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Validation of assessment methods for the apparent diffusion coefficient in a clinical trial of axial spondyloarthritis patients treated with golimumab

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ABSTRACT

Purpose: To compare three region-of-interest (ROI) settings in the assessment of ADC in a clinical trial, and to evaluate the effectiveness of ADC in assessing therapy-induced changes and predicting clinical outcomes.

Methods: In a 52-week clinical trial involving patients with axial spondyloarthritis, mean sacroiliac joint (SIJ) ADC measurements using structured, lesion-based, and index-lesion ROI-settings were assessed at baseline and weeks 4, 16, and 52. Variation among the three ROI-settings, correlations with Spondyloarthritis Research Consortium of Canada (SPARCC)-bone marrow edema (BME) SIJ inflammation indices, standardized response means (SRMs), and effectiveness in predicting clinical outcomes were analyzed.

Results: Forty of the 53 patients had at least one assessable SIJ lesion on ADC at baseline. The mean of the structured ROI ADC (ADC_{struc}) was 230 μmm^2/s (standard deviation [SD] = 120). This was significantly lower ($p < 0.01$) than the means of the lesion-based ROI ADC (ADC_{lesion} = 420 μmm^2/s, SD = 210) and index-lesion ROI ADC (ADC_{index} = 471 μmm^2/s, SD = 278), which did not differ. ADC correlated with SPARCC-BME scores at baseline ($p < 0.01$) as did changes over time in ADC- and SPARCC-BME ($p \leq 0.05$). At all follow-up time points, responsiveness was high for ADC_{lesion} (SRM > 0.92) and ADC_{index} (SRM > 0.87) while moderate for ADC_{struc} (SRM:0.54-0.67). Baseline ADC and changes in ADC did not predict clinical outcomes.

Conclusions: Lesion-based and index-lesion ROI ADC could both be used to evaluate the effectiveness of tumor necrosis factor inhibitor therapy. None of the methods could predict clinical outcomes.

1. Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease with back pain and stiffness as main symptoms. The goal of treatment is low clinical disease activity and if possible inactive disease [1]. The key assessment method for assessment of clinical disease activity and of treatment response of axSpA is the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [2], which is a patient questionnaire comprising questions designed to assess fatigue, pain, and stiffness of the spine. Disease activity can also be measured using the novel composite Ankylosing Spondylitis Disease Activity Score (ASDAS) [3], which besides as measure of treatment response also includes a definition of inactive disease. In ASDAS, patient-reported pain, stiffness and global assessment of disease activity are combined with C-reactive protein (CRP) measurements [4].

In clinical trials, magnetic resonance imaging (MRI) of the sacroiliac joint (SIJ) is routinely used as a measure of disease activity, and most often the Spondyloarthritis Research Consortium of Canada (SPARCC)-bone marrow edema (BME) SIJ inflammation index is applied [5,6]. The SPARCC-BME is a reliable and responsive measure that in objectively assess changes in BME, which reflect responses to treatment [7]. However, other MRI sequences than T2 fat saturated sequences may be of

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value for assessment of inflammation in patients with axSpA such as diffusion weighted imaging (DWI).

In DWI, the diffusion of free fluids within intercellular spaces can be quantified by measuring apparent diffusion coefficients (ADC). Intercellular diffusion involves the random motion of fluid within intercellular spaces, which are restricted by macromolecules and cell membranes. The pattern of diffusion is directly related to the cellularity of the tissue [8] and, therefore, reflects levels of inflammation. It is anticipated that ADC measurements may provide more information on disease activity characteristics compared to conventional MRI scans.

A few longitudinal clinical studies have used ADC measurements to monitor the response to tumor necrosis factor (TNF) inhibitor treatment in patients with axSpA, and these measurements were correlated with conventional BME MRI results [9–11]. These studies, and in cross-sectional studies involving ADC measurements in patients with axSpA used a variety of different region-of-interest (ROI) settings, and no consensus regarding the best assessment methods has been established. Therefore, the present study was considered highly relevant.

The primary objective of this study was to compare three different ROI settings, which were used to measure ADCs and evaluate the response to TNF inhibitor treatment in patients with axSpA over 52 weeks. Furthermore, the aim was to correlate ADC obtained using these three ROI settings correlated with SPARCC-BME scores and, finally, to investigate whether baseline ADC or early changes in ADC during TNF inhibitor treatment predicted clinical responses, including inactive disease (ID), at the end of the study.

2. Materials and methods

This study was based on data from the MANGO (Novel MRI ANd biomarkers in GOlimumab-treated patients with axial spondyloarthritis) trial, which was an open-label 52-week longitudinal study involving 53 patients with axSpA. The study was approved by the local ethics committee for the capital region of Denmark, approval number: H1-2013-118, and all patients provided written consent. Trial registration: ClinicalTrials.gov, NCT02011386.

