Persistent reduction of spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis after 2 yrs of treatment with the anti-tumour necrosis factor agent infliximab

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Objectives. Patients with ankylosing spondylitis (AS) benefit from anti-TNF therapy both on a clinical basis and as depicted by magnetic resonance imaging (MRI). It is not known whether spinal inflammation remains suppressed over time. Our objective was to assess spinal inflammation by MRI in AS patients after 2 yr of continuous infliximab treatment.

Methods. Twenty patients with active AS were examined by MRI at baseline, after 3 months (end of placebo-controlled-phase) and after 2 yr of continuous infliximab therapy (5 mg/kg/6 weeks). T1 pre- and post-gadolinium (T1/gadolinium-diethylenetriamine-pentaacetic acid) and short tau inversion recovery (STIR) MRI sequences were performed and read by one blinded reader using the ASspiMRI score.

Results. Spinal inflammation, detected by MRI in all patients at baseline, decreased after 3 months only in the infliximab group in both MRI sequences. Persistent improvement of spinal inflammation was seen after 2 yr by scoring STIR sequences, with a mean score of 4.6 ± 5.9 vs 15.2 ± 13.2 at baseline (P = 0.01). On an individual level, inflammatory spinal lesions decreased from 6.7 ± 5.0 per patient at baseline to 2.2 ± 1.8 after 2 yr (P = 0.003). Improvement in spinal inflammation was found in all patients by both MRI sequences. Only a minor degree but some spinal inflammation was still present after 2 yrs.

Conclusion. Spinal inflammation in MRI was persistently reduced in all patients constantly treated with infliximab, but it was not completely eradicated. Disease activity parameters did not directly correlate with MRI, but both pointed in the same direction. Both types of information may be useful for the definition of response to anti-TNF therapy.

Key words: Ankylosing spondylitis, Infliximab, Magnetic resonance imaging, Spinal inflammation.

Ankylosing spondylitis (AS), the main subtype of the group of spondyloarthritides (SpA), is a chronic inflammatory rheumatic disease with a prevalence of 0.1–1.1% [1]. AS affects young male and female patients in the second and third decade of life and starts in the sacroiliac joints [1, 2], with the leading clinical symptom of inflammatory low back pain [3]. During the course of the disease the inflammation may spread to the spine where imaging findings indicate spinal inflammation such as spondylitis, spondylodiscitis, spondyloarthritis and new bone formation with syndesmophytes and ankylosis [4]. X-ray examinations of the spine and the pelvis, which mainly detect chronic changes, have been the standard for diagnosis and classification for decades [5], while recent studies using magnetic resonance imaging (MRI) have shown better assessment and localization of inflammatory lesions in AS [6, 7].

Treatment of patients with active AS with the anti-tumour necrosis factor-α (TNF-α) antibody infliximab in a dosage of 5 mg/kg i.v. given every 6 weeks in a randomized controlled trial (RCT) recently performed in Germany [8] (still ongoing), showed definite improvement of disease activity and other clinical and laboratory parameters in short-term [8, 9] and long-term [10, 11] follow-up studies. No loss of efficacy was reported after 2 and 3 yr of continuous treatment with infliximab. Similar results have been reported by other groups [12–17].

MRI of the spine is increasingly used to detect spinal lesions in early and active phases in AS [18]. The novel scoring system ASspiMRI was recently described to be reliable for assessment and quantification of acute (ASspiMRI-a) and chronic (ASspiMRI-c) spinal lesions of AS patients [6, 19, 20]. Importantly, it was also sufficiently sensitive to change [19].

In the present study, we evaluated MR images of the German RCT [8, 10] at different time points including those after continuous long-term treatment with infliximab. For the first time we show that spinal inflammation, although persistently reduced in all patients, is still detectable in some.
Patients and methods

Patients and study protocol

The AS patients included in this study came from the same centre. After giving informed consent they agreed to undergo MRI at baseline, and at the 3-month and 2-year follow-up examinations. The study was approved by the ethical committee of the hospital.

