendon insertion.

Figure 2. Clustering of different measures of disease activity in patients with axial spondyloarthritis.

Numbers at clustering points indicate how strongly each cluster is supported by the data (bootstrap probability, the frequency with which a cluster appears in 10,000 bootstrap replicates). TEC-33, tender entheses count of 33 entheses; TJC-70, tender joint count of 70 joints; SJC-68, swollen joint count of 68 joints; WBMRI enth. infl., whole-body MRI enthesal inflammation index; WBMRI joint infl., whole-body MRI joint inflammation index; CRP, C-reactive protein; SPARCC Spine/SIJ, Spondyloarthritis Research Consortium of Canada MRI Spine and Sacroiliac Joint Index added together.

Table 1. Percentage of joints with clinical tenderness and MRI lesions at baseline and the resolution and development of “MRI positive” joints during follow-up.

	Clinical tenderness	MRI synovitis	MRI osteitis	MRI synovitis and/or osteitis	MRI erosion	Resolution of MRI inflammation at week 24	Resolution of MRI inflammation at week 48	Development of MRI inflammation at week 48
Number of patients	49	49	49	49	49	44	39	39
Temporomandibular	5/98 (5%)	ND	ND	ND	ND	ND	ND	ND
Sternoclavicular	18/98 (18%)	1/58 (2%)	5/56 (9%)	6/58 (10%)	2/73 (3%)	4/4 (100%)	3/3 (100%)	0
Acromioclavicular	6/98 (6%)	12/86 (14%)	6/86 (7%)	14/86 (16%)	8/92 (9%)	1/14 (7%)	2/11 (18%)	0
Shoulder	9/98 (9%)	1/86 (1%)	2/86 (2%)	3/86 (3%)	3/91 (3%)	1/3 (33%)	1/3 (33%)	0
Elbow	3/98 (3%)	ND	ND	ND	ND	ND	ND	ND
Wrist	7/98 (7%)	11/93 (12%)	2/91 (2%)	11/93 (12%)	0/95 (0%)	3/11 (27%)	7/11 (64%)	6
1 st carpometacarpal	4/98 (4%)	6/92 (7%)	1/90 (1%)	6/92 (7%)	0/95 (0%)	5/6 (83%)	4/4 (100%)	2
1 st -5 th MCP	1/98 (1%)	1/93 (1%)	0/91 (0%)	1/93 (1%)	0/96 (0%)	1/1 (100%)	1/1 (100%)	0
1 st IP and 2 nd -5 th PIP (hands)	3/98 (3%)	1/89 (1%)	0/87 (0%)	1/89 (1%)	0/92 (0%)	0/1 (0%)	1/1 (100%)	0
2 nd -5 th DIP (hands)	0/98 (0%)	0/83 (0%)	0/82 (0%)	0/83 (0%)	0/87 (0%)	0/0	0/0	0
Hip	6/98 (6%)	7/96 (7%)	3/96 (3%)	8/96 (8%)	0/98 (0%)	6/8 (75%)	3/6 (50%)	1
Knee	6/98 (6%)	9/92 (10%)	0/92 (0%)	9/92 (10%)	0/98 (0%)	1/9 (11%)	0/5 (0%)	1
Ankle	6/98 (6%)	8/98 (8%)	0/98 (0%)	8/98 (8%)	0/98 (0%)	0/4 (0%)	0/4 (0%)	2
Tarsometatarsal	2/98 (2%)	3/96 (3%)	1/96 (1%)	3/96 (3%)	0/97 (0%)	2/3 (67%)	2/3 (67%)	3
1 st MTP	9/98 (9%)	32/94 (34%)	7/94 (7%)	36/94 (38%)	7/98 (7%)	7/33 (21%)	7/28 (25%)	5
2 nd MTP	10/98 (10%)	2/13 (15%)	0/11 (0%)	2/13 (15%)	0/98 (0%)	0/2 (0%)	0/2 (0%)	0
3 rd MTP	12/98 (12%)	2/13 (15%)	0/11 (0%)	2/13 (15%)	0/98 (0%)	0/2 (0%)	0/2 (0%)	0
4 th MTP	8/98 (8%)	2/13 (15%)	0/11 (0%)	2/13 (15%)	0/98 (0%)	0/2 (0%)	1/2 (50%)	0
5 th MTP	3/98 (3%)	2/13 (15%)	0/11 (0%)	2/13 (15%)	0/98 (0%)	1/2 (50%)	1/2 (50%)	0
1 st IP and 2 nd -5 th PIP (feet)	2/98 (2%)	ND	ND	ND	0/96 (0%)	ND	ND	ND

