Radiographic progression in patients with ankylosing spondylitis after two years of treatment with the tumor necrosis factor-α antibody infliximab

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Abstract

Background: Anti-TNF therapy is clinically efficacious in patients with active ankylosing spondylitis (AS) and leads to improvement of spinal inflammation, as assessed by magnetic resonance imaging (MRI). It is unclear whether anti-TNF therapy has influence on chronic spinal changes in AS.

Objectives: To analyze the effect of infliximab on the radiographic course of AS over 2 years.

Methods: Complete sets of lateral radiographs of the cervical (CS) and the lumbar spine (LS) were available from 82 patients from two sources: 41 patients (group 1) had been treated with infliximab (5mg/kg/6 weeks) as part of a recent randomized controlled trial and 41 patients (group 2) were part of the early German AS cohort (GESPIC), without controlled interventions. Radiographs performed at baseline (BL) and after 2 years (FU) and were scored by the modified SASSS (mSASSS).

Results: Patients in the infliximab group were older, had a longer disease duration and more radiographic damage at baseline. The mean mSASSS change was 0.4 (±2.7) and 0.7 (±3.4) for group 1 and 2, respectively (p=n.s.). Radiographic damage at BL was a predictor for more radiographic progression. Patients with baseline damage who were treated with infliximab showed a trend for less radiographic progression. There were no correlations between clinical parameters and radiographic progression.

Conclusions: AS patients treated with infliximab showed somewhat less radiographic progression after 2 years. Patients with prevalent radiographic damage are prone to develop more damage over time. Infliximab may decelerate radiographic progression in such patients. Larger studies are needed to prove that anti-TNF therapy inhibits structural damage.

Introduction

Ankylosing spondylitis (AS) is a frequent chronic inflammatory rheumatic disease that affects young male and female patients [1] in the 2nd and 3rd decade of life. The leading clinical symptom is inflammatory back pain. The disease starts in the sacroiliac joints and spreads to the spine in most patients [2]. There are characteristic inflammatory features of AS such as sacroiliitis, spondylitis, spondylodiscitis and spondylarthritis which can be detected by conventional x-rays and, usually even better by magnetic resonance imaging (MRI) techniques [2, 3]. Most characteristic and pathognomonic for AS is the growth of syndesmophytes and other features of new bone formation possibly leading to ankylosis and spinal fusion. Typical osteoproliferative changes which can be detected by imaging techniques such as radiography and MRI can be found in different spinal structures such as vertebrae, discs, zygapophyseal and costovertebral joints, entheses and ligaments. Conventional radiography, the gold standard in imaging of AS for the last decades, has been included in the internationally accepted ASAS core set for AS [4].

Conventional treatment of AS with non-steroidal anti-inflammatory agents (NSAIDs) and physiotherapy is the standard of care, while therapy with disease controlling anti-rheumatic therapy (DCART) such as sulfasalazine and methotrexate is only used in subgroups of AS patients with peripheral arthritis and remitting anterior uveitis. Therapy of active AS patients with the anti-TNF agents infliximab and etanercept has shown a much stronger clinical efficacy in randomized controlled trials (RCT) [5, 6].
The changes assessable by imaging techniques that can be attributed to therapy may be acute and/or chronic. While improvement of active spinal lesions after therapy with infliximab has been demonstrated by using MRI even within a short time period [7], chronic spinal changes are mainly assessed by conventional x-rays [8]. Scoring of T1-weighted MR images has also been successfully used [9], but only by one group to date. The modified Stokes ankylosing spondylitis spinal score (mSASSS, [10]) has been identified as the most sensitive scoring method [11] for the evaluation of chronic spinal changes as assessed by conventional spinal x-rays in AS.

Since the ability of anti-TNF treatment to reduce or stop chronic structural changes in the spine of AS patients has not been evaluated to date, we analysed the data of the first investigator driven multicenter study performed in Germany which had a major influence on the approval of this drug [5, 12, 13]. Since no long-term placebo-controlled data are available to answer the question of structural changes we evaluated the chronic spinal changes in patients with AS who had been treated with infliximab for two years and compared these data with the available 2-year follow up x-rays of patients who had participated in the early cohort of German AS patients (GESPIC).

Methods

**Patient groups and study protocol**

All 82 patients included in this study fulfilled the modified New York diagnostic criteria for AS [14] and were taken from two different groups of AS patients: Group 1 consisted of 41 AS patients, taken from the first RCT on infliximab recently published [5, 13]. In this group, all patients were treated according to a standard protocol with 5mg/kg Infliximab i.v. continuously every 6 weeks. Group 2 consisted of another 41 AS patients selected randomly from the German AS cohort (GESPIC) and which were treated conventionally. The observation time period for all patients was 2 years, with assessment of two different time points: baseline (BL) and 2 years follow-up (FU). The patient’s characteristics at baseline are shown in Table 1.

