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SCIENTIFIC ARTICLE

Monitoring ankylosing spondylitis therapy by dynamic contrast-enhanced and diffusion-weighted magnetic resonance imaging

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Abstract
Objective The effects of different therapies on enthesitis/osteitis in active ankylosing spondylitis (AS) were evaluated by magnetic resonance imaging (MRI). The aim was to assess the role of quantitative MRI in the evaluation of AS treatment efficacy.
Materials and methods Thirty patients with active spondylitis or bilateral sacroilitis were selected and followed up for 1 year. Ten of the patients were treated only with non-steroidal anti-inflammatory drugs, 10 patients additionally received at baseline an intravenous pulse of glucocorticoids and 10 patients were treated with regular infusions of infliximab. Disease activity was measured according to clinical instruments and laboratory tests. For each patient, one selected inflamed lesion was followed from baseline through control visits quantitatively by diffusion-weighted imaging (DWI) measuring the apparent diffusion coefficient (ADC) and by dynamic contrast-enhanced imaging (DCEI) with evaluation of the enhancement factor (f_{enh}) and enhancement gradient (g_{enh}).
Results Clinical and quantitative MRI parameters diminished significantly with regression of the inflammatory activity. The improvement in AS was most pronounced in patients treated with infliximab; after 12 months the ADC diminished from an average of 1.31 to 0.88×10^{-3} mm^2/s, f_{enh} from 1.85 to 0.60, and g_{enh} from 3.09 to 1.40 %/s.
Conclusion Diffusion-weighted imaging and DCEI were shown to be effective in quantifying changes in inflammation in skeletal lesions during the treatment of AS, and could therefore be convenient for assessing treatment efficacy. To the best of our knowledge this is the first time DWI was used to evaluate the activity of skeletal inflammation in rheumatic diseases such as AS.

Keywords Ankylosing spondylitis · Disease activity · Treatment · Diffusion-weighted MRI · Dynamic contrast-enhanced MRI

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease, characterized by enthesitis/osteitis and resulting in axial diseases such as sacroiliitis, spondylitis, spondylodiscitis, and spondylarthritis, in addition to peripheral disease manifestations such as synovitis [1]. Until recently, AS treatment was mainly based on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy. Glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) are believed to have only limited value [2]. A major breakthrough in the overall treatment of AS occurred with the introduction of the inhibitors of the proinflammatory cytokine tumor necrosis factor α (anti-TNF-α), the efficacy of which has been confirmed in patients with active AS in previous studies [3, 4].

Magnetic resonance imaging (MRI) is a sensitive noninvasive imaging method that can detect inflammation in soft tissue and bone. As such it allows visualization of axial enthesitis/osteitis in AS that cannot be assessed by clinical means or by conventional radiography. Short tau inversion recovery (STIR) and T1-weighted spin-echo imaging (T1SE) with and without contrast enhancement are sequences most frequently used to image inflammatory lesions in AS, although T2-weighted spin-echo imaging can also be used. MRI is now being increasingly used to evaluate the efficacy of anti-inflammatory drugs (such as anti-TNF-α) by quantifying inflamed skeletal lesions in patients with AS using special MRI scoring methods [5–7].

Dynamic contrast-enhanced imaging (DCEI) and diffusion-weighted imaging (DWI) are not routinely used in imaging AS, but they could provide additional quantitative information about inflammatory activity in a particular inflamed skeletal region. Furthermore, these methods may make it possible to follow the inflammatory activity throughout the special treatment modality, and to provide a quantitative assessment of treatment efficacy. DCEI has already been reported to be valuable in detecting early- and late-stage inflammation in the sacroiliac joints (SIJ) of patients with spondylarthropathy [8]. DWI has been shown to be particularly useful in evaluating vertebral lesions, such as benign compression fractures, metastases, hemangiomas, for early identification of disk degeneration and disk herniations [9], and is with some limitations also useful for differentiating malignancy and spinal infection, such as tuberculosis or pyogenic infections [10]. DWI is sensitive to the random motion of water protons in tissue; the greater the mean free path of water molecules, the greater the signal loss obtained by the diffusion-weighted sequence [11]. The method has proven to be an effective diagnostic tool whenever a change in the ratio of extracellular water (with low DWI signal) to intracellular water (with high DWI signal) occurs, which may be due to inflammation. However, its value in the assessment of enthesitis and osteitis in AS has not yet been evaluated.

