RESEARCH ARTICLE

Spinal Radiographic Progression in Patients with Ankylosing Spondylitis Treated with TNF-α Blocking Therapy: A Prospective Longitudinal Observational Cohort Study

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Abstract

Objectives

To evaluate spinal radiographic damage over time and to explore the associations of radiographic progression with patient characteristics and clinical assessments including disease activity in ankylosing spondylitis (AS) patients treated with tumor necrosis factor-alpha (TNF-α) blocking therapy in daily clinical practice.

Methods

Consecutive outpatients from the Groningen Leeuwarden AS (GLAS) cohort were included based on the availability of cervical and lumbar radiographs before start of TNF-α blocking therapy and after 2, 4, and/or 6 years of follow-up. Clinical data were assessed at the same time points. Radiographs were scored by two independent readers using the modified Stoke AS Spine Score (mSASSS). Spinal radiographic progression in relation to clinical assessments was analyzed using generalized estimating equations.

Results

176 AS patients were included, 58% had syndesmophytes at baseline. Median mSASSS increased significantly from 10.7 (IQR: 4.6–24.0) at baseline to 14.8 (IQR: 7.9–32.8) at 6 years. At the group level, spinal radiographic progression was linear with a mean progression rate of 1.3 mSASSS units per 2 years. Both spinal radiographic damage at baseline and radiographic progression were highly variable between AS patients. Male gender, older age, longer disease duration, higher BMI, longer smoking duration, high CRP, and high...
ASDAS were significantly associated with syndesmophytes at baseline. Significantly more radiographic progression was seen in patients with versus without syndesmophytes (2.0 vs. 0.5 mSASSS units per 2 years) and in patients >40 versus ≤40 years of age (1.8 vs. 0.7 mSASSS units per 2 years). No longitudinal associations between radiographic progression and clinical assessments were found.

Conclusions
This prospective longitudinal observational cohort study in daily clinical practice shows overall slow and linear spinal radiographic progression in AS patients treated with TNF-α blocking therapy. At the individual level, progression was highly variable. Patients with syndesmophytes at baseline showed a 4-fold higher radiographic progression rate than patients without syndesmophytes.

Introduction
Ankylosing spondylitis (AS) is a chronic rheumatic inflammatory disorder which usually begins before the fourth decade of life. AS is characterized by inflammation in combination with new bone formation and bone loss. The disease mainly affects the axial skeleton and causes pain, stiffness, and impaired functioning of the spine. The disease course is found to be highly variable between AS patients. Excessive bone formation is an important disease outcome of AS. In the spine, this comprises the formation of syndesmophytes which may lead to complete fusion of the spine, resulting in a so-called ‘bamboo spine’. In most AS patients, it takes years from the first disease symptoms to manifestations of bone formation on radiographs [1]. Therefore, long-term follow-up is needed to investigate radiographic progression.

Tumor necrosis factor-alpha (TNF-α) blocking therapy leads to a clear improvement in disease activity, functional outcome measures, and quality of life in the majority of AS patients who do not respond to conventional treatment [1]. However, variable results have been reported regarding the effect of TNF-α blocking therapy on the development of spinal radiographic damage in AS. Multiple open-label extension studies did not show a significant difference in spinal radiographic progression after 2 years of TNF-α blocking therapy compared to TNF-α blocker naive AS patients from historical cohorts [2–5]. Two other open-label extension studies could not demonstrate an inhibition of spinal radiographic progression during 4 years of TNF-α blocking therapy [6,7]. However, in a retrospective study in only 22 AS patients, diminished radiographic progression was found after 4 to 8 years of TNF-α blocking therapy compared to AS patients from a historical cohort [8]. Furthermore, a large prospective longitudinal observational study with 1.5 to 9 years of follow-up reported that TNF-α blocker exposure (2.5 ± 2.8 years) was associated with less spinal radiographic progression [9].

