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Development and Validation of Three Preliminary MRI Sacroiliac Joint Composite Structural Damage Scores in a 5-year Longitudinal Axial Spondyloarthritis Study

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A short running head (maximum 4 words):
MRI SIJ Composite score
ABSTRACT

Objective
In axial spondyloarthritis (axSpA), sacroiliac joint (SIJ) erosion is often followed by fat metaplasia in an erosion cavity (backfill), and subsequently ankylosis. We aimed to combine Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ Structural score for Erosion, Backfill and Ankylosis into 3 versions of a novel preliminary Composite axSpA MRI SIJ Structural Damage Score (CSDS) and test these.

Methods
Thirty-three axSpA patients followed for 5 years after initiation of tumor necrosis factor inhibitor had MRI of SIJs at baseline, and yearly thereafter. Three versions of CSDSs were calculated based on different weightings of erosion, backfill and ankylosis: Equal weighting: CSDS_{equal}=(erosion x0.5)+backfill+ankylosis; Advanced stages weighting more: CSDS_{stepwise}=(erosion x1)+(backfill x4)+(ankylosis x6); Advanced stages overruling earlier stages (“hierarchical”) with “<” meaning “overruled by”: CSDS_{hierarchical}=(erosion x1)<(backfill x4)<(ankylosis x6).

Results
At baseline all CSDSs correlated positively with SPARCC Fat and Ankylosis, modified New York-radiography grading and negatively with BASDAI and SPARCC SIJ Inflammation. CSDS_{stepwise} and CSDS_{hierarchical} (not CSDS_{equal}) correlated positively with symptom duration and BASMI, and closer with SPARCC ankylosis and Modified New York-radiography grading than CSDS_{equal}. The adjusted annual progression rate for CSDS_{stepwise} and CSDS_{hierarchical} (not CSDS_{equal}) was higher the first year compared with fourth year (p=0.04 and p=0.01). Standardized response mean (baseline-week 46) was moderate for CSDS_{hierarchical} (0.64) and CSDS_{stepwise} (0.59) and small for CSDS_{equal} (0.25).

Conclusion
Particularly CSDS$_{\text{stepwise}}$ and CSDS$_{\text{hierarchical}}$ showed construct validity and responsiveness, encouraging further validation in larger clinical trials. The potential clinical implication is assessment of sacroiliac joint damage progression by one composite score.

**INTRODUCTION**

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease which causes inflammation and structural damage in sacroiliac joints (SIJs) and spine(1, 2). Other characteristics include back and buttock pain and reduced physical function and spine mobility(3). Conventional radiography of SIJs and spine has to date been the standard imaging method for assessing structural progression. However, on radiography definite sacroiliitis is usually not present until after several years of disease activity and structural damage progression can only be reliably detected over 2-4 years(4-7). Magnetic resonance imaging (MRI) of the SIJs captures structural lesions more accurately than conventional radiography when computed tomography (CT) is considered the standard reference(8). MRI also reliably detects structural lesions such as fat lesion, erosion, backfill (i.e. fat metaplasia in an erosion cavity) and ankylosis in the SIJs(9) and it can reliably display changes in fat, erosion and backfill over time periods as short as 3 months(10, 11). In patients with AS, several MRI studies have indicated an evolution of lesions in the SIJs where bone erosion(12) often is followed by new onset of fat metaplasia in the erosion cavity (backfill)(13), ultimately leading to ankylosis(11, 14, 15). Based on the sequence of MRI lesions in the development of structural damage progression (erosion to backfill to ankylosis)(11, 14, 15) it could be relevant to combine these MRI pathologies by creating a composite score that would be able to capture the sequential development of structural lesions during the progression of the disease. Fat lesions (i.e. fat metaplasia inside the bone marrow) represent another construct, which is not a part of the development of erosion into backfill into ankylosis (all lesions located adjacent to or within the joint space) as described and therefore, it
would be most logical not to include fat lesion in the above-mentioned composite score of structural damage. Combining the individual structural lesions (i.e. erosion, backfill and ankylosis) would make it possible to assess SIJ damage with one single outcome measure, which can illustrate if there is structural progression or not and would be a useful tool in clinical trials. One combined measure of overall SIJ damage progression may also increase sensitivity to change and potentially reduce the needed sample size and/or follow up time in clinical trials.

The Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ Structural Score (SSS)(9) is a reliable and validated method to assess structural lesions of the SIJs and it gives information on the amount of the individual structural lesions, i.e. fat lesion, erosion, backfill and ankylosis. Therefore, SPARCC SSS could provide a basis for a SIJ composite structural damage score.

The aim of the study was to combine the SPARCC scores for erosion, backfill and ankylosis into a composite score for SIJ structural damage, calculated with three different preliminary formulas. We tested these scores in a 5-year follow-up study of patients with axSpA treated with a tumor necrosis factor (TNF) inhibitor.

MATERIALS AND METHODS

Patients

The Biomarkers in Spondylarthritis (BIOSPA) study(16, 17) was a prospective investigator-initiated open-label observational multicenter study of patients treated with a TNF inhibitor for the first time. The study was carried out from 2004 to 2012 as a collaboration between 9 Departments of Rheumatology in Denmark.