The aim of the present study was to assess the role of two quantitative MRI sequences, DCEI and the newer DWI, in the measurement of inflammation in AS patients treated with different therapeutic regimes. This is, to the best of our knowledge, the first study where the two methods, especially DWI, were used for quantitative assessment of the therapeutic effect of AS treatments.

Materials and methods

This study was designed as a 12-month, single-center trial, approved by the local ethics committee, and all participants gave their written informed consent. Thirty patients with AS diagnosed according to the modified New York criteria [12] (21 male, 9 female) with a mean age of 38.4 years (range 23–58) and mean disease duration of 3.4 years (range 0.1–18.9) were selected for the study. All patients had active disease as defined by Assessments in AS (ASAS) Working Group criteria [13] and/or had elevated acute phase reactants (C-reactive protein [CRP] ≥ 20 mg/l and/or erythrocyte sedimentation rate [ESR] ≥ 40 mm/h). Patients on concomitant DMARDs (sulfasalazine or methotrexate) because of peripheral arthritis were included only when medication doses were stable for at least 2 months prior to the inclusion; they also continued the treatment at the same stable dose throughout the study follow-up. Previous treatment with pulse glucocorticoids was allowed when the last infusion was at least 6 months prior to the beginning of the study. Patients were divided into three subgroups according to the therapy they received. Ten patients who were not taking a stable dose of NSAIDs prior to inclusion in the study were treated only with full-dose NSAIDs (NSAID group). The remaining 20 patients were randomly assigned to either the GC group, 10 patients who received at baseline an intravenous pulse of glucocorticoids (375 mg for 3 successive days), or the INF group, 10 patients who were treated with regular infusions of infliximab (5 mg/kg body weight) at baseline, week 2, 6, and every 6–8 weeks thereafter. Patients were permitted to use NSAIDs at their own discretion for treatment of AS symptoms throughout the study follow-up. Table 1 summarizes the patients' demographics and characteristics at baseline.

Clinical assessments

The patients' clinical status was assessed at baseline and then at 2 and 12 months after the start of the study. Clinical parameters were collected at each visit including the respiratory index (the difference between the chest circumference at maximal inspiration and maximal expiration measured at the fourth intercostal space), the Bath AS Disease Activity Index (BASDAI) [14], the Bath AS Functional Index (BASFI) [15], the Bath AS Metrology Index (BASMI) [16] and the Bath AS Patient Global Score (BAS-G) [17]. These parameters range between 0 and 10 points on a 10-cm visual analog scale (VAS). Routine laboratory tests including renal and liver function tests, a full blood count, ESR, CRP and electrolyte levels were performed at each visit.

Efficacy of the therapy was clinically evaluated by the previously proposed ASAS criteria (ASAS 20%) [13], based on an improvement of at least 20% and 1 cm (on a 10-cm VAS) in at least three of the following four domains: BAS-G, pain, BASFI, and morning stiffness. The fourth domain could not deteriorate by more than 20%. Addition-

Table 1 Baseline patient demographics, clinical and functional characteristics. Values presented are mean (range) unless stated otherwise

	Infliximab (n=10)	Glucocorticoids (n=10)	NSAID (n=10)	p value
Male:female	7:3	7:3	7:3	–
AS:bilateral sacroilitis	9:1	9:1	9:1	–
Concomitant DMARDs; n	1	2	1	–
Age (years)	33.6 (23–44)	44.3 (33–58)	37.4 (23–52)	0.066
Disease duration (years)	5.0 (1–14)	1.7 (0–4)	3.5 (0–19)	0.088
BAS-G	7.23 (3.7–9.7)	7.92 (4.8–10.0)	4.81 (0.2–9.4)	0.048 *
BASDAI	5.96 (3.4–7.8)	5.71 (2.4–8.9)	2.51 (0.4–7.6)	0.007 *
BASFI	5.56 (1.6–8.5)	6.00 (2.2–9.1)	2.16 (0.3–6.8)	0.003 *
BASMI	2.8 (1–5)	2.8 (0–6)	1.4 (0–5)	0.081
RI (cm)	5.6 (4.0–10.0)	6.4 (4.0–10.0)	5.8 (2.5–10.5)	0.593
ESR (mm/h)	28.8 (4–96)	30.7 (2–52)	17.5 (1–44)	0.189
CRP (mg/l)	25.6 (0–107)	21.4 (0–33)	14.4 (0–34)	0.619

AS, ankylosing spondylitis; DMARDs, disease modifying antirheumatic drugs; BAS-G, Bath Ankylosing Spondylitis Patient Global Score 0-10; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index 0–10; BASFI, Bath Ankylosing Spondylitis Functional Index 0–10; BASMI, Bath Ankylosing Spondylitis Metrology Index 0–10; RI, respiratory index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NSAID, non-steroidal anti-inflammatory drugs

*p<0.05, Kruskal–Wallis test comparing three groups

ally, the recently proposed ASAS 40% was applied (improvement of at least 40% and 2 cm in three of the four domains and no deterioration in the remaining domain) [18].