These findings triggered the debate about the effect of TNF-α blocking therapy and the relationship between disease activity and spinal radiographic progression in AS. In previous cross-sectional and longitudinal studies in AS patients with a large variability in disease duration, disease activity, and treatment regimens, disease activity at baseline and over time were associated with spinal radiographic damage and progression [10–12]. Also, elevated inflammatory markers at baseline were found to be associated with the presence of syndesmophytes at baseline and with radiographic progression in AS patients and in early axial spondyloarthritis (SpA) [10,11]. Very recently, a longitudinal association between the AS Disease Activity Score...
(ASDAS) and radiographic progression was observed during 12 years of follow-up in a large cohort of AS patients mainly treated with non-steroidal anti-inflammatory drugs (NSAIDs) [12].

The aim of this prospective longitudinal cohort study was to evaluate spinal radiographic damage over time and to explore the associations of radiographic progression with patient characteristics and clinical assessments including disease activity in AS patients treated with TNF-α blocking therapy in daily clinical practice.

**Methods**

The present analysis was based on data from the Groningen Leeuwarden Ankylosing Spondylitis (GLAS) cohort. GLAS is an ongoing prospective longitudinal observational cohort study in the northern part of the Netherlands. Since November 2004, this cohort included consecutive AS outpatients who started TNF-α blocking therapy at the University Medical Center Groningen (UMCG) or the Medical Center Leeuwarden (MCL) because of active disease [13]. All patients were over 18 years of age, fulfilled the modified New York criteria for AS [14], and the ASAS criteria to start TNF-α blocking therapy (active disease defined as Bath AS Disease Activity Index (BASDAI) ≥4 and/or based on expert opinion) [15].

The choice of the TNF-α blocking agent (infliximab, etanercept, or adalimumab) was based on the judgment of the treating rheumatologist and/or the specific preference of the patient. As described previously, the standard regimen for infliximab was 5 mg/kg intravenously at 0, 2, 6 weeks and then every 8 weeks, for etanercept 50 mg (once) or 25 mg (twice) subcutaneous injection every week, and for adalimumab 40 mg subcutaneous injection every two weeks [16].

Patients were clinically evaluated at baseline, after 3 months, and then every 6 months according to a fixed protocol. Disease activity was measured at each follow-up visit and treatment continuation was based on BASDAI improvement (≥50% or two units compared with baseline) and/or expert opinion. Patients were allowed to switch between different TNF-α blocking agents and to receive concomitant medication as usual in daily clinical practice. Type, dose, and frequency of TNF-α blocking therapy were recorded at all follow-up visits. Temporary stop was registered and the total duration of exposure to TNF-α blocking therapy was expressed as the percentage of follow-up time.

Patients included in the analysis started with TNF-α blocking therapy between 2004 and October 2011 and had lateral radiographs of the cervical and lumbar spine available at baseline and after at least 1 follow-up visit at 2, 4 and/or 6 years.

The GLAS cohort was approved by the local ethics committees of the MCL and the UMCG. All patients provided written informed consent according to the Declaration of Helsinki.

**Data collection**

Baseline characteristics included: gender, age, symptom duration, time since diagnosis, HLA-B27 status, history of smoking (duration in years), and history of extra-articular manifestations.

At baseline and at each follow-up visit, disease activity was assessed with BASDAI [18], ASDASCRP [19,20], physician’s and patient’s global assessment (GDA), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Since all patients had high disease activity at baseline and in order to analyze whether baseline disease activity status was associated with spinal radiographic progression, cut-off values for very high disease activity as defined in previous studies were used to stratify patients: BASDAI >6 [12], ASDAS >3.5 [21], physician’s and patient’s GDA >6 [21], CRP >10 mg/L, and ESR >20 mm/hr [11]. Furthermore, body weight
and height were assessed to calculate body mass index (BMI), NSAID use was recorded, and ASAS-NSAID index was calculated [17].