2.1. Subjects

The patients were recruited from four departments of rheumatology in Copenhagen. The inclusion criteria were: Age, 18–85 years old; the presence of spondyloarthritis according to the ASAS classification criteria for axSpA [12,13]; sacroiliitis on conventional X-rays or MRI as defined by ASAS [14]; a BASDAI score >40 mm despite treatment with non-steroidal anti-inflammatory drugs; and clinical indication for TNF inhibitor treatment by the treating physician with no contraindications for TNF inhibitor treatment or MRI.

The exclusion criteria were: Previous treatment with a TNF inhibitor; treatment with an oral, intra-articular, or intramuscular glucocorticoid within 4 weeks prior to inclusion whereas treatment with disease-modifying anti-rheumatic drugs was permitted during the study; however, the dose of these drugs could not be changed during the period beginning 4 weeks prior to the first MRI scan and ending in week 16.

2.2. Clinical assessment

BASDAI [2], Bath Ankylosing Spondylitis Functional Index (BASFI) [15], and ASDAS [3] assessments were recorded at all patient visits. In addition, visual analog scales were used for patient global assessments (VAS-G) [16] and to record pain (VAS-pain). Serum CRP measurements were also recorded.

2.3. MRI technique

All examinations were performed using a 3 T system (Ingenia; Philips, Best, the Netherlands) with a combination of posterior and anterior

phased-array coils. For this study, coronal oblique short tau inversion recovery (STIR), T1-weighted, and single-shot echo planar imaging DWI sequences were performed. The technical parameters are listed in Table 1.

2.4. Image analysis

MRI examinations from all four time points were anonymized using random numbers. ADC maps were created using dedicated software (Intellispace ver. 6.01; Philips, Best, the Netherlands), based on four *b*-values. Three ADC methods (structured, lesion-based, and index-based) were applied (Fig. 1).

The ***structured ROI setting*** assessments were performed on each of six consecutive slices through the cartilaginous part of the SIJ. The SIJ was divided into four quadrants, with upper and lower parts of equal height, by a horizontal line (i.e. 48 quadrants in total). A band-shaped anatomic ROI covered the length of the quadrant and extended perpendicularly from the joint surface to a subchondral depth of 5 mm. A total of 48 ADC measurements were recorded for each patient and the mean ADC was calculated to yield the structured ROI ADC ($ADC_{structured}$).

For the ***lesion-based and index-lesion ROI settings***, anonymization was modified so that assessments could be performed in known chronological order. The lesion-based ROI setting was defined on baseline STIR images in which BME lesions were encircled and copied to the same area of the corresponding ADC maps at all four time points. The index-lesion ROI setting was defined by identifying the largest BME lesion on the baseline STIR sequence or the lesion with the highest signal intensity, if two lesions were similar in size. The lesion-based ROI ADC (ADC_{lesion}) was the mean ADC of all slices in all lesions and the index-lesion ROI ADC (ADC_{index}) was the mean ADC of all slices in the index lesion.

Conventional MRI inflammation evaluations were performed, in accordance with the method described by the SPARCC-BME [17].

2.5. Statistical analysis

The mean value of all ADC measurements at each time point was calculated for all three ROI settings. The association between sex and ADC was tested using independent *t*-tests, and the association between ADC and age was tested using Pearson's r correlation coefficient. Differences among ADC measurements obtained using the three different ROI-settings were analyzed using one-way analysis of variance (ANOVA), with the Bonferroni correction, and Bland–Altman plots. The correlation between SPARCC-BME scores and ADC was assessed at each time point using Spearman's ρ correlation coefficient. Changes in mean ADC (i.e., Δ values) and SPARCC-BME scores at different time points were assessed using one-way repeated-measures ANOVA and the Greenhouse–Geisser correction. The Bonferroni correction was used for *post hoc* tests. In addition, the standardized response mean (SRM) between two time points was calculated as the mean change-score divided by the standard deviation of the corresponding change-scores. The SRMs were defined as small (0.2–0.5), moderate (0.5–0.8), or large (>0.8) [18]. The primary outcome at week 52 was a reduction in BASDAI score of at least 50% (ΔBASDAI–50%). The secondary outcomes were: a clinically important improvement (CII) in ASDAS, defined as ΔASDAS >1.1; ASDAS-ID, defined as an ASDAS of <1.3; a reduction in CRP of at least 50% (ΔCRP–50%); and a reduction in SPARCC-BME score of at least 50% (ΔSPARCC-BME–50%). Independent *t*-tests were used to compare primary and secondary outcomes in responders with non-responders. Univariate logistic regression analyses were used to investigate the association between outcomes (dependent variables) and baseline ADC and among changes in ADC scores (ΔADC; independent variables). A *p*-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (ver. 22.0; IBM, Armonk, NY, USA).

Table 1

MRI parameters.