Radiological assessment

Magnetic resonance imaging scans were performed using a 1.5-T Signa LX Echospeed (General Electric, Waukesha, WI, USA) MRI scanner. For locating sites of inflamed tissue, standard STIR and pre-contrast T1SE MRI sequences of the SIJ in the oblique coronal plane and of the thoracolumbar spine in the sagittal plane were acquired. One lesion where the signal intensity was high for STIR and low for T1SE MRI sequences was then selected for each patient at baseline as the region of interest (ROI). This was independently confirmed by a qualified radiologist who did not have access to the patient's clinical data. The ROIs, unchanged in the location and size for each patient throughout the whole study, were further examined in detail at baseline and then after 2 and 12 months at follow-up controls with a series of axially (for spine) or oblique coronally (for SIJ) oriented scans. The protocol for investigating the chosen ROI consisted of the following imaging sequences:

1. STIR;
2. DWI;
3. DCEI, using the paramagnetic contrast agent gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA; Magnevist; Schering, Berlin, Germany), administered intravenously using an MR injection system (Spectris Solaris, Medrad, Indianola, PA, USA) in a concentration of 0.1 mmol/kg body weight just before starting the DCEI sequence;
4. Delayed post-contrast T1SE (approximately 8.4 min after contrast agent administration).

The following parameters were used: field of view 240 mm (DCEI), 300 mm (T1SE, STIR) and 320 mm (DWI), slice thickness 4 mm (T1SE, STIR) and 5 mm (DWI, DCEI), the imaging matrix was equal to 256×192 points for all methods except for DWI where the matrix was equal to 128×96 points. Echo time (TE) and repetition rate (TR) were TR/TE=440/14 ms for T1SE and TR/TE=3,000/67 ms for STIR; the inversion time (TI) for STIR was 150 ms. DWI was based on the echo-planar imaging (EPI) method using the spin-echo single-shot technique at TR/TE=8,000/75 ms. In order to calculate the apparent diffusion coefficient (ADC) two acquisitions were performed—one without diffusion weighting (b=0 s/mm^2) and the other with diffusion weighting (b=400 s/mm^2). Based on preliminary DWI measurements at different b values, the b value of 400 s/mm^2 was selected as the best compromise between efficient diffusion weighting and image deterioration associated with diffusion weighting. DCEI was performed by the three-dimensional enhanced fast gradient echo (EFGRE3D) method by which images were acquired dynamically in four consecutive slices across the lesion every 14 s in 36 time frames. Images were in some places distorted since DCEI and DWI sequences are prone to flow artifacts. Despite these distortions, which were more frequent when ROIs were selected on the spine, they were of sufficient quality to be used for quantitative analysis in all cases. When necessary, imaging was repeated until a

satisfactory image quality for quantitative measurement was reached. The whole imaging protocol was approximately 1 h long for follow-up controls and approximately 20 min longer for the examination at baseline.

The DCEI images were quantitatively analyzed using image processing software (ImageJ; NIH, Bethesda, MD, USA) by measuring changes in the average signal intensity for the selected ROI. Each DCEI measurement yielded a time–intensity curve and the following mathematical model was fitted to the measured data using OriginPro (Origin Lab, Northampton, MA, USA):

$$SI = SI_0 + (SI_{max} - SI_0)(1 - \exp(-t/\tau)); \quad (1)$$

where SI_0, the signal intensity before Gd-DTPA bolus administration, approaches the maximum signal intensity (SI_{max}) exponentially in the characteristic time (τ). Two parameters were extracted from the formula in Eq. (1): the enhancement factor (f_{enh})

$$f_{enh} = \frac{SI_{max} - SI_0}{SI_0}, \quad (2)$$

which is a dimensionless quantity, and the enhancement gradient (g_{enh})

$$g_{enh} = 100\frac{SI_{max} - SI_0}{SI_0\,\tau}, \quad (3)$$

which yields the percentage increase in signal intensity per unit of time.