Eight joints in 5 patients were judged clinically swollen at baseline: 3 sternoclavicular joints and one wrist, elbow, PIP, shoulder and knee joint, 6 of these were “MRI negative” and 2 were not assessable by MRI. At some sites, the total number of joints assessed by MRI was lower than 98 (i.e. 49 patients, left and right side) when sites were not in field of view or overall image quality was too poor to allow evaluation. Resolution of MRI inflammation at week 24 or 48 was calculated as the number of “MRI negative” joints at week 24 or 48 divided by the number of “MRI positive” joints at baseline among 44 or 39 patients. Development of MRI inflammation at week 48 is reported as the number of “MRI positive” joints at week 48 that were “MRI negative” at baseline among 39 patients. DIP, distal interphalangeal. IP, interphalangeal. MCP, metacarpophalangeal. MTP, metatarsophalangeal. PIP, proximal interphalangeal.

Table 2. Percentage of entheses with clinical tenderness and MRI lesions at baseline and the resolution and development of “MRI positive” entheses during follow-up.

	Clinical tenderness	MRI soft tissue inflammation	MRI osteitis	MRI soft tissue inflammation and/or osteitis	Resolution of MRI inflammation at week 24	Resolution of MRI inflammation at week 48	Development of MRI inflammation at week 48
Number of patients	49	49	49	49	44	39	39
Supraspinatus tendon insertion at humerus	18/98 (18%)	2/86 (2%)	7/86 (8%)	9/86 (10%)	1/7 (14%)	1/7 (14%)	1
5 th lumbar spinous process	14/49 (29%)	0/48 (0%)	0/48 (0%)	0/48 (0%)	0/0	0/0	0
Iliac crest	26/98 (27%)	2/96 (2%)	1/96 (1%)	3/96 (3%)	0/3 (0%)	0/3 (0%)	0
Ischial tuberosity	13/98 (13%)	14/96 (15%)	9/96 (9%)	15/96 (16%)	7/15 (47%)	3/10 (30%)	1
Pubic symphysis	ND	1/48 (2%)	3/48 (6%)	3/48 (6%)	2/2 (100%)	1/2 (50%)	0
Greater femoral trochanter	34/98 (35%)	19/96 (20%)	5/96 (5%)	20/96 (21%)	7/19 (37%)	7/15 (47%)	6
Collateral ligament insertion on medial femoral condyle	16/98 (16%)	3/90 (3%)	1/91 (1%)	3/91 (3%)	2/3 (67%)	2/3 (67%)	0
Calcaneal Achilles tendon insertion	12/98 (12%)	4/36 (11%)	2/36 (6%)	6/36 (17%)	2/4 (50%)	0/3 (0%)	2

Clinical tenderness was present in the following sites not assessed by WBMRI: 1st costosternal joint, 42/98 (43%); 7th costosternal joint, 33/98 (34%); medial epicondyle of humerus, 18/98 (18%); lateral epicondyle of humerus, 11/98 (11%); anterior superior iliac spine, 19/98 (19%); posterior superior iliac spine, 37/98 (38%); quadriceps tendon insertion into patella, 8/98 (8%); patellar ligament insertion into patella, 8/98 (8%); patellar ligament insertion into tibial tuberosity, 4/98 (4%); plantar aponeurosis insertion into calcaneus, 14/98 (14%). ND, not done. Resolution of MRI inflammation at week 24 or 48 was calculated as the number of “MRI negative” entheses at week 24 or 48 divided by the number of “MRI positive” entheses at baseline among 44 or 39 patients. Development of MRI inflammation at week 48 is reported as the number of “MRI positive” entheses at week 48 that were “MRI negative” at baseline among 39 patients.