MRI sequence	TR, ms	TE, ms	TI, ms	b-value s/μmm²	Slice thickness, mm	Inter-slice gap, mm	Matrix	FOV, mm	Scan time, seconds
STIR	3454–3738	70	210	–	4	0.4	251 × 200	300 × 181	172–187
T1W	444–577	8	–	–	4	0.4	252 × 246	200 × 200	260–349
DWI	555	71	–	0; 150; 500; 1000	4	0.5	160 × 160	400 × 350	202

MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; FOV, field of view; STIR, short tau inversion recovery; T1W, T1-weighted spin echo images; TE, echo time; TI, inversion time; TR, repetition time.
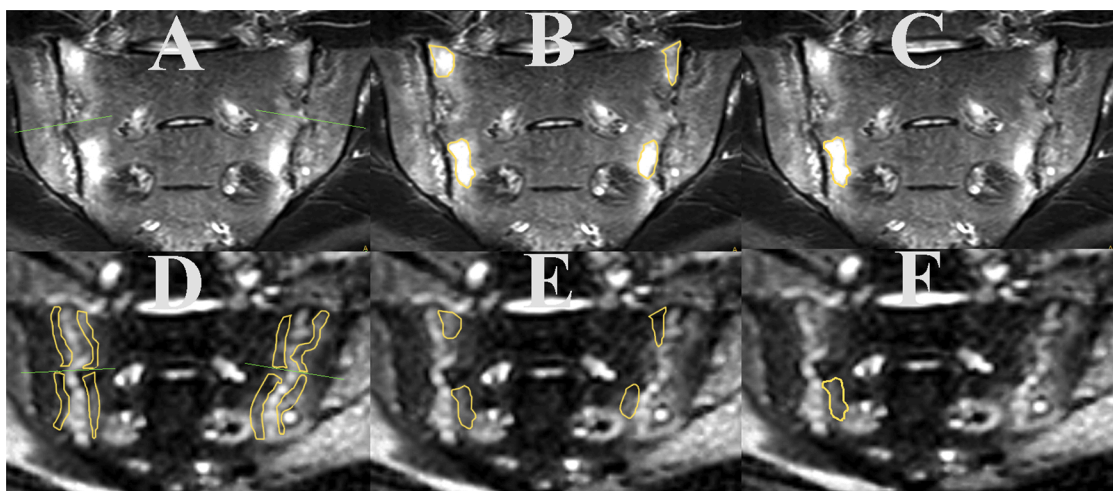
Fig. 1. The 3 region of interest (ROI) assessment methods: The structured ROI method (D) where the sacroiliac joints are divided into 8 quadrants by horizontal lines through the middle of the joints. In each quadrant on six consecutive slices of the apparent diffusion (ADC) map an anatomic band shaped ROI was drawn covering the length of the quadrant in a 5 mm depth form the articular cavity. The lesion-based ROI method (B, E), where all bone marrow edema (BME) lesions on short tau inversion time (STIR) (B) were encircled and copied to the respective ADC map (E). This was done in all slices where BME were present on STIR. And finally the index lesion ROI method, where the largest BME lesion on STIR (C) was encircled and copied to the ADC map (F). This was done in all slices where the lesion was present on STIR.

3. Results

A total of 53 patients were included in this study, and 40 (75%) of these patients had at least one assessable BME lesion on the ADC-map at baseline. Six of these 40 patients did not complete MRI scans at week 52 and three patients did not complete the clinical visit at week 52. No statistically significant differences were observed between ADC measurements from male and female patients for any of the three ROI settings at any time point. Baseline characteristics are shown in Table 2.

3.1. Differences among the ROI methods

Pairwise comparisons with the Bonferroni correction showed that ADC$_{structured}$ measurements were significantly lower than ADC$_{lesion}$ and ADC$_{index}$ measurements at baseline ($p < 0.01$), week 4 ($p < 0.01$), and week 16 ($p < 0.01$) but not at week 52 ($p = 0.41$). The Bland–Altman plots (Fig. 2) showed large differences at baseline in ADC$_{structured}$ − ADC$_{lesion}$ (–187 μmm²/s) and ADC$_{structured}$ − ADC$_{index}$ (–239 μmm²/s). These difference decreased at week 4 (–96 μmm²/s and –127 μmm²/s), decreased further at week 16 (–55 μmm²/s and –64 μmm²/s), and almost disappeared at week 52 (–8 μmm²/s and –24 μmm²/s). Moreover, ADC differences at baseline and week 4 increased proportionally with increasing mean ADCs. Differences in ADC$_{lesion}$ − ADC$_{index}$ were small at all time points. Similarly, differences in ADC$_{lesion}$ − ADC$_{index}$ were small compared to those between the other two parameter pairs at all time points.

### 3.2. Correlations with conventional MRI

At baseline, all three ADC assessments correlated with SPARCC-BME

Table 2

Baseline characteristics for the 40 patients included in the study.