In DWI, two image sets, generated with different diffusion sensitizing factors (b values), were analyzed with linear regression analysis using Image J in order to generate an ADC map. The ADC for each ROI was then calculated from the ADC maps.

Statistics

The non-parametric Kruskal–Wallis test was performed to test for differences between the NSAID, GC and INF group at baseline, and the Wilcoxon signed rank test was used to compare changes between values of quantitative parameters at baseline and at control visits. A probability (p) value of less than 0.05 was considered statistically significant.

Results

At baseline, each patient's clinical parameters were assessed and the ROI selected either on SIJ (in 8 patients from the NSAID group, 4 from the GC group, and 6 from the INF group) or on the thoraco-lumbar spine (in the remaining patients). ADC, f_{enh} and g_{enh} were calculated as shown in Fig. 1. There was no statistically significant difference found between the INF and GC groups in the clinical parameters assessed, but the NSAID group showed statistically significantly lower scores in the BASDAI, BASFI, and BAS-G (Table 1). ADCs calculated from the ADC maps (an example shown in Fig. 2a) were similar in all three groups of patients at baseline (see Table 3), with an average ADC value of $1.30\pm0.32\times10^{-3}$ mm^2/s. There was also no statistically significant difference in f_{enh} (an average 1.64±1.14) and g_{enh} (an average 3.88±3.36 %/s) values among all three groups (see Table 3, Fig. 4).

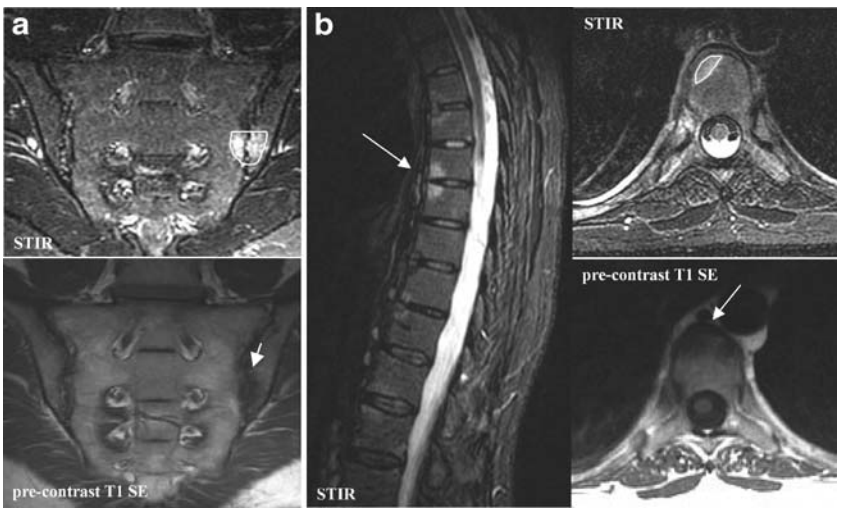

Fig. 1 Selection of an inflamed skeletal lesion by short tau inversion recovery (STIR) and pre-contrast T1-weighted spin-echo (T1SE) sequences. **a** The region of interest (ROI) was selected within the posterior aspect of the left sacroiliacal joint on the oblique coronal STIR (*encircled area*). The lesion was hyperintense on STIR and hypointense on pre-contrast T1SE (*arrow*). **b** Sagittal STIR of the thoracal spine shows active anterior spondylitis on almost all visible vertebrae. For further evaluation, the lower part of the 8th thoracal vertebra was selected (*arrow*). On axial STIR the inflamed bone was hyperintense (*oval* represents selected ROI) while the same region was hypointense on axial pre-contrast T1SE (*arrow*)