**Radiographic assessment of the spine**

Lateral radiographs of the lumbar spine (CS) and the cervical spine (CS) were available from all patients who were included in this study. Radiographs were performed in all patients at two time points, at BL and at FU. After blinding for patients’ treatment and time order all images were scored by one experienced observer using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS, [10]). Comparison of the radiographic progression in each individual and every group was performed by evaluating the change of the mSASSS between time points.
**Radiographic scoring by the modified SASSS**

This scoring method is a modification of the original SASSS [15, 16]. It evaluates the anterior part of the lumbar and the cervical spine by assessing chronic changes using a score between 0 and 3 (Fig.1). The LS is scored from the lower border of the 12th thoracic vertebral body to the upper border of the first sacral vertebral body. The CS is scored from the lower border of the 2nd cervical vertebral body to the upper border of the first thoracic vertebral body. Thus, the score ranges from 0 – 72 scoring points. It is a known methodological problem of imaging and scoring procedures, that not all images may appear in perfect quality (over- or underexposure of the radiograph) or that the spinal segments are not always completely captured on one film, which might lead to missing of some sites. In this study, we excluded patients who had more than three vertebral sites missing. In the cases with ≤ 3 vertebral sites missing, the missing scores were substituted by the mean score of the vertebra of the same spinal segment of the patient.

With respect to the definition of mSASSS, definite radiographic damage at baseline was defined as a mSASSS score of ≥ 2 (appearance of at least one syndesmophyte) in at least one vertebral edge of each individual patient. Definite radiographic change (including worsening or improvement), was defined as a mSASSS change of more or equal than 2 scoring points in the mSASSS - in accordance with the data provided by Creemers et al. [17].

**Statistical analysis**

The correlation of the data at the two time points was calculated by Pearson’s correlation coefficient. Non parametric tests were applied to identify radiographic progression. For simple comparisons within each group the Wilcoxon test was used. For the comparison of the radiographic progression between group 1 and group 2 a test recently proposed by Brunner et al [18] was applied. This test adjusts for the observed differences at BL when actually comparing the differences in radiographic progression. A SAS macro provided by the authors [19] was used for this calculation. As scoring with mSASSS is very skewed but not normally distributed and the usual means are biased by extreme values, the pooled mSASSS scores of both time points and both groups were transformed into normalized rank scores (van der Waerden scores) which have a mean of 0 and a SD = 1 in order to further assess evaluation of radiographic progression. Changes in normalized rank scores were compared by analysis of covariance.

**Results**

**Patient’s characteristics at baseline**

Patients in the GESPIC cohort group were younger than patients in the infliximab group, and the mean disease duration was significantly longer in the infliximab group (p = 0.005 and p < 0.001, respectively). Furthermore, patients in the infliximab group showed a higher overall level of radiographic damage at BL (p = 0.026). Patients in
the infliximab group also had a higher level disease activity, as assessed by the Bath AS disease activity index (BASDAI [20]) at baseline. In order to be included in the RCT with infliximab, patients had to fulfill the criterion of a BASDAI > 4. Furthermore, there were significant differences between the two groups regarding the mean CRP level, the mean BASMI and the mean BASFI (data not shown). There were no differences between the groups regarding the proportion of male patients and of HLA-B27-positive patients, respectively (Tab. 1).

Descriptive analysis of the radiographic scorings over two years

The mean mSASSS for the patients in the infliximab group was 12.07 (± 16.9) and 12.48 (± 17.0) at BL and FU, respectively (p = 0.12), while the values for the patients in the GESPIC cohort were 5.85 (± 13.4) and 6.55 (± 14.8) for BL and FU, respectively (p = 0.07). Thus, the mean mSASSS change in the infliximab group was less than in the conventionally treated patients. Nevertheless, the comparison of the changes between the two groups did not reveal significant differences (Fig. 1 and 2).

When using normalized rank scores, a similar progression of chronic changes was found: patients in the infliximab group slightly worsened from a mean of 0.23 at BL to a mean of 0.27 at FU (p = n.s.), while the patients in the GESPIC cohort worsened from a mean of - 0.17 at BL to a mean of - 0.11 at FU (p = n.s.).

The proportion of patients with definite baseline damage (score ≥ 2 in at least one vertebral edge) was higher in the infliximab group with 24/41 patients (58.5%) compared to the GESPIC cohort with 13/41 patients (31.7%), (p = 0.015).

The proportion of patients with definite radiographic progression was similar in both groups: 7/41 patients (17.1%) in the infliximab group and 5/41 patients (12.2%) in the GESPIC cohort showed progression of ≥ 1 scoring point after 2 years (p = n.s.).