Variable	Baseline
Age in years	36.7 (34.5, 28–43.5)
Females – no. (%)	19 (48%)
Body mass index	25.2 (24.5, 21.2–27.8)
Positive for HLA-B27 – no. (%)	28 (70%)
hsCRP, mg/L	11.4 (5.9, 1.0–18.3)
ASDAS	3.6 (3.7, 3.1–4.1)
BASDAI (range, 0–10)	6.2 (6.1, 5.1–7.3)
BASFI (range, 0–10)	4.8 (4.6, 3.2–6.2)
Pain score (range, 0–10)	6.7 (7.0, 5.4–8.2)
Patient's global assessment (range, 0–10)	7.4 (7.7, 6.5–8.7)
SPARCC MRI SIJ inflammation index (SPARCC-BME) (range, 0–72)	17.6 (16.0, 8.1–23.9)
SPARCC MRI SIJ structural score - Fat (range, 0–40)	5.3 (2.0, 0.3–8.9)
SPARCC MRI SIJ structural score - Erosion (range, 0–40)	8.0 (8.3, 3.2–12.3)
SPARCC MRI SIJ structural score - Backfill (range, 0–20)	1.8 (0.2, 0–2.7)
SPARCC MRI SIJ structural score - Ankylosis (range, 0–20)	0.35 (0, 0–0)

Values are means (median, inter-quartile range) unless otherwise stated. ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; HLA, human leucocyte antigen; hsCRP, high-sensitivity serum C-reactive protein; MRI, magnetic resonance imaging; SIJ, sacroiliac joint; SPARCC, Spondyloarthritis Research Consortium of Canada.

scores and the ΔADCs all correlated with the ΔSPARCC-BME scores (Table 3). The ADC$_{index}$ was correlated with age in female patients at baseline ($p = 0.04$) and week 52 ($p = 0.03$).
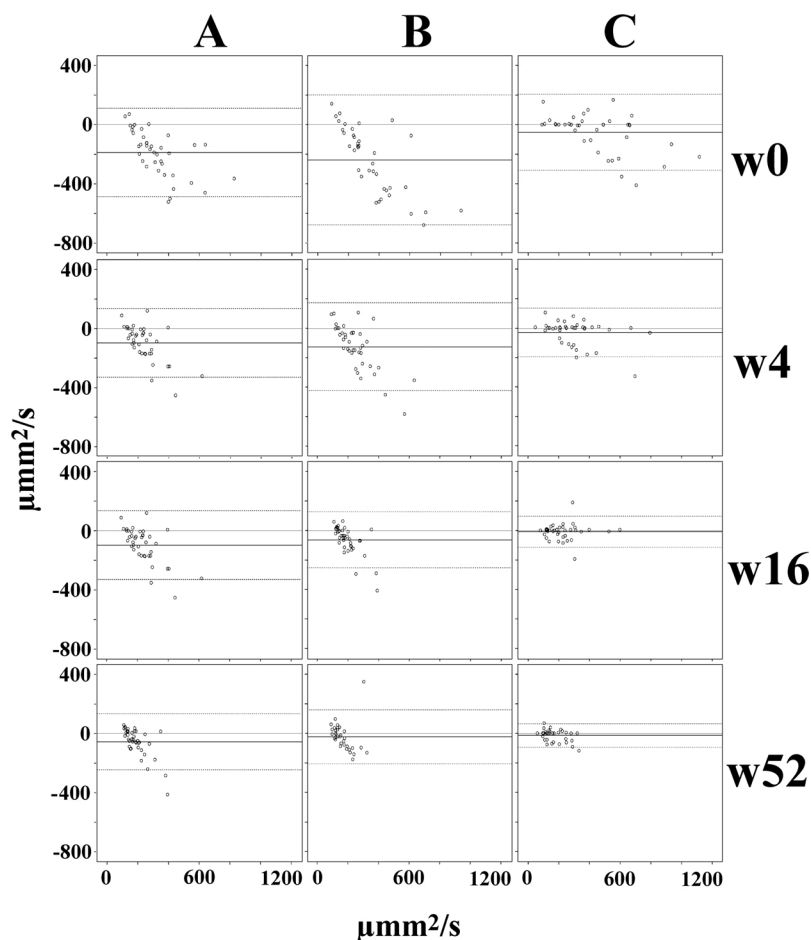
Fig. 2. Bland–Altman plots of mean apparent diffusion coefficients (ADC; x-axis) and differences (y-axis) between structured and lesion-based ADC (A), structured and index-lesion based ADC (B), and lesion-based and index-lesion ADC (C) at baseline, week 4, week 16, and week 52. Means of the differences (black line) and the level of agreement (dotted lines) are shown.

Table 3

Spearman's correlation ρ (and p-values) between apparent diffusion coefficients (ADC) and bone marrow edema scores (SPARCC-BME at baseline, as well as correlations among changes in these parameters at different time points.