The study was approved by the regional scientific ethical committee (H-KF-02-050/04) and patients’ writing informed consent were obtained. Clinical trial registration number was NCT00133315. Patients were eligible if they: fulfilled the European Spondyloarthropathy Study Group (ESSG)
classification criteria for spondylarthritis(18); had a Bath Ankylosing Spondylitis Disease Index (BASDAI) > 3.0 despite treatment with non-steroidal anti-inflammatory drugs (NSAIDs) at a maximum dose; had clinical indication for TNF-inhibitor therapy as judged by the treating rheumatologist; fulfilled the radiographic part of the modified New York Criteria (mNYc)(19) or had inflammation and/or structural lesions on MRI as evaluated by a musculoskeletal radiologist. Disease activity was evaluated repeatedly with BASDAI and C-reactive protein (CRP), and the Ankylosing Spondylitis Disease Activity Score (ASDAS) was calculated retrospectively. At week 22 clinical responders, defined by 50% reduction in BASDAI or change of 2 (BASDAI range 0-10) since initiation of TNF inhibitor, continued the original TNF inhibitor therapy while the non-responders changed TNF inhibitor at the discretion of the treating rheumatologist.

After 46 weeks patients were invited to join an open-label extension of the study until year 5. In the 5-year open label study, patients were treated according to Assessment of SpondyloArthritis international Society (ASAS) recommendations(20, 21).

**Imaging**

MRIs of SIJs and lower spine (T9-S1) were obtained on a 1.5T system with a 5-element phased-array spine coil with slice thickness 4 mm and slice gap 0.8 mm. SIJs were visualized with semi-coronal T1-weighted turbo spin-echo images (repetition time: 550 msec, echo time 14msec, field of view 320 mm, matrix 320 x 192) and short tau inversion recovery (STIR) MRI images (repetition time 1,650 msec, echo time 22 msec, inversion time 170 msec, field of view 400 mm, matrix 256 x 177). Images were obtained at weeks 0 and 46 and years 2, 3, 4 and 5 and were evaluated according to the SPARCC SSS for fat, erosion, backfill and ankylosis. Radiographs of the SIJs were acquired at baseline, week 46, year 3 and 5, and evaluated according to the mNYc. Images were anonymized and read by an experienced reader (UW) in known time order.
SPARCC SIJ Structural Score

The SPARCC SSS was applied according to the method as described by Maksymowych et al.(9). In brief, the evaluation included five consecutive semi-coronal slices through the cartilaginous portion of the SIJ on T1-weighted sequences. Lesions were scored dichotomously (present/absent) in SIJ quadrants (fat metaplasia, erosion) or halves (backfill, ankylosis). Erosion was scored 0-1 per joint quadrant (i.e. max score 4 per SIJ per slice, total score range 0-40), fat metaplasia 0-1 per joint quadrant (i.e. max score 4 per SIJ per slice, total score range 0-40), backfill 0-1 per joint half (i.e. max score 2 per SIJ per slice, total score range 0-20) and ankylosis 0-1 per joint half (i.e. max 2 per SIJ per slice, total score range 0-20)(9). SPARCC SIJ Inflammation was scored 0-1 per joint quadrant (i.e. max score 4 per slice) on 6 consecutive semi-coronal slices on STIR sequences. Additional 1 point was given per joint per slice if signal intensity was homogenous across the inflammatory lesion and if >1 cm deep. Furthermore, 1 point was given per joint per slice if signal intensity was as bright as the cerebrospinal fluid at the same horizontal level (i.e. max score 12 per SIJ, total score range 0-72)(22).

Patients were subdivided into two groups: patients with almost complete bilateral ankylosis (baseline SPARCC SSS for ankylosis >18) and patients with no-to-moderate ankylosis (baseline SPARCC SSS for ankylosis <7). This was based on the assumption that patients with almost complete ankylosis at baseline would not progress further or progress minimally during the 5 years of follow-up.

Calculation of axSpA MRI SIJ Composite Structural Damage Scores

Based on the SPARCC scores for erosion, backfill and ankylosis in the BIOSPA study, 3 different versions of a preliminary axSpA MRI SIJ Composite Structural Damage Score (CSDS) were
calculated. Each of the 3 CSDSs had different weightings of erosion, backfill and ankylosis as described below:

Equal weighting: \( \text{CSDS}_{\text{equal}} \): \((\text{erosion score} \times 0.5) + \text{backfill score} + \text{ankylosis score}\), total score range: 0-60.

Advanced stages weighing more: \( \text{CSDS}_{\text{stepwise}} \): \((\text{erosion score} \times 1) + (\text{backfill score} \times 4) + (\text{ankylosis score} \times 6)\), total score range: 0-240.

Advanced stages overruling earlier stages (“hierarchical”): \( \text{CSDS}_{\text{hierarchical}} \): \((\text{erosion score} \times 1) < (\text{backfill score} \times 4) < (\text{ankylosis score} \times 6)\), total score range: 0-120.

The “<” indicates a hierarchical order, meaning that erosion was not included in the calculation if backfill was present in the same joint half and erosion and backfill were not included in the calculation if ankylosis was present in the joint half. Rationales for selecting these algorithms are elaborated below.