Of the 20 AS patients included at baseline, nine were assigned to infliximab and 11 to placebo. All patients fulfilled the modified New York criteria for AS [5], and had active disease as defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI [21]) of >4. Nine female and 11 male patients, with a mean age of 40.9 yr (range 29–54 yr) were examined by MRI (Table 1). The patients had received infliximab at baseline, after 2 and 6 weeks and then at 6-week intervals until week 102 of the clinical study [8, 10]. MRI examinations were performed before the first application of infliximab (baseline), after 12 weeks (end of the placebo-controlled phase of the clinical trial) and after 102 weeks (all patients treated with infliximab).

Magnetic resonance imaging (MRI)

MRI investigations were executed with a 1.5 T unit (Magnetom Vision, Siemens, Erlangen, Germany), using a spine-array coil and/or a body-array coil. The MRI techniques applied to assess spinal inflammation in AS patients were performed as described [4]. The sagittal section orientation was chosen and the following sequences were used:

(i) T1-weighted spin-echo (SE) sequences (repetition time (TR)/echo time (TE) 500/12 ms, slice thickness 3 mm, four acquisitions, field of view (FOV) 20 cm×40 cm, matrix 128×512 pixels) for assessment of chronic spinal lesions, such as erosions and syndesmophytes [20].

(ii) The same sequence with fat saturation after application of gadolinium-diethylenetriamine-pentaacetic acid (Gd-DTPA; Schering AG, Berlin, Germany, at 0.1 mmol/kg body weight) allows for assessment of acute spinal lesions by depiction of enhancement of Gd-DTPA as a sign of hypervascularization due to spinal inflammation [7].

No dynamic imaging was performed. Taking C2 and L5 as orientation points the spine was examined in two parts, always starting with the upper part. After rapid adjustment of the table into the appropriate position the lower part of the spine was examined.

(iii) Similarly, fat-saturated short tau inversion recovery (STIR) sequences (TR/inversion time (TI)/TE 4000/150/60 ms, slice thickness 3 mm, five acquisitions, FOV 25 cm×40 cm, matrix 121×256 pixels) were performed. The STIR MRI technique is able to visualize acute spinal lesions by depiction of bone marrow oedema caused by inflammation and hypervascularization [7].

Evaluation of the MRI examinations

The MRIs were scored by one reader (XB) who was blinded for time sequence of the images and treatment allocation (infliximab or placebo) of the patients in all three study phases. The MR images were scored by the recently evaluated ASspiMRI score [19]. Acute and chronic spinal lesions were scored on the basis of a vertebral unit (VU), which is defined as the region between two virtual horizontal lines drawn through the middle of a vertebral body [19]. Inflammatory spinal lesions were assessed by the $T_1$/Gd-DTPA and the STIR MRI sequence and chronic spinal lesions were assessed by using the $T_1$-weighted MRI sequence. The MRIs at baseline and at week 12 of this study had already been scored by different readers in a slightly different way in an earlier study [19].

Since MRI examinations were not mandatory for participation in the clinical study, not all patients had a complete series of MRI investigations (baseline = 20 patients, week 12 = 17 patients, week 102 = 14 patients). However, the clinical and efficacy parameters of the patients who did not undergo MRI examinations after 12 weeks and 102 weeks were similar to the patients who were included in the MRI examinations. Comparisons between time points were performed when paired samples were available for evaluation.

Statistical analysis

The paired Wilcoxon rank sum test was used to compare the readings before and after treatment and the Mann-Whitney U-test was used to compare the results between treatment groups at each single time point. The activity score (ASspiMRI-a) was assessed by comparing the changes detected by the MRI sequences and changes in clinical parameters, such as disease activity (BASDAI [21]), function (Bath Ankylosing Spondylitis Functional Index, BASFI [22]), mobility (Bath Ankylosing Spondylitis Metronomy Index, BASMI [23]), and laboratory parameters, such as C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR). Linear regression analysis was performed and correlation coefficients were calculated.