Assessments of spinal radiographic damage

Lateral radiographs of the cervical and lumbar spine were independently scored by two trained readers (FM and RC). In order to blind readers for patient characteristics and time sequence, all identifying information including exam dates were removed from the radiographs. Radiographs were scored using the modified Stoke AS Spine Score (mSASSS). The anterior corners of lower C2 until upper Th1 and lower Th12 until upper S1 were scored for the presence of erosions, sclerosis, and/or squaring (1 point per vertebral site), non-bridging syndesmophytes (2 points per site), and bridging syndesmophytes (complete bridging of vertebrae; 3 points per site). The mSASSS was calculated as the sum of the scores of all individual sites (range 0–72). Patients with complete spinal ankylosis (mSASSS of 72) at baseline were excluded since no radiographic progression could occur in these patients. If ≥3 scores of vertebral sites were missing, the scores of these sites were substituted by the mean score of the vertebrae of the corresponding spinal segment, as proposed by Wanders et al. [22,23]. If >3 scores of vertebral sites were missing, the radiograph was excluded from the analysis. Radiographs were reassessed if the mSASSS total score of both readers differed by >5 units. When the discrepancy of >5 units persisted after reassessment, consensus was reached. The average mSASSS total score of both readers was used for the analysis.

Inter-observer reliability between readers for baseline mSASSS was very good, with an intra-class correlation coefficient (ICC; two-way mixed effects model, single measures, absolute agreement; before reassessment) of 0.987 (95% confidence interval (CI); 0.982–0.991). Inter-observer reliability for mSASSS change scores was moderate to good with ICC’s of 0.690 (95% CI: 0.596–0.765) for 0–2 year interval, 0.690 (95% CI: 0.545–0.794) for 2–4 year interval, and 0.400 (95% CI: 0.110–0.626) for 4–6 years interval. Bland-Altman plots revealed no systematic error. The mean difference in progression scores between the two readers was 0.1 (95% CI -3.2 –3.4) for all 2-years intervals (S1 Fig).

Presence of syndesmophytes at baseline was defined when both readers scored a non-bridging or bridging syndesmophyte (≥2 points) at one or more vertebral sites. Inter-observer reliability for presence of syndesmophytes was very good with Cohen’s kappa of 0.89 (95% CI 0.83 –0.96) and absolute agreement of 95%.

Definitions of spinal radiographic progression according to Baraliakos et al. were used to distinguish between slow progression (<2 mSASSS units within 2 years), moderate progression (2 to 5 mSASSS units within 2 years), and fast progression (>5 mSASSS units within 2 years) [24].

Statistical analysis

Results were expressed as mean ± SD or median (interquartile range (IQR)) for normally distributed and non-normally distributed data, respectively. Independent samples T-test, Mann-Whitney U test, Chi-Square test, and Fisher Exact test were used to compare differences in baseline characteristics between groups.

Generalized estimating equations (GEE) was used to analyze spinal radiographic progression over time within subjects and to calculate mean radiographic progression rate at the group level. Because correlations of spinal radiographic damage were approximately equal at different time points, the exchangeable correlation structure was used. Different models of time (linear, quadratic, cubic, square, logarithmic, and exponential) were used to investigate whether time was linear or non-linear associated with radiographic progression. In case residuals were non-
normally distributed, parameters were transformed (log or square root) before entered into the equation.

In the baseline analysis, interactions between time and the following patient characteristics and baseline clinical assessments were tested: gender, age, symptom duration, time since diagnosis, HLA-B27 status, BMI, duration of smoking, NSAID use, disease activity (BASDAI, ASDAS, physician’s and patient’s GDA, CRP, ESR), and presence of syndesmophytes. If interaction effects with time were found (p-values ≤ 0.05), the mean radiographic progression rate was calculated after stratification into subgroups based on clinically relevant or median values.

In the longitudinal analysis, the relationship between radiographic progression and disease activity, BMI, and NSAID use over time was investigated with an autoregressive marginal time-lag model. This model investigates the influence of disease activity at the start of a 2-year interval (eg. BASDAIt), BMI at the start of a 2-year interval (BMIIt), or mean cumulative NSAID use during a 2-year period (ASAS-NSAIDt−t+1) on the radiographic score at the end of a 2-year interval (mSASSSt+1), adjusted for the radiographic score at the start of this interval (mSASSSt) so radiographic progression was modeled. The following models were tested: mSASSSt+1 modeled by mSASSSt and BASDAIt, ASDASIt, physician’s GDAIt, patient’s GDAIt, CRPt, ESRT, BMIT, and ASAS-NSAIDt−t+1.