**Rationale for selection of the CSDS algorithms**

When combining erosion, backfill and ankylosis into a composite score, the composite score may benefit from adjusting the weighting so the earliest changes (represented by erosion) will not be overweighted. Simple addition of scores for erosion, backfill and ankylosis would not fulfil this, since a maximum score for erosion per joint half is 2 and the maximum score for backfill and ankylosis per joint half is 1. To adjust for this, the erosion score could be multiplied by 1/2 (as done in \( \text{CSDS}_{\text{equal}} \)). However, if erosion evolves to backfill or if backfill evolves to ankylosis this approach would not result in an increased composite score. Since backfill is considered a more advanced lesion that often develops after erosion it could be argued that it should count more in a composite score. Moreover, ankylosis often develops after backfill and since ankylosis is considered the ultimate structural damage lesion, ankylosis may deserve a higher weighting than backfill and erosion. To ensure that
structural progression is expressed in the composite score backfill could be weighted twice as much per joint half as the maximum erosion score per joint half and ankylosis could be weighted three times as much per joint half as the maximum score for erosion per joint half which gives weightings of 1, 4 and 6 for erosion, backfill and ankylosis, respectively (CSDS\textsubscript{stepwise}). Thirdly, a further argument could be that more advanced lesions in the natural course (ankylosis > backfill > erosion) should “overrule” the earlier stages, i.e. a hierarchical order (CSDS\textsubscript{hierarchical}).

Statistics

The two groups were compared with the Chi-squared test and Fisher’s exact test for dichotomous variables and Mann Whitney U-test for continuous variables. The annual change in MRI was calculated as the change from baseline-week 46, week 46-year 2, year 2-3, year 3-4, year 4-5 and divided with the exact time interval (in years) between assessments. The change scores from baseline to week 46 were compared with the other time intervals (cf. as mentioned above) using Wilcoxon signed rank test. Erosion, backfill and ankylosis scores for missing MRI scans were replaced by linear interpolation; e.g. if an MRI from year 3 was missing, MRIs from years 2 and 4 were used for linear interpolation. To assess responsiveness of the measure standardized response mean (SRM) was calculated as mean change divided by SD of the change and interpreted as follows: no: <0.20; small: ≥0.20 and <0.50; moderate: ≥0.50 and <0.80; large ≥0.80(23). Sensitivity analyses were performed for the annual progression rate with missing data replaced by using ‘last observation carried forward’. Statistical analyses were conducted in SPSS version 25.0 (IBM Corp., Armonk, NY, USA); p<0.05 was considered statistically significant.

RESULTS
Study population

Forty-two of the 60 patients included in the BIOSPA study were included in the 5-year open-label extension of the study. All the 42 patients fulfilled the ASAS criteria for axSpA. Thirty-three of the 42 patients were followed from initiation of TNF inhibitor (baseline) to year 5. Data from these 33 patients (infliximab, n=21; etanercept, n=8; adalimumab, n=4) were used for the analyses in this study (Supplementary figure 1, DATA SUPPLEMENTS). Ten patients had almost complete bilateral ankylosis (baseline SPARCC SSS for ankylosis >18) and 23 patients had no-to-moderate ankylosis (baseline SPARCC SSS for ankylosis <7). Nineteen out of 198 MRI scans (9.6 %) for these 33 patients were missing. The proportions of missing MRIs in the group with no-to-moderate ankylosis (7 out of 60, i.e. 9%) and in the group with almost-complete-ankylosis (12 out of 138, i.e. 12%) were comparable.

Baseline characteristics

Twenty-nine of the 33 patients (88%) fulfilled the mNYc for AS. Patients with no-to-moderate ankylosis were statistically significantly younger, had shorter symptom duration, lower BASMI, higher SPARCC SIJ Inflammation, lower SPARCC SSS for fat and ankylosis and higher SPARCC SSS for erosion and backfill as compared with patients with almost complete bilateral ankylosis (Table 1).

Changes in SPARCC SSS and axSpA MRI SIJ CSDSs over time

Table 2 provides the mean (SD) SPARCC SSS scores for erosion, backfill and ankylosis and the scores of CSDS_{equal}, CSDS_{stepwise} and CSDS_{hierarchical} over the five years. SPARCC scores for erosion
decreased statistically significantly from week 46 and onwards, and SPARCC scores for backfill decreased numerically during the five years after initiation of TNF inhibitor in the group of 33 patients (“all patients”) as well as in the group with no-to-moderate ankylosis, whereas SPARCC scores for ankylosis increased significantly from week 46 and onwards. In the group with almost complete ankylosis SPARCC scores for erosion and backfill were 0 and ankylosis score did not change during the 5 years. Both CSDS_{stepwise} and CSDS_{hierarchical} increased statistically significantly from week 46 and onwards for all patients and for patients with no-to-moderate ankylosis, whereas CSDS_{equal} did not change.

Figure 1 shows the individual scores for each patient for SPARCC SSS for erosion (1A), backfill (1B) and ankylosis (1C) and for the CSDS_{equal} (1D), CSDS_{stepwise} (1E) and CSDS_{hierarchical} (1F) at baseline and at year 2-5 in each of the 23 patients with no-to-moderate ankylosis at baseline. Although large individual variation was seen, overall most erosion and backfill scores either decreased or remained unchanged, whereas the ankylosis scores either increased or remained unchanged over the 5 years.

Figure 2 illustrates the structural SIJ damage progression on MRI in a patient with no-to-moderate ankylosis at baseline.