Radiographic progression in relation to the degree of baseline damage

When the pooled data of all 82 patients were analyzed regarding definite radiographic damage (at least one score ≥ 2 in at least one vertebral edge) at BL (37/82 patients = 45.1%), patients with radiographic damage at BL showed significantly higher rates of radiographic progression (mean mSASSS change 1.1 ± 3.9) over the entire study period of 2 years, compared to patients with no radiographic damage at BL (mean mSASSS change 0.2 ± 0.8), (p = 0.028), indicating that definite radiographic damage at BL is a prognostic factor associated with ongoing radiographic progression over time, possibly independent of therapy.

In the subgroup of patients with definite radiographic damage at BL there was no difference in the mSASSS between the two groups at baseline: the mean mSASSS in the infliximab group (n = 24) was 20.1 ± 18.0, while it was 17.1 ± 19.4 in the GESPIC cohort (n = 13), (p = n.s.).

However, in a subgroup analysis of those patients with definite damage at BL, the mean radiographic progression over 2 years showed a clear tendency for less progression of the mSASSS in the infliximab group (0.46 ± 3.5), compared to the GESPIC cohort (2.2 ± 4.8), (p = 0.08 by Brunner test), (Fig. 3).

Finally, by calculating normalized rank scores a similar trend with a mean radiographic progression of 0.002 for patients in the infliximab group and 0.1 for patients in the GESPIC cohort (p = 0.08) was found.
Correlation of mSASSS scores with clinical parameters

The mean mSASSS values correlated well with scores for spinal mobility for both groups. There was significant correlation between mSASSS and BASMI values in both groups at BL (r = 0.49 and r = 0.51 for the infliximab group and the GESPIC cohort, respectively, both p = 0.01) and at FU in the infliximab group (r = 0.59 and p = 0.01 for the infliximab group, r = 0.48 for the GESPIC cohort, p = 0.01). There was no correlation between mSASSS and all other clinical parameters at both time points. Similarly, there was no significant correlation between changes of clinical parameters and the change of the mSASSS over the entire study period (data not shown).

Discussion

The present study suggests that treatment with the anti-TNF antibody infliximab may have influence on the progression of chronic radiographic changes in patients with AS since a tendency for deceleration of x-ray progression with continuous infliximab therapy over 2 years was found by concentrating on the subgroup with most damage at baseline and over time.

Since our investigator driven clinical study was accepted by the European medicines agency (EMEA) as the major data source to approve infliximab for the treatment of the signs and symptoms of active AS patients in Europe we thought it important to analyze the 2-year data also in relation to structural damage. To achieve this we used the best x-ray scoring method available, the mSASSS [8, 17], which concentrates on lateral radiographs of the cervical and the thoracic spine with only the anterior rim of the vertebral bodies being scored, the total range is 0 – 72. The thoracic spine (TS) and zygapophyseal joints are not part of this x-ray based system because of the limited capacity of two-dimensional imaging at these sites.

As randomized controlled studies performed to compare the efficacy of anti-TNF agents vs. placebo in AS patients over 2 years are considered ethically not feasible at present, the only to way to gain information on the issue of structural damage is the comparison of the actual data with historical control populations.

In the moment there are only two cohorts available and only one has a large enough data set of radiographs, while the other data set is currently undergoing further analysis: the international longitudinal observational study of outcome in AS (OASIS, [8]) and the German Spondyloarthritis Inception Cohort [21]. While the data of the latter were directly available for us, we could only make the comparison with the OASIS data set on the basis of a recent publication with 133 patients from this cohort [8] who showed similar characteristics at baseline as the patients included in our infliximab group. Although the populations studied have different demographics, we were confident to do the analyses because we had data of more than 200 AS patients altogether available to compare the rates of radiographic progression.

In comparison to other cohorts, patients treated with infliximab showed somewhat less radiographic changes over 2 years (mean mSASSS change = 0.4) despite a higher mean age, a longer disease duration and a higher level of radiographic damage at baseline (all predictive of more damage over time) in comparison to the patients from the younger AS population (GESPIC, mean mSASSS change = 0.7) which were conventionally treated. In addition, the comparable patients of the OASIS
cohort showed clearly more mean radiographic progression (mSASS score 2.8 points) after two years, as compared to the infliximab group. When the two groups were compared after adjustment for baseline damage, the main predictor for radiographic progression, we saw a clear tendency for more radiographic progression after 2 years in the patients of the GESPIC cohort as compared to the patients treated with infliximab.