Results

Evaluation of active spinal changes

Comparison of the treatment groups before application of study medication. At baseline, at least one inflammatory spinal lesion (ASspiMRI-a score ≥1) was seen in all 20 patients when using STIR (100%) and in 18/20 patients (90%) when using $T_1$/Gd-DTPA. Inflammatory spinal lesions in combination with at least one erosion (ASspiMRI-a score ≥4) were seen in 16/20 patients (80%) with STIR and in 13/20 patients (65%) with $T_1$/Gd-DTPA.

The mean ASspiMRI-a score for all patients available at baseline was not significantly different between both treatment groups with $17.1±15.2$ in the infliximab and $11.9±8.7$ in the placebo group by STIR and $13.8±15.2$ in the infliximab group and $10.6±8.4$ in the placebo group by $T_1$/Gd-DTPA.

In the comparison of the three spinal segments, the thoracic spine (TS) had most inflammatory lesions, with $0.4±0.3$ and $0.3±0.2$ mean scoring points per VU in the STIR and the $T_1$/Gd-DTPA sequence, respectively. In comparison, both the cervical spine (CS) and the lumbar spine (LS) had a mean of

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Table 1. Demographic data of the 20 AS patients included in this study

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
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<td>40.9</td>
<td>29</td>
<td>54</td>
<td>7.4</td>
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<tr>
<td>Disease duration (yr)</td>
<td>16.5</td>
<td>3.0</td>
<td>35</td>
<td>9.1</td>
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<tr>
<td>BASDAI score</td>
<td>6.1</td>
<td>4.0</td>
<td>8.6</td>
<td>1.3</td>
</tr>
<tr>
<td>BASFI score</td>
<td>5.5</td>
<td>2.4</td>
<td>8.5</td>
<td>1.9</td>
</tr>
<tr>
<td>BASMI score</td>
<td>5.5</td>
<td>2.4</td>
<td>8.5</td>
<td>1.9</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>3.7</td>
<td>1.0</td>
<td>9.0</td>
<td>2.3</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>22.0</td>
<td>3.0</td>
<td>89.0</td>
<td>22.3</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>3.7</td>
<td>1.0</td>
<td>9.0</td>
<td>2.3</td>
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</table>
2-year follow-up

The patients treated initially with infliximab showed improvement of active inflammatory lesions at week 102 in comparison with baseline (17.7 ± 5.0 at baseline vs 2.2 ± 1.8 (P = 0.005) after 102 weeks when using STIR and from 5.1 ± 3.8 at baseline to 2.4 ± 2.2 (P = 0.02) after 102 weeks when using Gd-DTPA.

Overall, improvement of active inflammatory lesions at week 102 was depicted in both MRI sequences for all patients. However, after this time period at least one active spinal lesion was still present in 79% and in 84% of patients in the STIR and in the \( T_1/Gd-DTPA \) sequence, respectively.

**Evaluation of chronic spinal changes after 2 yr**

In the evaluation of the \( T_1 \)-weighted MRI sequence, chronic spinal changes deteriorated during the entire study period in both

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**Fig. 1. Change of acute and chronic spinal lesions after a follow-up of 3 months and 2 yr of placebo/infliximab treatment or open-label infliximab treatment.** (A) Placebo-12 weeks change of spinal lesions between baseline and 3 months follow-up in the placebo group. (B) Infliximab-12 weeks change of spinal lesions between baseline and 3 months follow-up in the infliximab group. '2-year follow-up' change of spinal lesions for all patients between baseline and 2 yr follow-up. \( T_1/Gd-DTPA = T_1 \)-weighted MRI after i.v. application of Gd-DTPA and STIR = short tau inversion recovery MRI for assessment of acute spinal lesions, \( T_1 = T_1 \)-weighted MRI sequence for assessment of chronic spinal lesions. Improvement of spinal lesions was detected only in patients under infliximab treatment after the first 3 months and not in patients treated with placebo. In the open-label phase after 2 yr, active spinal lesions showed even more improvement under continuous infliximab treatment in the entire study population.