Figure 3 shows the development over time for SPARCC SSS erosion, backfill, and ankylosis and CSDS_{equal}, CSDS_{stepwise} and CSDS_{hierarchical}.

**Correlation between axSpA MRI SIJ CSDSs and clinical and MRI findings**

At baseline, CSDS_{equal}, CSDS_{stepwise} and CSDS_{hierarchical} correlated positively with SPARCC scores for fat and ankylosis as well as with the mNYc grading of SIJ radiography, and negatively with BASDAI.
and SPARCC SIJ inflammation (Table 3). CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical} also correlated positively with symptom duration and BASMI.

In the group with no-to-moderate ankylosis CSDS\textsubscript{equal}, CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical} correlated positively with SPARCC scores for fat, erosion and backfill and negatively with BASDAI at baseline. Furthermore, CSDS\textsubscript{hierarchical} correlated positively with SPARCC ankylosis in this group. In the group of patients with almost complete bilateral ankylosis CSDS\textsubscript{equal}, CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical} correlated negatively with SPARCC SIJ inflammation and positively with SPARCC ankylosis.

Changes year 0-5 in CSDS\textsubscript{equal}, CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical} in all 33 patients and in the group with no-to-moderate ankylosis correlated positively with change in SPARCC scores for fat. Change in CSDS\textsubscript{equal} also correlated positively with change in erosion and backfill, whereas CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical} correlated positively with ankylosis and negatively with SPARCC SIJ inflammation.

**Annual changes in axSpA MRI SIJ CSDSs**

In the group of all 33 patients and in the group with no-to-moderate ankylosis the adjusted annual progression rate for CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical} was statistically significantly more pronounced over the first year (baseline-week 46) compared to the annual progression for the fourth year (year 3-4). The SRMs were highest for change at baseline-week 46 for the group of patients with no-to-moderate ankylosis where CSDS\textsubscript{hierarchical} (0.64) was slightly higher than for CSDS\textsubscript{stepwise} (0.59), i.e. both had moderate responsiveness. SRM of CSDS\textsubscript{equal} (0.25) was lower than CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical}, i.e. only had small responsiveness (Supplementary table 1, DATA SUPPLEMENTS). Results were comparable with missing data replaced by using ‘last observation carried forward’ (Supplementary table 2, DATA SUPPLEMENTS).
DISCUSSION

This study introduces three novel preliminary composite scores of MRI SIJ structural damage (CSDS) which are based on the primary scores of the individual lesions from SPARCC SSS assessment of erosion, backfill and ankylosis. A composite score of erosion, backfill and ankylosis has to our knowledge not previously been reported. The three preliminary algorithms had various profiles to capture structural progression in the SIJ. CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical}, in which backfill and ankylosis weighed more than erosion, showed a more pronounced progression in structural damage scores, a correlation with BASMI, a closer correlation with progression in ankylosis and radiographic SIJ damage, and finally a higher sensitivity to change than CSDS\textsubscript{equal}.

The rationale for the selection of the three CSDS algorithms are described in the Methods section. CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical} showed stronger correlation with ankylosis at baseline and over time, compared to CSDS\textsubscript{equal}. Further, The CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical} performed similarly regarding annual progression rate and regarding correlation with SPARCC scores for ankylosis in contrast to CSDS\textsubscript{equal}. SRM was, albeit mostly small, moderate for CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical} over the first 46 weeks (up to 0.64), which was higher than for CSDS\textsubscript{equal}. Thus, CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical} seemed best suited as sensitive outcome measures for structural progression.

The responsiveness of CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical} was also higher than previously reported for other MRI lesion scores in studies of axSpA/AS patients treated with TNF inhibitor in 46/48 weeks (SRMs from 0.19-0.48 (24)), and over 2 years for the modified Stoke AS Spine Score (mSASSS)(25, 26) in studies of AS patients (median 0.35 (range: 0.22-0.57)(27-34)). This suggest, that CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical} captures structural progression over relatively short time frames, in contrast to the traditional measures of structural progression in axSpA.
Methodological studies of SIJ radiography have all reported small changes in mNY score over 1, 2 and 4 years and proposed that change should only be reported in studies of at least 2 year’s duration and only as the percentage of patients with a change score >0(6, 35, 36). A lower sensitivity to change/responsiveness of SIJ radiography can partly be explained by three dimensional anatomy being projected into two dimensions on radiographs(37). In contrast, the MRI of the SIJs provides detailed tomographic images of the three-dimensional anatomy making it possible to perform a slice-based, i.e. granular, lesion-based evaluation which is not possible on radiography.