	$ADC_{structured}$	ADC_{lesion}	ADC_{index}
SPARCC-BME			
Baseline, $n = 40$	**0.71 $p < 0.01$**	**0.48 $p < 0.01$**	**0.52 $p < 0.01$**
Week 0–4, $n = 40$	**0.55 $p < 0.01$**	**0.32 $p < 0.01$**	**0.37 $p = 0.03$**
Week 0–16, $n = 40$	**0.72 $p < 0.01$**	**0.43 $p < 0.01$**	**0.47 $p < 0.01$**
Week 0–52, $n = 34$	**0.62 $p < 0.01$**	**0.34 $p = 0.05$**	**0.39 $p = 0.03$**

$ADC_{structured}$, structured ROI ADC; ADC_{lesion}, lesion-based ROI ADC; ADC_{index}, index-based ROI ADC; SPARCC-BME, Spondyloarthritis Research Consortium of Canada-bone marrow edema.

3.3. Responsiveness

For all three ROI-settings, statistically significant decreases in ADCs were observed between baseline and week 4, as well as between week 16 and week 52. Similar decreases in SPARCC-BME scores were also observed (Fig. 3). At all three time points, the SRM for the SPARCC-BME score was large, as it was for ADC_{lesion} (0.92–1.47) and ADC_{index} (0.87–1.29). However, the SRM for $ADC_{structured}$ was moderate. The SRM was large for all clinical outcome measures but moderate for CRP measurements (Table 4).

3.4. Prediction of clinical, laboratory, and conventional MRI outcomes

Neither baseline ADCs nor early changes in ADCs (baseline to week 4 or baseline to week 16) were able to predict any clinical, laboratory, or conventional MRI outcomes at week 52 (Table 5).

3.5. Outcomes

At week 52, a total of 25 (68%) patients met the ΔBASDAI–50% primary clinical outcome. The secondary outcomes ASDAS-CII, ASDAS-ID, ΔCRP–50%, and ΔSPARCC-BME–50% were met by 28 (76%), 14 (38%), 23 (62%), and 29 (94%) patients, respectively. Patients who were ΔBASDAI–50% responders at week 52 showed no statistically significant differences with regard to any of the ADC measures at baseline or weeks 4, 16, or 52 compared to non-responders. Similar results were obtained for the other response definitions (i.e., ASDAS-CII, ΔCRP–50%, and ΔSPARCC-BME–50%) and for ID (i.e., ASDAS-ID; Table 6).

4. Discussion

In this study of patients with axSpA treated with golimumab, the ADC was a highly responsive biomarker when it was measured using lesion-based and index-based ROI settings. However, it was unable to predict clinical or imaging outcomes. ADC measurements correlated with SIJ inflammation as assessed by conventional MRI inflammation scores.
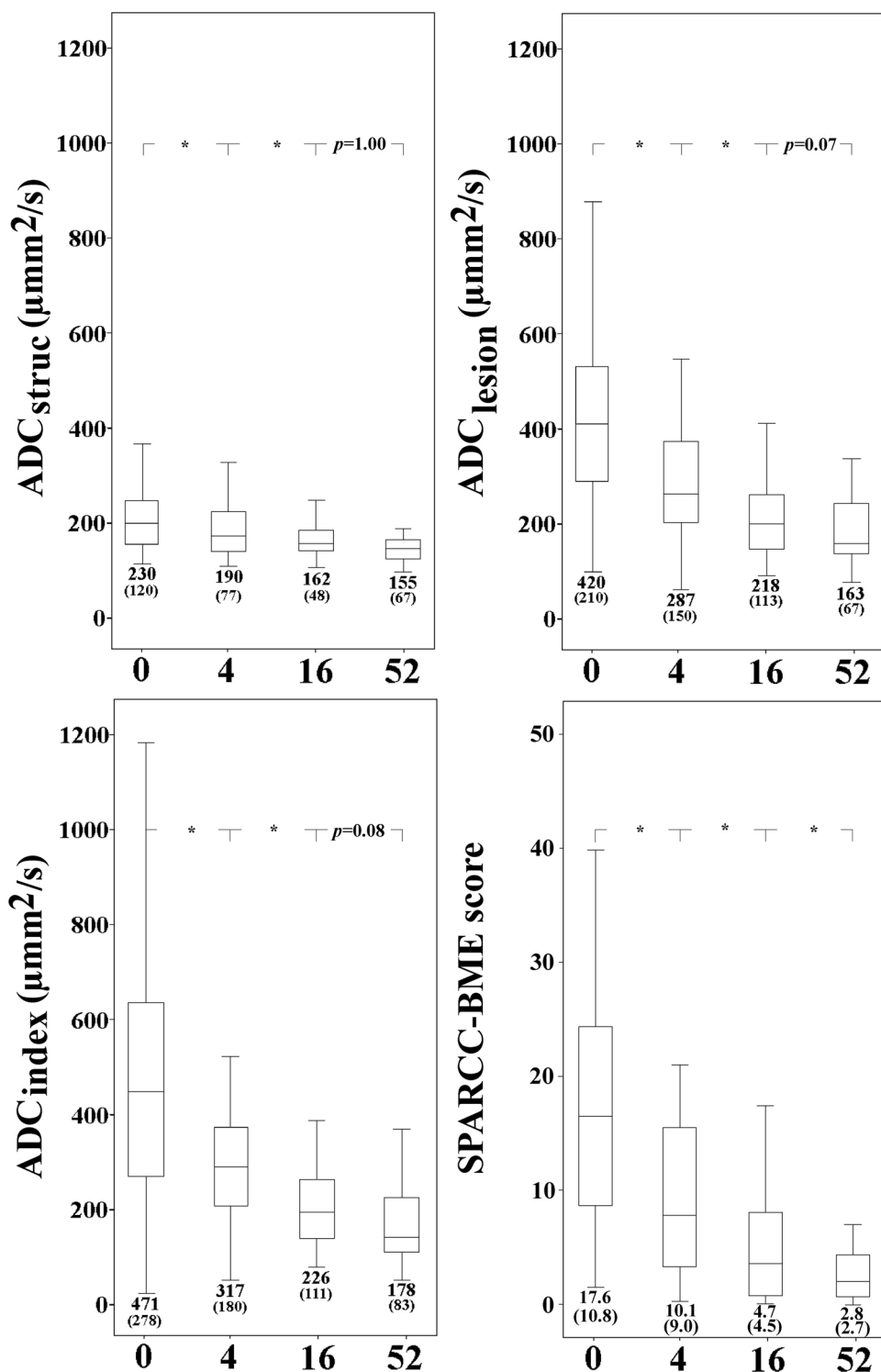
Fig. 3. Boxplots of mean apparent diffusion coefficient (ADC) at baseline, week 4, week 16, and week 52 for structured (upper left), lesion-based (upper right), and index-lesion (lower left) region-of-interest settings and the Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint inflammation index (lower right). Mean ADC (standard deviation [SD]) and SPARCC-bone marrow edema (BME) scores (SD) are shown. Bonferroni corrected p-values for pairwise tests between weeks 16 and 52 are shown. All other pairwise tests revealed $p < 0.05$.