Statistical analysis was performed with IBM SPSS Statistics 22 (SPSS, Chicago, IL, USA). P values ≤ 0.05 were considered statistically significant.

Results

In total, 176 of the 267 AS patients who started with TNF-α blocking therapy between November 2004 and October 2011 were included in the analysis (Fig 1). Baseline characteristics of included patients were comparable to those who were excluded because of missing radiographs (n = 78) or >3 missing vertebral edges (n = 5) at baseline or at follow-up, except for symptom duration (median 14 vs. 17 years, p<0.05). Eight patients were excluded because of complete spinal ankylosis at baseline. These patients were older (mean 55 vs. 42 years, p<0.01) and had longer symptom duration (median 38 vs. 14 years, p<0.01).

Of the 176 included patients, 69% were male, mean age was 42 ± 11 years, median symptom duration 14 years (IQR: 7–24), and 77% were HLA-B27 positive (Table 1). History of inflammatory bowel disease, uveitis, psoriasis, and peripheral arthritis were seen in 11%, 32%, 7%, and 34% of the patients, respectively.

All patients had high disease activity at baseline (91% BASDAI ≥4, 99% ASDAS ≥2.1, and 68% CRP ≥6mg/L). Twenty-seven (15%) patients started with infliximab, 110 (63%) with etanercept, and 39 (22%) with adalimumab. During follow-up, 45 (26%) switched to another TNF-α blocking agent. Patients were exposed to TNF-α blocking therapy for 97% of the follow-up time (IQR: 83%- 100%).

Spinal radiographic damage and clinical assessments before the start of TNF-α blocking therapy

At baseline, median mSASSS was 11 (IQR: 5–24) and 102 (58%) patients had at least one syndesmophyte according to both readers. Patients with syndesmophytes at baseline were more frequently male, older, had longer symptom and diagnosis duration, higher BMI, longer duration of smoking, and had more often very high disease activity based on ASDAS (>3.5) and CRP (>10 mg/L) (Table 1).
Mean clinical follow-up time was 3.8 ± 1.8 years (range 1–7). During this period, 176, 151, 98, and 50 patients had mSASSS data available at baseline and after 2, 4, and 6 years of follow-up, respectively. Baseline characteristics were comparable in all these groups, only a significantly longer symptom duration and higher ASAS-NSAID index were seen in patients with 6 years data (Table 1 and S1 Table).

Median mSASSS increased significantly from 10.7 (IQR: 4.6–24.0) at baseline to 14.8 (IQR: 7.9–32.8) at 6 years (Table 2). At the group level, a linear time model revealed the best fit for the data. Mean progression rate was estimated at 1.3 mSASSS units per 2 years.

At the individual level, both spinal radiographic damage at baseline and radiographic progression over time were highly variable between AS patients (Fig 2). During the 2-years intervals, no or slow progression was found in 59–70%, moderate progression in 18–33%, and fast progression in 5–12% of the patients (Table 2).

The presence of syndesmophytes and older age were significantly associated with spinal radiographic progression. Patients with syndesmophytes at baseline had a 4-fold higher radiographic progression rate than patients without syndesmophytes (2.0 vs. 0.5 mSASSS units per 2 years). This increased progression rate also applies for patients with only 1 syndesmophyte compared to patients without syndesmophytes (1.8 vs. 0.5 mSASSS units per 2 years). Patients >40 years of age showed a 2.5-fold higher radiographic progression rate than patients ≤40 years (1.8 vs. 0.7 mSASSS units per 2 years) (Table 3).