To our knowledge this is the first study to combine structural MRI scores into an overall combined structural score to describe the overall evolution of SIJ structural damage. To date, studies have only focused on single lesion scores. In the EMBARK trial erosion scores decreased statistically significantly and backfill scores increased statistically significantly after 12 weeks’ treatment with a TNF inhibitor compared with placebo, and the study reported that it may reflect an early healing process(10). However, it could in principle also be considered a progression in structural damage observed over a short time period. Other studies reported that erosion scores decreased significantly over 12 weeks in patients treated with adalimumab compared to placebo(11). Development of new erosion was more often seen in patients treated with NSAIDs compared with TNF inhibitor and a statistically significantly higher proportion of patients treated with TNF inhibitor developed new fat metaplasia(15), associated with resolution of inflammation. Erosion is the first structural lesion that occurs following inflammation whereas backfill and ankylosis occur at later stages. Combining the structural lesions (i.e. erosion, backfill and ankylosis) into one outcome measure would allow comprehensive ascertainment of structural lesion progression in one single measurement, which may be useful in clinical trials. Bone erosion, backfill and ankylosis represent different aspects in the disease development in axSpA, and the introduced combined CSDS-assessment should be considered an addition to the current outcome measures, i.e changes in the individual components of structural
damage should of course still be analysed. Future studies are needed to elucidate whether the individual components or a CSDS better reflect the outcomes that are most relevant to the patient and which are most useful in clinical trials for comparison of the amount of structural progression during different treatments.

Limitations of our study include the relatively low number of patients evaluated. Furthermore, 10 patients had almost complete ankylosis at baseline which meant that almost all change observed over time derived from the 23 patients with no-to-moderate ankylosis at baseline. Most of the 23 patients had some ankylosis at baseline. In a patient group with less baseline ankylosis more changes may have been observed over time. Moreover, all patients were treated with TNF inhibitors. Investigation of other populations, eg. with less SIJ damage or receiving other treatments, are important for further validation and to clarify the most useful algorithm.

Furthermore, the weighting of scores was not evidence-based, but the study should also be considered as exploratory, and the CSDSs need further validation. CT could have been interesting as a reference standard, but this was not done due to the radiation exposure involved. Regarding MRI, it would have been optimal to have 2 readers allowing assessment of interreader agreement.

Regarding statistical analyses, we did not correct for multiple comparisons. This was not done since the study was an exploratory, hypothesis-generating study.

In conclusion, we have developed three preliminary Composite Structural Damage Scores (CSDSs) for MRI assessment of the sacroiliac joints in patients with axial spondyloarthritis that allow aggregate assessment of MRI progression from erosion through backfill to ankylosis. CSDS_{stepwise} and CSDS_{hierarchical}, in which backfill and ankylosis weighed more than erosion, showed a more pronounced progression in structural damage scores and a clear correlation with changes in the individual structural lesions, and a higher sensitivity to change than CSDS_{equal}. The proposed novel approaches may be useful for monitoring and comparing structural progression in axSpA patients.
receiving different therapies but need further validation in observational cohorts and randomized controlled trials.

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REFERENCES


**Figure Legends**

**Figure 1.** A, B and C show the development in SPARCC SIJ structural scores for erosion, backfill and ankylosis over 5 years after initiation of TNF inhibitor for patients with no-to-moderate ankylosis and each line represents one of the 23 patients illustrating the diversity of the course of the structural damage progression. Erosion and backfill overall had a decreasing tendency whereas ankylosis tended to increase. D, E and F show the change in the axSpA MRI SIJ Composite Structural Damage Scores ($CSDS_{equal}$, $CSDS_{stepwise}$, $CSDS_{hierarchical}$) over the 5 years. $CSDS_{equal}$ generally seemed to increase less than $CSDS_{hierarchical}$ and $CSDS_{stepwise}$.

AxSpA, axial spondyloarthritis; CSDS, Composite Structural Damage Score; MRI, magnetic resonance imaging; SIJ, sacroiliac joint; SPARCC, Spondyloarthritis Research Consortium of...
Canada; TNF inhibitor, tumor necrosis factor inhibitor; MRI, magnetic resonance imaging; w, week; yr, year.

**Figure 2.** T1-weighted MRIs illustrating structural damage progression (i.e. change in erosion, backfill and ankylosis) at baseline, week 46, year 2, 3 and 5 in a patient initiating TNF inhibitor therapy. The images are from the same patient from the mid section (upper panel) and the posterior section (lower panel) of the cartilaginous part of the joint, respectively, and shown with the best possible slice match.

**Right upper sacroiliac joint:** At baseline extensive erosion is seen in the mid and posterior section of the SIJ (short thin arrows) and at week 46 backfill is seen in these areas (long thin arrows). From year 2, ankylosis appears and it progresses to year 5 (thick arrows).

**Right lower sacroiliac joint:** At baseline erosion is particularly seen in midsection (short thin arrow) and backfill in the posterior section (long thin arrow). At week 46 ankylosis is seen in the posterior section and at year 2 in mid sections (thick arrows), and the ankylosis progresses to year 5.

**Left upper sacroiliac joint:** At baseline erosion is seen in mid and posterior section (short thin arrows) and at week 46 backfill is seen in midsection (long thin arrow). From year 2 ankylosis is seen in both the mid and posterior sections (thick arrows).

**Left lower sacroiliac joint:** At baseline a few small erosions are seen (short thin arrows). At week 46 one ankylosing bone bridges are seen and at year 3 two ankylosing bone bridges is seen in in posterior section (thick arrows).

MRI, magnetic resonance imaging; TNF inhibitor, tumor necrosis factor inhibitor.
Figure 3. The development over time for SPARCC SSS erosion, backfill, and ankylosis and CSDS_{equal}, CSDS_{stepwise} and CSDS_{hierarchical}.

SPARCC SSS, Spondyloarthritis Research Consortium of Canada Sacroiliac joint Structural Score structural scores; CSDS, Composite Structural Damage Score; w, week; yr, year.