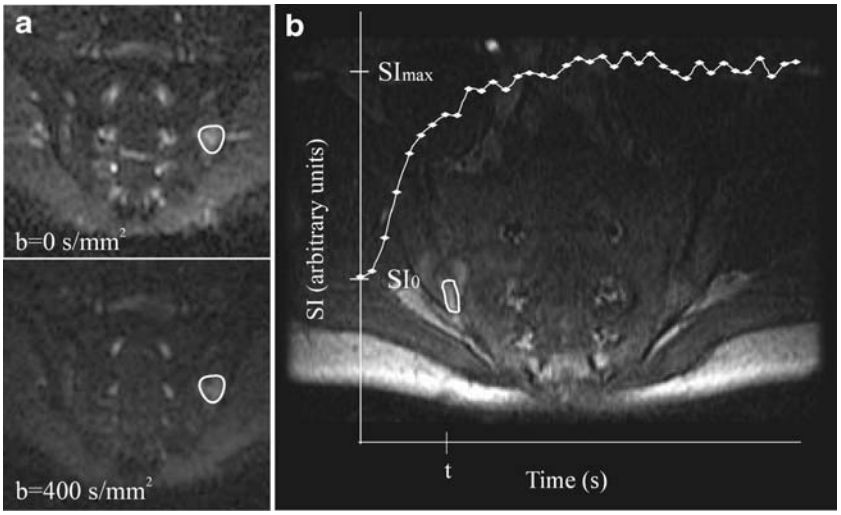

Fig. 2 Quantitative MR assessment of sacroiliacal joints (SIJ). **a** Two coronal oblique diffusion-weighted images of the SIJ in a 39-year-old man from the GC group, performed with different diffusion strengths (b values). The inflamed region in the middle of the left SIJ, which is encircled on both images, was selected as the region of interest (ROI). The regression analysis of both images allowed the calculation of the apparent diffusion coefficient (ADC) for the selected ROI. **b** The last oblique coronal image of 36 successive dynamic contrast-enhanced images in a 24-year-old man from the non-steroidal anti-inflammatory drugs (NSAID) group shows hyperintensity in the posterior aspect of the right SIJ; the superimposed signal intensity vs. the time curve shows an increase in the signal intensity (y axis) over a time interval of 14 s (x axis) in the *encircled* ROI. The parameters are: SI_0, signal intensity before contrast administration; SI_{max}, maximum signal intensity; t, characteristic time for the signal intensity increase

At month 2, statistically significant improvements in BASDAI, BASMI, CRP, and ESR were detected in the INF group, and 9 out of 10 patients met the ASAS 20% and 8 out of 10 patients met the ASAS 40% criteria. In the GC group, the only statistically significant change was a reduction in the CRP value, while in the NSAID group there were no statistically significant changes in any clinical parameters (Table 2). Similarly, a lower number of patients met the ASAS criteria; in the GC group, 4 out of 10 patients met the ASAS 20% criteria, and 3 out of 10 met the ASAS 40% criteria, while in the NSAID group 2 out of 10 and 1 out of 10 patients met the respective criteria. In accordance with significant clinical improvement in the INF group, there was a statistically significant decrease in the f_{enh} (mean 0.96, range 0.3–2.1) and g_{enh} (mean 1.81 %/s, range 0.6–4.2) values (both $p<0.05$). A decrease in f_{enh} and g_{enh} was also observed in the GC group, with a corresponding increase in the NSAID group. These changes were, however, statistically insignificant (Fig. 4). There was no characteristic change in the ADC in any group at month 2.

At month 12, a statistically significant improvement in BASDAI, CRP and ESR was preserved in patients from the INF group, while the clinical status of the GC and NSAID groups was similar to the status at baseline (Table 2). Clinical improvement in the INF group was in accordance with a statistically significant decrease in the ADC (mean 0.88×10^{-3} mm^2/s, range 0.4–1.6; $p=0.022$) for the same time period (Fig. 3, Table 3). These improvements were

Table 2 Analysis of clinical outcomes at two end points. Values are given as means (range)

	Infliximab group			Glucocorticoids group			NSAID group		
	Baseline	Month 2	Month 12	Baseline	Month 2	Month 12	Baseline	Month 2	Month 12
BASDAI	5.96 (3.4–7.8)	1.79* (0.0–4.6)	1.43* (0.0–4.5)	5.71 (2.4–8.9)	5.03 (0.4–9.2)	4.43 (0.3–9.4)	2.51 (0.4–7.6)	2.94 (0.2–5.6)	1.75 (0.0–7.5)
BASMI	2.8 (1–5)	2.1* (0–4)	2.3 (0–5)	2.8 (0–6)	2.7 (0–6)	2.5 (0–7)	1.4 (0–5)	1.8 (0–6)	1.8 (0–6)
CRP (mg/l)	25.6 (0–107)	2.6* (0–5)	2.0* (0–4)	21.4 (0–33)	13.0* (0–29)	14.7 (0–34)	14.4 (0–34)	11.9 (0–43)	8.7 (0–41)
ESR (mm/h)	28.8 (4–96)	6.8* (1–20)	8.2* (1–28)	30.7 (2–52)	25.4 (5–37)	27.2 (6–54)	17.5 (1–44)	15.3 (1–34)	14.8 (1–35)