A few prospective studies have used ADC measurements to investigate responses to TNF inhibitor treatment. These studies used index-based ROIs [19] or a combination of structured (if BME was absent) and lesion-based ROIs [9,10]. A structured ROI setting has also been used in one retrospective study [11]. In these studies, ADC was reportedly responsive to therapy. In our study, all three methods yielded responsive ADC measurements, although ADC$_{structured}$ measurements were less responsive than ADC$_{lesion}$ and ADC$_{index}$ measurements. Previous studies that assessed ADC measurements used paired t-tests to evaluate responses to treatment over time. Gaspersic et al. [19] found

that mean ADC decreased from 1310 μmm^2/s to 880 μmm^2/s in 10 patients ($p < 0.05$), Qin et al. [10] observed a decrease from 505 ± 110 μmm^2/s to 434 ± 55 μmm^2/s in 42 patients ($p < 0.01$), and Bradbury et al. [9] reported a decrease from 450 ± 433 μmm^2/s to 154 ± 230 μmm^2/s in 18 patients ($p < 0.01$). These decreases in ADC over time fall within the same range as our observations in this study, which furthermore were statistically significant.

Whereas paired t-tests can only confirm that differences are statistically significant, SRMs provide an estimate of the magnitude of change in ADC during treatment that is independent of sample size. For

Table 4
Standardized response means.

	Week 0–4, *n = 40*	Week 0–16, *n = 40*	Week 0–52, *n = 34*
ADC variables			
Lesion-based ROI	1.04	0.92	1.47
Index ROI	0.87	0.90	1.29
Structured ROI	0.54	0.68	0.67
Clinical variables			
ASDAS	1.49	1.57	1.51
BASDAI	1.39	1.40	1.62
SPARCC-BME	1.21	1.31	1.47
BASFI	0.98	1.24	1.24
CRP	0.70	0.51	0.49

ADC, apparent diffusion coefficient; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, serum C-reactive protein; ROI, region-of-interest; SPARCC-BME, Spondyloarthritis Research Consortium of Canada-bone marrow edema sacroiliac joint inflammation index.

example, Bradbury et al. [9] used a combination of structured and lesion-based ADC measurements after a 13-week treatment period and reported an ADC SRM of 0.88 and a SPARCC score of 0.91. These results are consistent with our study, which found SRMs of 0.68 and 0.92 at week 16 for $ADC_{structured}$ and ADC_{lesion}, respectively and reported a SPARCC-BME score of 1.31. The lower $ADC_{structured}$ SRM may be due to measurements from many apparently normal regions of bone marrow, resulting in $ADC_{structured}$ measurements that are less responsive than ADC_{lesion} and ADC_{index} measurements.