Supplementary figure 1. Patient flow diagram during the study.
Table 1. Baseline characteristics for clinical/MRI variables and The Composite axSpA MRI Structural Damage Scores (CSDS<sub>equal</sub>, CSDS<sub>stepwise</sub>, CSDS<sub>hierarchical</sub>) for all patients, patients with no-to-moderate ankylosis and patients with almost complete ankylosis

<table>
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<th>Almost complete ankylosis, n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male (%)</td>
<td>26 (78.8)</td>
<td>17 (73.0)</td>
<td>9 (90.0)</td>
</tr>
<tr>
<td>Age, years</td>
<td>40 (21.62)</td>
<td>35 (21.62)</td>
<td>46 (30.62)*</td>
</tr>
<tr>
<td>Symptom duration, years</td>
<td>12.0 (1;45)</td>
<td>5.5 (1;33)</td>
<td>20.0 (12;45)*</td>
</tr>
<tr>
<td>HLA-B27 positivity, n (%)</td>
<td>26 (78.8)</td>
<td>17 (73.9)</td>
<td>9 (90.0)</td>
</tr>
<tr>
<td>ASDAS</td>
<td>3.9 (2.0;6.0)</td>
<td>3.9 (2.1;6)</td>
<td>3.5 (2.0;4.8)</td>
</tr>
<tr>
<td>BASDAI (0-10)</td>
<td>5.1 (3.0;9.9)</td>
<td>5.4 (3.2;9.8)</td>
<td>4.8 (3.8;1)</td>
</tr>
<tr>
<td>BASFI (0-10)</td>
<td>4.6 (1.0;9.9)</td>
<td>4.5 (1.0;8.3)</td>
<td>5.0 (1.5;9.9)</td>
</tr>
<tr>
<td>BASMI (0-10)</td>
<td>3.0 (0.0;6.0)</td>
<td>3.0 (0.0;6.0)</td>
<td>4.0 (3.0;6.0)*</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>18.0 (1.6;149.0)</td>
<td>18.0 (1.6;149.0)</td>
<td>18.5 (1.7;107.0)</td>
</tr>
<tr>
<td>SPARCC SIJ Inflammation (0-72)</td>
<td>0 (0.37)</td>
<td>4 (0.37)</td>
<td>0 (0.4)**</td>
</tr>
<tr>
<td>SPARCC SSS Fat (0-40)</td>
<td>24 (0;40)</td>
<td>12 (0;40)</td>
<td>39 (0;40)*</td>
</tr>
<tr>
<td>SPARCC SSS Erosion (0-40)</td>
<td>1 (0.22)</td>
<td>6 (0.22)</td>
<td>0 (0.0)**</td>
</tr>
<tr>
<td>SPARCC SSS Backfill (0-20)</td>
<td>0 (0.19)</td>
<td>2 (0.19)</td>
<td>0 (0.0)**</td>
</tr>
<tr>
<td>SPARCC SSS Ankylosis (0-20)</td>
<td>0 (0;20)</td>
<td>0 (0;7)</td>
<td>20 (18;20)**</td>
</tr>
<tr>
<td>mSASSS (0-72)</td>
<td>8 (0.46)</td>
<td>4 (0.29)</td>
<td>17 (0;46)</td>
</tr>
<tr>
<td>Total SIJ score (mNY grade 0-8)</td>
<td>7.5 (0.8)</td>
<td>6.0 (0.8)</td>
<td>8.0 (8;8)**</td>
</tr>
<tr>
<td>SIJ score met mNY criteria, n (%)</td>
<td>29 (88)</td>
<td>19 (83)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>CSDS&lt;sub&gt;equal&lt;/sub&gt; (0-60)</td>
<td>11.5 (0.0;23.5)</td>
<td>8.0 (0.0;23.5)</td>
<td>20.0 (18.0;20.0)**</td>
</tr>
<tr>
<td>CSDS&lt;sub&gt;stepwise&lt;/sub&gt; (0-240)</td>
<td>47.0 (0.0;120.0)</td>
<td>24.0 (0.0;69.0)</td>
<td>120.0 (108.0;120.0)**</td>
</tr>
<tr>
<td>CSDS&lt;sub&gt;hierarchical&lt;/sub&gt; (0-120)</td>
<td>41.0 (0.0;120.0)</td>
<td>24.0 (0.0;76.0)</td>
<td>120.0 (108.0;120.0)**</td>
</tr>
</tbody>
</table>

Data are shown as n (%) or median (min;max). *p<0.05, **p<0.01, ***p<0.001, all 2-tailed. Tests are Chi-square test, Fisher’s exact test, Mann-Whitney U-test. No-to-moderate ankylosis defined as a baseline SPARCC SSS for ankylosis <7 and almost complete ankylosis defined as a baseline SPARCC SSS for ankylosis >18.