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**Evaluation of spinal inflammation during the placebo-controlled phase of the study (3 months).** The ASspiMRI-a showed a significant reduction of mean scoring points per patient in the infliximab group, with 10.7 ± 9.4 at first follow-up vs 20.5 ± 16.6 at baseline (\( P = 0.04 \)) in the STIR sequence after 12 weeks of continuous treatment. In contrast, patients in the placebo group showed only minor changes in the same time period, with 10.8 ± 6.5 mean scoring points at week 12 (baseline 11.9 ± 8.7, \( P = 0.4 \)) (Fig. 1).

When using \( T_1/Gd-DTPA \) sequences, mean ASspiMRI-a scores in the infliximab group decreased from 17.7 ± 17.7 at baseline to 9.9 ± 9.3 per patient at week 12 (\( P = 0.08 \)). In comparison, patients in the placebo group showed only minor changes, with a mean score of 8.6 ± 6.6 per patient at week 12 (baseline 10.6 ± 8.4, \( P = 0.4 \)) (Fig. 1).

The mean number of inflamed VUs per patient in the group treated initially with infliximab decreased from 10.0 ± 6.7 at baseline to 4.7 ± 3.9 at week 12 (\( P = 0.04 \)) when using STIR and from 6.8 ± 5.7 to 4.5 ± 3.9 (\( P = 0.08 \)) when using \( T_1/Gd-DTPA \). In the placebo group, the mean number of inflamed VUs per patient was 5.1 ± 2.9 at baseline vs 3.8 ± 2.1 at week 12 when using STIR and 4.2 ± 2.6 at baseline vs 3.4 ± 3.3 at week 12 with \( T_1/Gd-DTPA \) (both \( P = 0.08 \)).
groups, with a mean ASspiMRI-c of 33.9±14.1 at baseline and 40.9±12.2 per patient at week 102. However, this difference was not statistically significant (Fig. 1).

Overall, 83% (5/6) patients in the infliximab group and 88% (7/8) patients in the placebo group showed deterioration of chronic spinal lesions after 2yr.

**Fig. 2.** Improvement of spinal inflammation in the STIR sequence (a) and the $T_1$/Gd-DTPA sequence (b) in two patients allocated initially to placebo. A = baseline, B = end of the placebo-controlled phase, C = follow-up after 2yr of infliximab treatment. Inflammatory spinal lesions (C7/T1 and the Andersson lesion in T11/T12) did not change during the placebo-controlled phase (‘A’ to ‘B’) but only after switching to infliximab treatment (‘C’).

**Correlation between MRI findings and clinical parameters for disease activity**

There was no strong correlation between values of clinical parameters (BASDAI, BASFI, BASMI, CRP, ESR) and scoring of both MRI sequences for spinal inflammation.
In the analysis of changes between baseline and week 12, significant correlations were only found between STIR change and BASDAI change ($r = 0.50$, $P = 0.05$) and between STIR change and BASFI change ($r = 0.62$, $P = 0.01$).

Furthermore, there was also no correlation between values of clinical parameters and MRI scorings after 2 yr of follow-up and no correlation between response to the assessment of AS working group (ASAS [24]) criteria or to BASDAI improvement and improvement of the MRI results between baseline and week 102, respectively.

Discussion

The results of this study confirm the clinical data indicating that treatment with infliximab, applied continuously in a dosage of $5\,\text{mg/kg i.v.}$ every 6 weeks, significantly improved disease-related signs and symptoms after 3 months [8], and, without loss of efficacy, after 2 yr of follow-up [10].

Improvement of spinal lesions under infliximab treatment was of the order of 40–50% during the first 3 months (placebo-controlled phase) of this study. In contrast, there was only a minor change in spinal inflammation (10–20%) compared with baseline in the placebo patients. After switching to infliximab, these patients also improved significantly at the 2-yr follow-up. From another point of view, the number of spinal lesions per individual patient decreased significantly after 2 yr of infliximab treatment in the range of 50–70%, depending on the MRI sequence used. The overall improvement of spinal inflammation was in the range between 50–70% after 2 yr of infliximab treatment. It is important to note that the patients treated with infliximab during the first 3 months of the study even showed additional improvement of active spinal lesions after 2 yr. This observation confirms the anti-inflammatory potential of infliximab and suggests an ever increasing benefit after continuous long-term therapy.