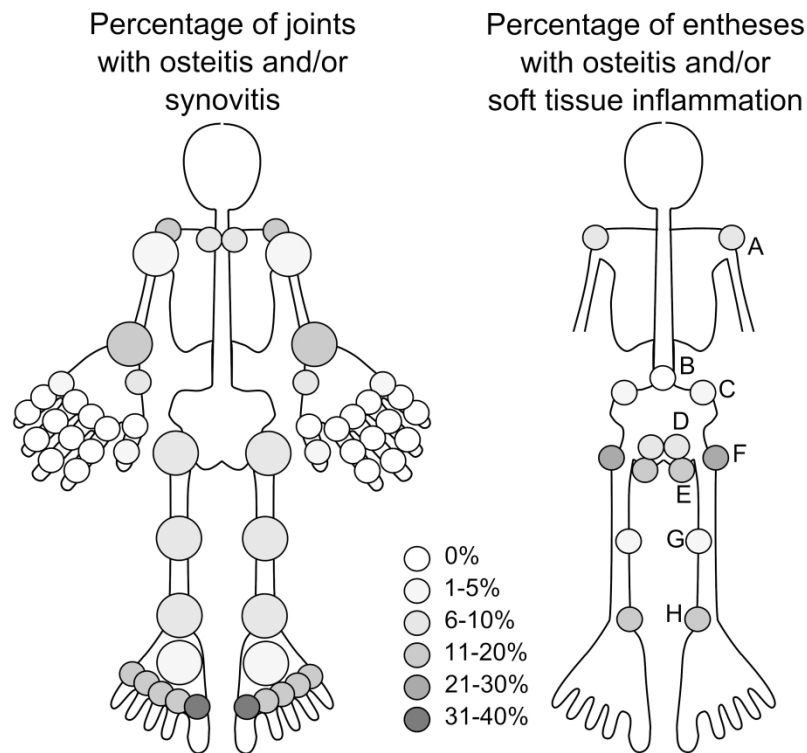
Table 3. Baseline characteristics of all patients and subgroups of patients with many discordant tender joints/entheses and many discordant “MRI positive” joints/entheses.

	All patients (n=49)	Subgroup A: Patients with ≥ 5 joints or entheses tender on palpation but negative on MRI (n=12)	Subgroup B: Patients with ≥ 5 joints or entheses positive on MRI but not tender (n=11)	P-values for difference between subgroups
Age (years)	36 (30-44)	38 (33-40)	43 (37-50)	0.20
Sex (men/women)	25 (51%) / 24 (49%)	2 (17%) / 10 (83%)	8 (73%) / 3 (27%)	0.01
Diagnosis duration (years)	1 (0-4)	1 (0-1)	4 (1-13)	0.004
HLA-B27	36 (73%)	7 (58%)	9 (82%)	0.37
Radiographic New York criteria	28 (57%)	4 (33%)	10 (91%)	0.009
CRP	3.9 (1.7-11)	3.8 (2.2-11.8)	4.2 (2.1-8.3)	0.95
BASDAI	6.3 (5.4-7.2)	6.6 (6.3-8.0)	6.0 (5.7-6.7)	0.21
Pain score	6.3 (5.0-8.0)	7.6 (5.0-9.4)	6.2 (4.9-8.1)	0.39
Fatigue score	7.6 (6.0-9.0)	8.5 (7.3-9.7)	6.3 (5.6-8.6)	0.06
SPARCC MRI SIJ Inflammation	5 (0-15)	5 (2-7)	4 (1-13)	0.76
SPARCC MRI Spine Inflammation	6 (2-15)	6 (1-8)	16 (9-32)	0.02
mSASSS	2 (0-6)	0 (0-3)	6 (4-34)	0.005
TEC-33	6 (2-10)	13 (9-18)	2 (0-6)	<0.001
TJC-70	1 (0-3)	6 (3-8)	0 (0-2)	0.001
WBMRI entheses inflammation index	1 (0-3)	2 (0-3)	4 (2-6)	0.14
WBMRI peripheral joint inflammation index	2 (0-4)	2 (0-2)	7 (6-8)	<0.001