ASDAS; Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; CSDS, Composite Structural Damage Score; MRI, magnetic resonance imaging; mNY criteria, modified New York criteria; mSASSS; modified Stoke Ankylosing Spondylitis Spine Score; SPARCC SIJ inflammation, Spondyloarthritis Research Consortium of Canada Sacroiliac joint inflammation; SPARCC SSS, Spondyloarthritis Research Consortium of Canada Sacroiliac joint Structural Score.
Table 2. SPARCC Sacroiliac Structural Scores (SSS) for erosion, backfill and ankylosis and Composite Structural Damage Scores (CSDS\textsubscript{equal}, CSDS\textsubscript{stepwise}, CSDS\textsubscript{hierarchical}) in all patients and patients with no-to-moderate ankylosis over time

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 46</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
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<tbody>
<tr>
<td><strong>Erosion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>4.7 (6.0)</td>
<td>3.8 (5.4)*</td>
<td>3.6 (5.2)**</td>
<td>3.1 (4.7)**</td>
<td>3.1 (5.2)*</td>
<td>3.0 (5.4)*</td>
</tr>
<tr>
<td>No-to-moderate ankylosis</td>
<td>6.7 (6.1)</td>
<td>5.5 (5.7)*</td>
<td>5.2 (5.5)**</td>
<td>4.3 (5.1)**</td>
<td>4.5 (5.8)*</td>
<td>4.3 (6.0)*</td>
</tr>
<tr>
<td><strong>Backfill</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>3.1 (5.2)</td>
<td>3.1 (5.2)</td>
<td>3.1 (4.9)</td>
<td>2.6 (4.4)</td>
<td>2.1 (3.7)*</td>
<td>2.1 (3.6)</td>
</tr>
<tr>
<td>No-to-moderate ankylosis</td>
<td>4.5 (5.8)</td>
<td>4.5 (5.8)</td>
<td>4.4 (5.4)</td>
<td>3.7 (4.9)</td>
<td>3.0 (4.1)*</td>
<td>3.0 (4.0)</td>
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<tr>
<td><strong>Ankylosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>6.8 (8.9)</td>
<td>7.4 (8.7)**</td>
<td>7.6 (8.7)**</td>
<td>8.2 (8.6)**</td>
<td>8.5 (8.6)**</td>
<td>8.8 (8.5)**</td>
</tr>
<tr>
<td>No-to-moderate ankylosis</td>
<td>1.1 (2.0)</td>
<td>2.0 (3.1)*</td>
<td>2.3 (3.7)**</td>
<td>3.1 (4.5)**</td>
<td>3.6 (4.9)**</td>
<td>4.0 (5.1)**</td>
</tr>
<tr>
<td><strong>CSDS\textsubscript{equal}</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>12.2 (8.1)</td>
<td>12.4 (8.0)</td>
<td>12.5 (7.9)</td>
<td>12.3 (7.7)</td>
<td>12.2 (7.5)</td>
<td>12.4 (7.6)</td>
</tr>
<tr>
<td>No-to-moderate ankylosis</td>
<td>8.9 (7.6)</td>
<td>9.2 (7.5)</td>
<td>9.3 (7.5)</td>
<td>9.0 (7.0)</td>
<td>8.9 (6.6)</td>
<td>9.2 (7.0)</td>
</tr>
<tr>
<td><strong>CSDS\textsubscript{stepwise}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>57.7 (47.0)</td>
<td>60.6 (46.7)**</td>
<td>61.6 (46.7)**</td>
<td>62.4 (46.7)*</td>
<td>63.2 (45.6)*</td>
<td>64.1 (45.1)*</td>
</tr>
<tr>
<td>No-to-moderate ankylosis</td>
<td>31.2 (27.7)</td>
<td>35.3 (30.9)**</td>
<td>36.7 (32.0)**</td>
<td>37.8 (33.0)*</td>
<td>39.0 (31.7)*</td>
<td>40.3 (33.6)*</td>
</tr>
<tr>
<td><strong>CSDS\textsubscript{hierarchical}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>55.4 (47.1)</td>
<td>57.7 (46.4)**</td>
<td>58.5 (46.4)**</td>
<td>59.7 (46.3)*</td>
<td>60.6 (46.1)*</td>
<td>61.7 (46.2)*</td>
</tr>
<tr>
<td>No-to-moderate ankylosis</td>
<td>27.9 (24.4)</td>
<td>31.1 (26.4)**</td>
<td>32.3 (27.6)**</td>
<td>34.0 (29.7)*</td>
<td>35.3 (29.7)*</td>
<td>36.8 (31.1)*</td>
</tr>
</tbody>
</table>

Data are shown as mean (SD). *p<0.05, **p<0.01, all 2-tailed. Wilcoxon signed-rank test was applied to compare scores at baseline with scores at other timepoints. No-to-moderate ankylosis was defined as a baseline SPARCC SSS for ankylosis <7.

CSDS, Composite Structural Damage Score; SPARCC, Spondyloarthritis Research Consortium of Canada.
Figure 1. A, B and C show the development in SPARCC SIJ structural scores for erosion, backfill and ankylosis over 5 years after initiation of TNF inhibitor for patients with no-to-moderate ankylosis and each line represents one of the 23 patients illustrating the diversity of the course of the structural damage progression. Erosion and backfill overall had a decreasing tendency whereas ankylosis tended to increase. D, E and F show the change in the axSpA MRI SIJ Composite Structural Damage Scores (CSDSequal, CSDSstepwise, CSDS_hierarchical) over the 5 years. CSDSequal generally seemed to increase less than CSDS_hierarchical and CSDS_stepwise.