These data are consistent with short-term experiences from previous MRI studies of our group with both anti-TNF-$\alpha$ agents, infliximab [19] and etanercept [25, 26], and also from reports of other groups [27]. This study extends those reports on the course of inflammatory spinal lesions to MRI data on long-term anti-TNF-$\alpha$ therapy after 2 yr. Evidence is provided on the basis of the best available imaging technique that the reduction of spinal inflammation persists in patients with active AS at baseline when treated with infliximab continuously. As already pointed out, this corresponds well to the clinical efficacy already reported [8, 10].

In this study we found a weak correlation between changes of BASDAI and BASFI only when analysing the STIR sequences after 12 weeks; this is similar to our first study [19]. However, both, clinical and imaging data point into the same direction and indicate improvement in back pain and spinal inflammation in patients treated with infliximab. As already mentioned, the number of patients examined in this study was relatively small. Thus, this question will hopefully be answered in future evaluations of larger patient cohorts such as ASSERT [17].

The issue of where the spinal inflammation predominantly takes place has recently been discussed intensively [6]. In the present study we detected inflammatory spinal lesions in 38% of the VUs in the TS, in comparison to 17–26% of the VUs of both the CS and the LS. These data support our recent study in which we showed that the TS is the most frequently affected spinal segment in AS [6, 26]. Thus, all spinal segments may be affected by AS but the TS is most important. The fact that the TS is easily and usually included in MRI examinations of the spine is an advantage over conventional radiography. The performance of MRI to detect chronic spinal changes is rather good [20], but X-rays are still considered the gold standard.

As indicated in previous MRI studies on AS patients [6, 7, 19], both MRI techniques used here, the STIR and the $T_1$/Gd-DTPA MRI sequence, are valid for evaluation of active spinal lesions in AS. In the present study, both MRI techniques performed similarly well in scoring spinal inflammation due to AS. The two different MRI sequences correlated well at the baseline ($r = 0.86$) and the follow-up examination ($r = 0.91$). While the $T_1$/Gd-DTPA MRI sequences seemed to provide more specific results [7], the STIR scores were more sensitive to change. Thus, these MRI techniques provide rather complementary information related to the identification of active spinal lesions. However, in clinical practice STIR sequences may be preferable for practical reasons, because (i) more time is needed to perform the examination with Gd-DTPA, (ii) because of the additional risk for allergic reactions due to Gd-DTPA and (iii) because of the higher costs of this contrast agent.

In summary, the anti-inflammatory effect of infliximab on active spinal lesions of patients with AS, as detected by MRI, occurs after only 12 weeks of treatment and persists over a time period of 2 yr without loss of efficacy. However, although spinal inflammation decreased significantly in the patients treated with infliximab, some inflammatory lesions were still present in patients with AS after long-term infliximab therapy. This observation rather supports the view that continuous anti-TNF treatment is necessary. The finding that the clinical assessment of disease activity does not correlate well with MRI scores suggests that both types of information may be needed to assess response to anti-TNF therapy. The thoracic spine is the main localization of spinal inflammation in AS patients. There is as yet limited evidence that infliximab is able to decrease the progression of chronic spinal lesions in AS patients after 2 yr [28]. Larger studies are needed to provide evidence on that important issue.

<table>
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<tr>
<th>Rheumatology</th>
<th>Key messages</th>
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<td>• Infliximab is efficacious in patients with AS. This is demonstrated by long-term clinical and MRI examinations.</td>
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<tr>
<td>• This anti-inflammatory effect occurs after only 12 weeks’ treatment and remains persistent over 2 yr without loss of efficacy.</td>
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<tr>
<td>• Minor spinal inflammation is still present in patients with AS after 2 yr of infliximab therapy.</td>
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References