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index 0–10; BASMI, Bath Ankylosing Spondylitis Metrology Index 0–10; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

*$p<0.05$, Wilcoxon signed rank test comparing baseline data with data at control month for each group (p values are not shown in the Table)

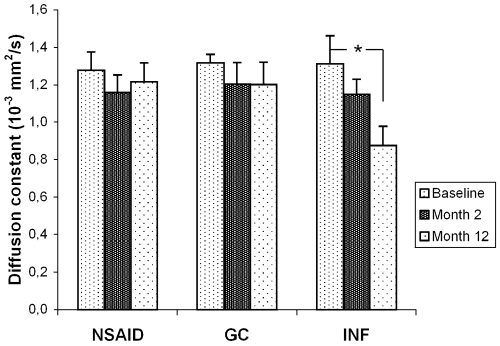

Fig. 3 The apparent diffusion coefficient (ADC; mean ± SE) at baseline, month 2, and month 12 for three differentially treated groups of ankylosing spondylitis patients respectively. *The decrease in the diffusion constant reached statistical significance in the INF group at month 12 compared with baseline ($p<0.05$). NSAID, non steroid anti-inflammatory drugs; GC, glucocorticoids; INF, infliximab

also apparent in the significantly decreased f_{enh} (mean 0.60, range 0.2–0.9) and g_{enh} (mean 1.40 %/s, range 0.3–3.4) values. Despite the complete disappearance of inflammatory lesions on STIR or T1SE images in the INF group, the complete flattening of the signal intensity curve was observed in only one patient for whom inflammation activity was reduced to the level of no inflammation ($f_{enh}=0.19$, $g_{enh}=0.27$ %/s). In other patients, quantitative measurements showed at least persisting latent inflammatory activity. In the GC and NSAID groups no improvement according to MRI parameters was observed (Fig. 4).

Although in the control MRI studies (at 2 and 12 months) we focused only on the lesions selected at baseline, we also observed the disappearance of neighboring lesions in patients from the INF group throughout follow-up. In the GC and especially the NSAID groups, however, new lesions were at times observed.

Discussion

Magnetic resonance imaging plays an important role in the diagnosis, staging, and follow-up of inflammatory diseases such as AS. Due to the different signal intensities of STIR, T1SE, and T2SE images, inflamed regions can be recognized at an early stage of the disease. Analysis of morphological patterns and distribution of the lesions is of the utmost importance for the differential diagnosis of AS. In order to achieve functional information of a pathologic process, perfusion imaging such as DCEI, and more recently DWI, has been used [19].

Diffusion-weighted imaging is a relatively new MRI technique in which image contrast is due to the different random motions of water protons in different biological tissue environments. In the present study on DWI, inflamed skeletal lesions were seen as hyperintense with the respect to the surrounding, presumably normal, skeleton. The ADC values calculated at baseline were similar for all three groups (ADC=1.30×10^{-3} mm^2/s) and were higher than that of the normal bone marrow (mean ADC=0.15×10^{-3} mm^2/s [20] to 0.23×10^{-3} mm^2/s [9]). They were, as expected, lower than for free water (mean ADC=2.80×10^{-3} mm^2/s at 37°C [21]). Higher ADC values reflect elevated diffusion compared with those of normal bone because of the increased water content in the extracellular space where water is less restricted [22]. DWI includes both T2-weighted and diffusion-weighted components, so the combined cell infiltration and vasogenic edema due to inflammation may appear as hypointense, isointense or slightly hyperintense signal on diffusion-weighted images, but always hyperintense on ADC images.