To ensure that ADC changes exceed measurement errors, the smallest detectable change (SDC) may be calculated. The SDC was reportedly 144 $\mu mm^2/s$ or 22% in a repeatability study of patients with axSpA [20]. The changes in all three ADC measurement methods recorded between baseline and week 52 in our study exceeded this SDC value, but changes in $ADC_{structured}$ measurements between baseline and week 4 did not. The SDC was not measured in our study because we did not have two observers.

Mean $ADC_{structured}$ measurements include large areas of normal uninflamed bone marrow and are, therefore, low compared to ADC_{lesion} and ADC_{index} measurements. For the same reason, the Bland–Altman plots showed that $ADC_{structured}$ measurements were much lower than

ADC_{lesion} and ADC_{index} measurements at baseline and week 4. At weeks 16 and 52 these differences had decreased, probably due to the effect of treatment on inflammation. When inflammation disappears, BME is absent and normal bone marrow ADC values are obtained for both lesion-based and index-based ROI settings, which are similar to $ADC_{structured}$ values. The large 95% limits of agreement between $ADC_{structured}$–ADC_{lesion} and $ADC_{structured}$–ADC_{index} at all time points and the corresponding proportional bias means that including $ADC_{structured}$ measurements in a mixed ROI setting is less practical. The small difference between ADC_{lesion} and ADC_{index} measurements suggests that ADC_{index} measurements may be representative of all lesions, potentially reducing the time necessary for assessments. The responsiveness and simplicity of the index-based ROI setting make it suitable for measuring outcomes in axSpA. However, further studies are needed to validate the use of the index-based ROI setting. Similar approaches have been used in studies on lymphomas in which target lesions were identified and assessed [21,22].

None of our three ADC ROI settings could differentiate between clinical responders and non-responders at week 52. One retrospective study of enthesitis-related arthritis in adolescents reported a significantly greater decrease in ADCs for clinical responders compared to non-responders [11]. However, different methodologies preclude direct comparisons. The difference between clinical and imaging results may be explained by imaging outcomes are objective measures of inflammation, whereas clinical outcomes are subjective measures of disease activity, which also may be influenced by other causes of back pain and other contextual factors.

In the ABILITY-3 study of non-radiographic axSpA, the SPARCC-MRI score (i.e., a combination of SPARCC-BME and SPARCC structural scores) was a predictor of clinical outcomes [23], whereas another study of SIJ BME scores from patients with ankylosing spondylitis only tended to predict clinical outcomes [24]. In our study, baseline ADCs and changes in ADC measurements were unable to predict clinical outcomes assessed with several different methods for assessment of clinical treatment response and inactive disease at week 52. To our knowledge, no other study has presented data on assessing the predictive value of ADC measurements. One reason for the failure to predict clinical outcomes may be that there were no significant differences between ADC measurements in clinical responders and non-responders.

Table 5
Outcome predictions based on baseline apparent diffusion coefficient (ADC) and changes of ADC from baseline. No statistically significant predictions were identified ($p > 0.05$).

	ΔBASDAI–50%	ASDAS-CII	ASDAS-ID	ΔCRP–50%	ΔSPARCC-BME–50%
$ADC_{structured}$					
Baseline	0.99	0.99	1.00	0.99	0.99
	(0.986–1.003)	(0.982–1.004)	(0.989–1.001)	(0.986–1.002)	(0.974–1.015)
Week 0–4	1.005	1.008	1.004	1.007	1.019
	(0.995–1.015)	(0.996–1.019)	(0.995–1.013)	(0.997–1.017)	(0.994–1.045)
Week 0–16	1.006	1.006	1.005	1.006	1.024
	(0.997–1.015)	(0.995–1.017)	(0.998–1.012)	(0.997–1.015)	(0.987–1.062)
ADC_{lesion}					
Baseline	1.00	1.00	1.00	1.00	1.00
	(0.996–1.003)	(0.966–1.003)	(0.994–1.001)	(0.996–1.003)	(0.990–1.006)
Week 0–4	1.00	1.001	1.0	1.001	1.016
	(0.994–1.005)	(0.994–1.007)	(0.995–1.006)	(0.995–1.007)	(0.99–1.042)
Week 0–16	1.001	1.001	1.001	1.0	1.004
	(0.998–1.005)	(0.997–1.005)	(0.997–1.005)	(0.996–1.003)	(0.997–1.011)
ADC_{index}					
Baseline	1.00	1.00	1.00	1.00	1.00
	(0.997–1.002)	(0.997–1.002)	(0.996–1.001)	(0.997–1.002)	(0.991–1.004)
Week 0–4	0.999	1.001	0.999	1.001	1.023
	(0.995–1.004)	(0.996–1.005)	(0.995–1.004)	(0.997–1.005)	(0.983–1.064)
Week 0–16	1.001	1.001	1.001	1.0	1.004
	(0.998–1.005)	(0.998–1.004)	(0.998–1.003)	(0.997–1.002)	(0.997–1.011)

Results are expressed as odds ratios (95% confidence intervals).
ADC, apparent diffusion coefficient; ROI, region-of-interest; $ADC_{structured}$, structured ROI ADC; ADC_{lesion}, lesion-based ROI ADC; ADC_{index}, index-based ROI ADC; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; CII, clinically important improvement; ID, inactive disease; CRP, C-reactive protein; SPARCC-BME, Spondyloarthritis Research Consortium of Canada-bone marrow edema.