AxSpA, axial spondyloarthritis; CSDS, Composite Structural Damage Score; MRI, magnetic resonance imaging; SIJ, sacroiliac joint; SPARCC, Spondyloarthritids Research Consortium of Canada; TNF inhibitor, tumor necrosis factor inhibitor; MRI, magnetic resonance imaging; w, week; yr, year.

177x133mm (1000 x 1000 DPI)
Figure 2. T1-weighted MRIs illustrating structural damage progression (i.e. change in erosion, backfill and ankylosis) at baseline, week 46, year 2, 3 and 5 in a patient initiating TNF inhibitor therapy. The images are from the same patient from the mid section (upper panel) and the posterior section (lower panel) of the cartilaginous part of the joint, respectively, and shown with the best possible slice match. Right upper sacroiliac joint: At baseline extensive erosion is seen in the mid and posterior section of the SIJ (short thin arrows) and at week 46 backfill is seen in these areas (long thin arrows). From year 2, ankylosis appears and it progresses to year 5 (thick arrows). Right lower sacroiliac joint: At baseline erosion is particularly seen in midsection (short thin arrow) and backfill in the posterior section (long thin arrow). At week 46 ankylosis is seen in the posterior section and at year 2 in mid sections (thick arrows), and the ankylosis progresses to year 5. Left upper sacroiliac joint: At baseline erosion is seen in mid and posterior section (short thin arrows) and at week 46 backfill is seen in midsection (long thin arrow). From year 2 ankylosis is seen in both the mid and posterior sections (thick arrows). Left lower sacroiliac joint: At baseline a few small erosions are seen (short thin arrows). At week 46 one ankylosing bone bridges are seen and at year 3 two ankylosing bone bridges is seen in in posterior section (thick arrows). MRI, magnetic resonance imaging; TNF inhibitor, tumor necrosis factor inhibitor.
Figure 3. The development over time for SPARCC SSS erosion, backfill, and ankylosis and CSDS\textsubscript{equal}, CSDS\textsubscript{stepwise} and CSDS\textsubscript{hierarchical}. SPARCC SSS, Spondyloarthritis Research Consortium of Canada Sacroiliac joint Structural Score structural scores; CSDS, Composite Structural Damage Score; w, week; yr, year.

109x82mm (1000 x 1000 DPI)
Table 3. Correlation between clinical/MRI variables and The Composite axSpA MRI Structural Damage Scores (CSDS<sub>equal</sub>, CSDS<sub>stepwise</sub>, CSDS<sub>hierarchical</sub>) at baseline and change year 0-5 in all patients, patients with no-to-moderate ankylosis and patients with almost complete ankylosis at baseline

<table>
<thead>
<tr>
<th>Variables</th>
<th>CSDS&lt;sub&gt;equal&lt;/sub&gt;</th>
<th>CSDS&lt;sub&gt;stepwise&lt;/sub&gt;</th>
<th>CSDS&lt;sub&gt;hierarchical&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change 0-5 yrs</td>
<td>Baseline</td>
</tr>
<tr>
<td>Symptom duration (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom duration (years)</td>
<td>0.40</td>
<td>-0.01</td>
<td>-0.40</td>
</tr>
<tr>
<td>ASDAS</td>
<td>-0.29</td>
<td>-0.16</td>
<td>0.06</td>
</tr>
<tr>
<td>BASDAI (0-10)</td>
<td>-0.40*</td>
<td>-0.46*</td>
<td>-0.06</td>
</tr>
<tr>
<td>BASMI (0-10)</td>
<td>0.18</td>
<td>-0.03</td>
<td>-0.24</td>
</tr>
<tr>
<td>SPARCC SIJ inflammation (0-72)</td>
<td>-0.37*</td>
<td>-0.04</td>
<td>-1.00**</td>
</tr>
<tr>
<td>SPARCC SSS Fat (0-40)</td>
<td>0.56**</td>
<td>0.62**</td>
<td>-0.31</td>
</tr>
<tr>
<td>SPARCC SSS Erosion (0-40)</td>
<td>-0.02</td>
<td>0.74**</td>
<td>-0.57**</td>
</tr>
<tr>
<td>SPARCC SSS Backfill (0-20)</td>
<td>0.20</td>
<td>0.86**</td>
<td>-0.47**</td>
</tr>
<tr>
<td>SPARCC SSS Ankylosis (0-20)</td>
<td>0.61**</td>
<td>0.29</td>
<td>1.00**</td>
</tr>
<tr>
<td>mSASSS (0-72)</td>
<td>0.24</td>
<td>0.07</td>
<td>0.18</td>
</tr>
<tr>
<td>Total SIJ score (mNY grade 0-8)</td>
<td>0.61**</td>
<td>0.35</td>
<td>-0.09</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, all 2-tailed. Test is Spearman Rank Correlation analysis of baseline variables versus baseline CSDS and change in variables versus change in CSDS. No-to-moderate ankylosis defined as a baseline SPARCC SSS for ankylosis <7 and almost complete ankylosis defined as a baseline SPARCC SSS for ankylosis >18.

ASDAS; Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CSDS, Composite Structural Damage Score; MRI, magnetic resonance imaging; mNY criteria, modified New York criteria; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; SPARCC SIJ inflammation, Spondyloarthritis Research Consortium of Canada Sacroiliac joint inflammation; SPARCC SSS, Spondyloarthritis Research Consortium of Canada Sacroiliac joint Structural Score.