In this study, it was found that the more effective the treatment was according to clinical and laboratory parameters, the more pronounced the decrease in diffusion. This was most apparent in the INF group. The study demonstrated a dramatic and rapid clinical improvement in the INF group compared with the GC and NSAID groups, and almost complete disappearance of selected lesions on STIR and T1SE images at month 2. ADC values were at that time still high, and similar in magnitude to baseline values. This implies persistently increased water proton motion in the observed parts, presumably due to residual inflammatory

Table 3 Magnetic resonance imaging parameters in the three groups of AS patients at all end points. Values are given as means (range)

	Infliximab group			Glucocorticoids group			NSAID group		
	Baseline	Month 2	Month 12	Baseline	Month 2	Month 12	Baseline	Month 2	Month 12
ADC (10^{-3} mm^2/s)	1.31 (0.6–2.3)	1.15 (0.7–1.6)	0.88* (0.4–1.6)	1.32 (1.0–1.5)	1.21 (0.6–1.8)	1.20 (0.6–1.8)	1.28 (0.8–1.9)	1.16 (0.8–1.7)	1.22 (0.8–1.7)
f_{enhs} (1)	1.85 (0.5–5.5)	0.96* (0.3–2.1)	0.60* (0.2–0.9)	1.34 (0.2–3.1)	1.16 (0.2–3.5)	1.31 (0.3–4.4)	1.74 (0.7–3.3)	1.79 (0.4–4.9)	2.06 (0.4–11.2)
g_{enh} (%/s)	3.09 (1.1–5.9)	1.81* (0.6–4.2)	1.40* (0.3–3.4)	3.67 (0.8–8.8)	2.62 (0.4–8.0)	3.28 (0.4–10.7)	4.9 (0.8–14.8)	3.29 (0.5–6.5)	3.60 (0.5–14.8)

ADC, apparent diffusion coefficient value; f_{enh}, enhancement factor; g_{enh}, enhancement gradient
*$p<0.05$, Wilcoxon signed rank test comparing baseline data with data at control month for each group (p values are not shown in the Table).

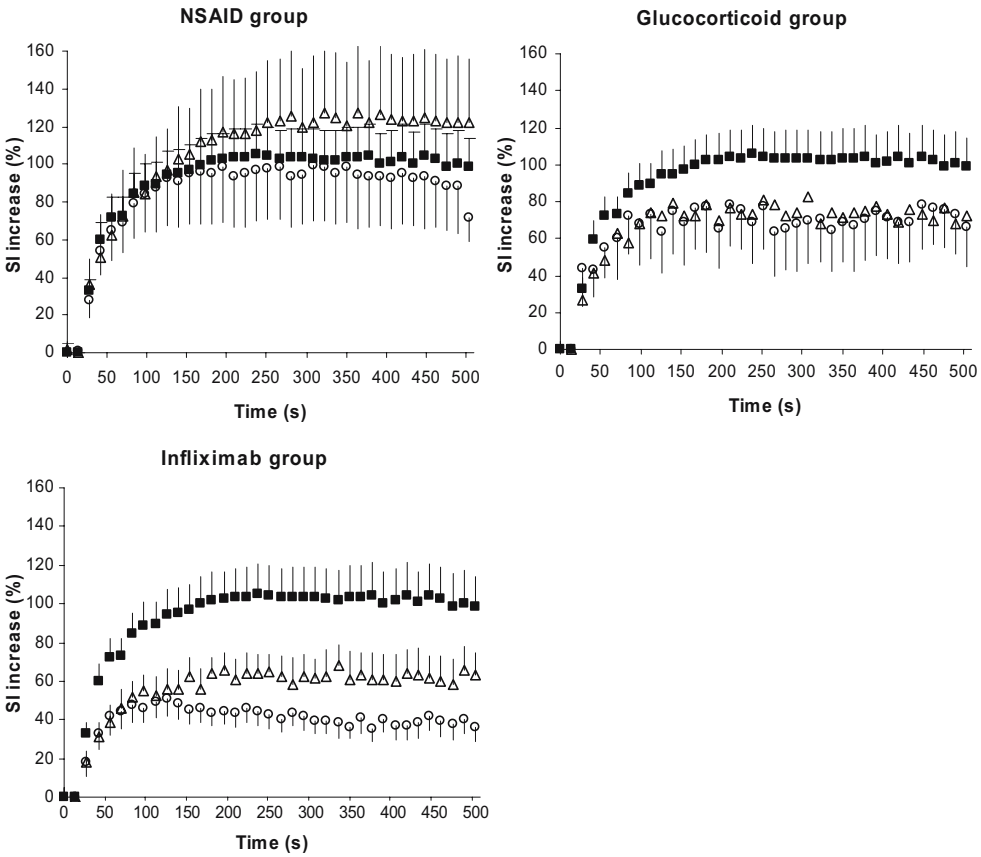

Fig. 4 Signal intensity (SI) increases (mean values ± SE) at baseline, month 2, and month 12 in the selected inflamed lesion after application of paramagnetic contrast agent. Signal intensities were measured in a ROI at particular times; increases were calculated according to the value at 14 s after administration of the contrast agent; mean values are shown. A statistically significant decrease was observed in the INF group at month 2 and month 12 compared with baseline ($p<0.05$). NSAID, non steroid anti-inflammatory drugs; *full squares*, baseline; *triangles*, month 2; *circles*, month 12