The finding that the radiographic progression in the whole population was not significantly different at the two time points can be mainly explained by the too small sample size of the study [13] which was not initially designed to look at structural damage as a primary endpoint. Secondly, as already mentioned, there are limitations to the scoring system because not all affected structures are included in the analyses. Thus, changes in the TS are not assessed by the mSASS because conventional x-rays of this part of the vertebral column are difficult to read and scores have a bad reliability due to the overimposed lung tissue. However, as recently confirmed this part of the spine is most frequently involved in AS [22]. Data from a recent imaging study have suggested that AS related chronic spinal changes can be reliably assessed using T1-weighted MRI sequences, also in the TS [9]. It is likely that the data set of the ASSERT [23] MRI study will help to further evaluate the usefulness of MRI to assess chronic changes in AS. The long term MRI data which have been partly obtained from this patient cohort treated with infliximab will be analysed in the near future.

Another important finding of this study is that AS patients with prevalent radiographic damage at presentation are significantly more disposed to more radiographic progression over time. This confirms a recent report published in abstract form [24]. As the efficacy of anti-TNF compounds on the progression of chronic spinal changes will be an important issue in ongoing and also in future studies, this needs to be taken into account when patients are selected and data are evaluated.

Most rheumatologists would assume that an increased disease activity is associated with chronic changes in AS patients. However, this is as yet unproven. Since infliximab has shown significant improvement of disease activity, both clinically and by MRI [7, 13, 25], it is possible that infliximab also affects chronic spinal changes demonstrated by x-rays in long term follow up studies. Interestingly, we did not find a correlation between the change of BASDAI scores or any other clinical parameters and the change of the mSASS over the entire study period for both groups. This might be due to the fact that improvement of disease activity is not directly linked to new bone formation and chronic changes. Thus, more extensive long term follow up examinations with larger patient numbers are needed to study this in more detail. Nevertheless, the radiographic scores at both time points correlated significantly with values of spinal mobility as assessed by the BASMI, which implicates that there is a direct relationship between radiological and clinical findings.

Taken together, this study suggests that chronic spinal lesions may progress more slowly in patients treated continuously with infliximab. More studies with larger patient numbers are needed to prove that radiographic progression can be inhibited by drug therapy. More evidence will hopefully derive from ongoing large trials with infliximab, etanercept and adalimumab. However, the spinal radiographs from in these trials will also be compared to historical cohorts since the study design did not include direct control groups.
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References


### Table 1: Patient’s characteristics for the two compared groups at baseline. Statistical significance between the two groups is marked with *.

<table>
<thead>
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<th>Infliximab group</th>
<th>GESPIC cohort</th>
<th>p-value</th>
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<tbody>
<tr>
<td>n</td>
<td>41</td>
<td>41</td>
<td>-------</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>38.9 (21-53)</td>
<td>34.8 (22-76)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Mean disease duration (disease rel. symptoms in years) (range)</td>
<td>15.5 (3-35)</td>
<td>5.5 (1-10)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Male</td>
<td>64.1%</td>
<td>70.7%</td>
<td>0.3</td>
</tr>
<tr>
<td>HLA-B27 pos.</td>
<td>91%</td>
<td>85.4%</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean BASDAI</td>
<td>6.3 (3.8-8.8)</td>
<td>3.2 (0.2-7)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Patients with mSASSS &gt; 0</td>
<td>56.1%</td>
<td>39%</td>
<td>0.05*</td>
</tr>
<tr>
<td>Mean mSASSS at baseline</td>
<td>12.1</td>
<td>5.9</td>
<td>0.026*</td>
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Figure legends:

**Fig. 1:** The modified Stokes Ankylosing Spondylitis Spine Score. Chronic spinal changes are assessed by scoring the anterior vertebral edge of each vertebra between the lower edge of C2 to the upper edge of Th1 and the lower edge of Th12 to the upper edge of S1.

**Fig. 2:** Comparison of the mean radiographic progression over the study period of 2 years for all patients in the two assessed groups.

**Fig. 3:** Example of a patient with radiographic progression. Erosion and sclerosis worsened to bridging syndesmophytes after the time period 2 years.

**Fig. 4:** Comparison of the mean radiographic progression over the study period of 2 years for patients with definite radiographic damage at baseline in the two assessed groups.
Figure 1

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>normal</td>
</tr>
<tr>
<td>1</td>
<td>erosion, sclerosis or squaring</td>
</tr>
<tr>
<td>2</td>
<td>syndesmophyte</td>
</tr>
<tr>
<td>3</td>
<td>bridging syndesmophyte</td>
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Figure 2

- Mean mSASSS change in the infliximab group: 0.41 ± 2.7
- Mean mSASSS change in the GESPIC cohort: 0.70 ± 2.8

Significance: p = 0.92
Figure 3
Figure 4

- Infliximab group: mean mSASSS change: 0.46 ± 3.5
- GESPIC cohort: mean mSASSS change: 2.20 ± 4.8

p = 0.085