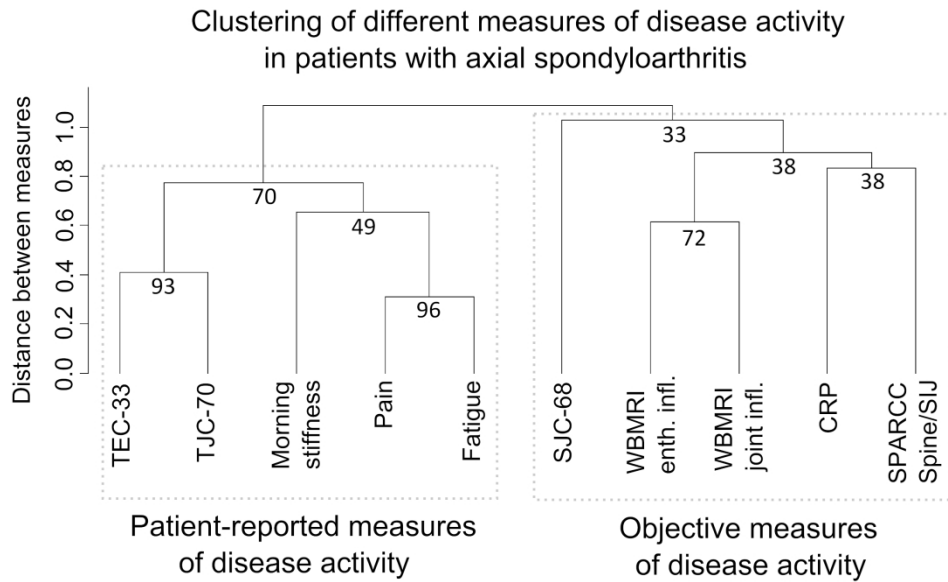
Values are number/percentages for binary outcomes and median/inter-quartile range for continuous outcomes. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; HLA-B27, human leucocyte antigen B27; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; SIJ, sacroiliac joint; SPARCC, Spondyloarthritis Research Consortium of Canada; TJC-70, tender joint count of 70 joints; TEC-33, tender entheses count of 33 entheses; WBMRI, whole-body magnetic resonance imaging.

Table 4. Disappearance of clinical tenderness from baseline to week 6, stratified by the presence or absence of baseline MRI inflammation.

	Resolution of tenderness at week 6 (Adalimumab group)	Resolution of tenderness at week 6 (Placebo group)
Number of patients	24	23
Tender joints at baseline		
"MRI positive"	8/13 (62%)	2/4 (50%)
"MRI negative"	9/34 (26%)	12/23 (52%)
Tender entheses at baseline		
"MRI positive"	5/12 (42%)	2/7 (29%)
"MRI negative"	23/55 (42%)	23/43 (53%)
"MRI positive" joints, presence of synovitis and/or osteitis; "MRI negative" joints, no synovitis and no osteitis; "MRI positive" entheses, presence of soft tissue inflammation and/or osteitis; "MRI negative" entheses, no soft tissue inflammation and no osteitis.		



Percentage of joints and entheses that were "MRI positive" at baseline. A, supraspinatus tendon insertion at humerus; B, 5th lumbar spinous process; C, iliac crest; D, pubic symphysis; E, ischial tuberosity; F, greater femoral trochanter; G, medial femoral condyle; H, calcaneal Achilles tendon insertion.



Clustering of different measures of disease activity in patients with axial spondyloarthritis. Numbers at clustering points indicate how strongly each cluster is supported by the data (bootstrap probability, the frequency with which a cluster appears in 10,000 bootstrap replicates). TEC-33, tender enthesis count of 33 entheses; TJC-70, tender joint count of 70 joints; SJC-68, swollen joint count of 68 joints; WBMRI enth. infl., whole-body MRI enthesal inflammation index; WBMRI joint infl., whole-body MRI joint inflammation index; CRP, C-reactive protein; SPARCC Spine/SIJ, Spondyloarthritis Research Consortium of Canada MRI Spine and Sacroiliac Joint Index added together.