Table 6

Are there any differences between responders and non-responders at baseline or at week 52? Mean ADC (standard deviation) $\mu mm^2/s$. * denotes independent t-test $p < 0.05$; ** denotes $p < 0.01$.

	ΔBASDAI–50%	ASDAS-CII	ASDAS-ID	ΔCRP–50%	ΔSPARCC- BME–50%
SPARCC-BME					
baseline	13.2 (2.5)	12.1 (5.9)	15.2 (8.9)	14.4 (7.9)	12.3 (6.6)
	20.4 (11.8)	20.0 (11.5)	22.7 (12.9)*	20.3 (12.2)	19.4 (10.7)
Week 52	3.5 (2.5)	3.0 (2.7)	2.5 (2.2)	2.0 (2.2)	9.5 (3.5)
	2.4 (2.7)	2.6 (2.7)	3.1 (3.3)	3.1 (2.9)	2.7 (2.0)**
*ADC*structured					
baseline	195 (65)	188 (67)	209 (98)	197 (59)	192 (18)
	255 (140)	251 (134)	278 (150)	259 (145)	242 (129)
Week 52	145 (26)	140 (30)	142 (32)	133 (28)	169 (21)
	160 (78)	160 (74)	176 (96)	168 (79)	156 (73)
*ADC*lesion					
baseline	409 (211)	417 (229)	400 (188)	426 (182)	362 (257)
	447 (212)	442 (206)	498 (237)	441 (229)	435 (210)
Week 52	172 (54)	159 (39)	148 (53)	163 (67)	198 (40)
	158 (73)	163 (73)	181 (82)	162 (69)	163 (70)
*ADC*index					
baseline	460 (280)	455 (293)	453 (257)	477 (240)	348 (244)
	504 (284)	503 (279)	557 (314)	499 (307)	491 (286)
Week 52	181 (60)	167 (35)	159 (61)	180 (68)	218 (67)
	177 (93)	180 (92)	203 (106)	176 (93)	176 (87)

ADC, apparent diffusion coefficient; ROI, region-of-interest; ADC$_{structured}$, structured ROI ADC; ADC$_{lesion}$, lesion-based ROI ADC; ADC$_{index}$, index-based ROI ADC; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; CII, clinically important improvement; ID, inactive disease; CRP, C-reactive protein; SPARCC-BME, Spondyloarthritis Research Consortium of Canada-bone marrow edema.

Similar strong positive correlation between ADC measurements and SPARCC-BME scores described in this study has also been reported in other studies [9,10,20], however, positive correlations between changes in ADC and SPARCC-BME scores are reported here for the first time and further supports the use of ADC as an outcome measure.

A major strength of this study was its prospective single center design. All patients were imaged using the same MRI system and the same protocol at predefined time points. Therefore, variations in scanner, sequences, and timing were minimized. However, this means that our study cannot be generalized to the entire population because differences among MRI systems and sequences have not been investigated. In addition, this was an open-label study with no control group, placebo, or blinding of patients, and the physician may have introduced sampling bias. Moreover, a single assessor selected the ROIs once. Therefore, there were no inter-observer variation assessments. However, reliability assessments in previous studies of ADC measurements in axSpA patients have shown excellent intra- and inter-observer reliability [9,20,25,26]. Another limitation was that the SDC was not calculated. However, we were able to compare SDC measurements from a recent study that were obtained using similar methods [20].

5. Conclusion

In conclusion, the lesion-based and index-lesion ROI-setting ADC assessments were highly responsive and could be used to monitor TNF inhibitor treatment response similar to conventional MRI inflammation score, but unable to predict clinical outcomes. The index-lesion ROI setting may reduce the time required to assess the sacroiliac joints of patients with axSpA.

Author contributions

All authors critically revised and approved the manuscript. All authors agreed to be accountable for appropriate portions of the content.

Ethical statement

The study was approved by the local ethics committee and all patients provided written consent. Trial registration: ClinicalTrials.gov,

CRediT authorship contribution statement

Jakob M. Møller: Conceptualization, Formal analysis, Investigation, Methodology, Writing - original draft. **Mikkel Østergaard:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing - review & editing. **Henrik S. Thomsen:** Resources, Supervison, Writing - review & editing. **Simon Krabbe:** Formal analysis, Resources, Writing - review & editing. **Inge J. Sørensen:** Conceptualization, Methodology, Resources, Writing - review & editing. **Bente Jensen:** Resources, Writing - review & editing. **Ole Rintek Madsen:** Resources, Writing - review & editing. **Mette Klarlund:** Resources, Writing - review & editing. **Susanne J. Pedersen:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing - review & editing.

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