activity. It was not until after 12 months that a significant decrease in ADC values was observed (Fig. 3). The inflammation reduction on a cellular level, reflected by ADC values in DWI, was probably much slower than would be inferred from the rapid clinical improvement. Due to ethical reasons we were unable to supplement the MRI data with histological evidence. It is possible that a clear correlation between histological changes and diffusion characteristics could be determined with further studies. Therefore, DWI may become a valuable tool in therapy, allowing the assessment of treatment response in AS and indicating when residual inflammation is still present, thus preventing premature termination of treatment.

The major limitations of DWI of the spinal column in vivo are severe image artifacts induced by physiological patient motion and substantial magnetic susceptibility variations around the spine (the presence of bone and air and closed vascular and cerebrospinal fluid pulsation) [23]. The EPI-based DWI used in the present study has the same disadvantages. It is therefore very challenging to acquire robust diffusion images with sufficient spatial resolution and within a reasonable acquisition time. Several DWI techniques have already been proposed to make MRI sensitive to water diffusion in the spine. Recently Dietrich et al. [24] reported a new DWI sequence, rapid acquisition with relaxation enhancement (RARE)-based single-shot, which is less distorted and more anatomically informative than single-shot EPI. Further optimization of DWI for anatomical regions with poor magnetic field homogeneity is, however, still needed.

Dynamic contrast-enhanced imaging quantifies the distribution profile of paramagnetic contrast agent in microvessels and in the interstitial space of the tissues investigated. This method was already reported to be a clinically relevant technique for diagnosis in early spondylarthropathies allowing quantitative measurements of inflammation [8, 25]. Previous studies demonstrated that DCEI is also useful in evaluating bone marrow perfusion [26, 27], showing a strong correlation with microsphere blood flow measurements [26], and for evaluating different musculoskeletal neoplasms [28], providing evidence of changed perfusion due to angiogenesis [29], and it enables the monitoring of patient responses to therapy [30].

In the present study the signal intensity first rapidly rose as the contrast agent diffused from the arterial capillaries into the extracellular space of an inflamed lesion. This process was determined by tissue microvascularization and perfusion. The signal intensity then reached a plateau that remained steady for the duration of the rest of our observations, except in the INF group in month 12 where there was a slight decrease in the signal intensity over time. Over time, the contrast agent is transported toward

intravascular compartments and is then filtered by the kidney. This process depends on capillary permeability and interstitial space components, and is, according to the results of the present study, more pronounced in the successfully healed inflamed lesion. DCEI therefore enables noninvasive assessment of blood perfusion in vivo and provides some insight into the microvascular structure of the tissue observed. But even in the INF group, which according to clinical parameters was the most successfully treated, there was still some contrast uptake in the ROI after 1 year of continuous treatment (Fig. 4). This could be due to some residual low-grade inflammatory activity that could cause the flare up of AS shortly after discontinuing the treatment with anti-TNF-α, which has been observed previously [31].

Dynamic contrast enhancement of normal bone marrow was described to be strongly influenced by age and fat content, decreasing with increasing age and conversion to fat [28, 32]. Since our study groups consisted primarily of young patients, we assumed this influence to be negligible.

Although the study groups were rather small due to a complicated protocol, we observed significant differences in the treatment efficacy confirmed by quantitative MRI. We focused on only one lesion because of the long imaging protocol. Protocol targeting more than one lesion would be accordingly longer and less convenient for AS patients. Exact information about other lesions is therefore not available.

In conclusion, we have demonstrated that DCEI and DWI have potential in the quantitative analysis of inflammatory skeletal lesions in patients with AS, and are therefore also useful for the assessment of treatment efficacy. They show the extent of inflammatory activity more precisely in comparison to anatomically more informative routinely used MRI techniques such as STIR or T1SE. In the future, novel therapeutic approaches to treatment of AS are expected. Therefore, reliable and precise quantitative methods will be of extreme importance for assessing their efficacy. It is in this context that we foresee MRI in general and especially DWI and DCEI to play significant roles.

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