Spinal radiographic progression and clinical assessments during TNF-α blocking therapy

Disease activity improved significantly during TNF-α blocking therapy. From baseline to 3 months, mean BASDAI improved from 6.1 to 3.2, mean ASDAS from 3.7 to 2.1, median physician’s GDA from 4 to 2, median patient’s GDA from 7 to 3, median CRP from 12 to 3 mg/L, and median ESR from 21 to 6 mm/hr (all p<0.001). These improvements remained stable.
Table 1. Baseline characteristics of the total AS study population and stratified by the presence or absence of syndesmophytes at baseline.

| Baseline syndemophytes | All patients (n = 176) | Present (n = 102) | Absent (n = 74) | p-value |
|-------------------------|-----------------------|-------------------|----------------|---------|
| Male gender             | 121 (69)              | 78 (77)           | 43 (58)        | 0.009   |
| Age (yrs)               | 42.3 ± 11.1           | 46.8 ± 10.1       | 36.2 ± 9.4     | <0.001  |
| Symptom duration (yrs)  | 14 (7–23)             | 18 (10–25)        | 10 (5–17)      | <0.001  |
| Time since diagnosis (yrs) | 5 (1–14)      | 8 (1–19)          | 3 (1–11)       | 0.011   |
| HLA-B27+                | 134 (77)              | 77 (76)           | 57 (77)        | 0.903   |
| BMI (kg/m²)             | 26.4 ± 4.1            | 27.2 ± 4.1        | 25.2 ± 3.7     | 0.004   |
| Smoking (yrs)           | 12 (0–22)             | 16 (0–25)         | 7 (0–16)       | 0.020   |
| NSAID use               | 130 (74)              | 79 (78)           | 51 (69)        | 0.203   |
| ASAS-NSAID index (0–100)| 50 (0–100)            | 50 (0–100)        | 40 (0–100)     | 0.602   |
| BASDAI (0–10)           | 6.1 ± 1.6             | 6.1 ± 1.5         | 6.0 ± 1.7      | 0.929   |
| BASDAI >6               | 84 (48)               | 52 (51)           | 32 (43)        | 0.310   |
| ASDASCRP                | 3.7 ± 0.8             | 3.8 ± 0.7         | 3.6 ± 0.8      | 0.150   |
| ASDAS >3.5              | 104 (60)              | 68 (68)           | 36 (49)        | 0.013   |
| Physician’s GDA (0–10)  | 4 (3–6)               | 4 (3–6)           | 4 (3–6)        | 0.701   |
| Physician’s GDA >6     | 34 (20)               | 23 (23)           | 11 (16)        | 0.238   |
| Patient’s GDA (0–10)    | 7 (5–8)               | 7 (5–8)           | 7 (6–8)        | 0.280   |
| Patient’s GDA >6       | 105 (60)              | 56 (55)           | 49 (66)        | 0.151   |
| CRP (mg/L)              | 12 (4–22)             | 14 (6–22)         | 9 (4–21)       | 0.141   |
| CRP >10 mg/L            | 97 (56)               | 63 (62)           | 34 (47)        | 0.038   |
| ESR (mm/hr)             | 21 (10–34)            | 20 (10–34)        | 21 (9–34)      | 0.832   |
| ESR >20 mm/hr           | 87 (50)               | 49 (49)           | 38 (52)        | 0.691   |
| mSASSS (range 0–72)     | 11 (5–24)             | 21 (12–38)        | 4 (2–7)        | <0.001  |

Values are presented as number of patients (%), mean ± SD, or median (IQR). AS: ankylosing spondylitis; HLA: human leukocyte antigen; BMI: body mass index; NSAID: non-steroidal anti-inflammatory drug; ASAS: Assessment of SpondyloArthritis international Society; BASDAI: Bath AS Disease Activity Index; ASDAS: AS Disease Activity Score; GDA: global disease activity; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; mSASSS: modified Stoke AS Spine Score.

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Table 2. mSASSS status and progression scores of AS patients who started with TNF-α blocking therapy.

| Status scores | Baseline (n = 176) | 2 year (n = 151) | 4 year (n = 98) | 6 year (n = 50) |
|---------------|--------------------|-----------------|----------------|---------------|
| Mean mSASSS   | 16.9 ± 16.7        | 17.5 ± 17.2     | 21.4 ± 18.5    | 21.4 ± 18.7   |
| Median mSASSS | 10.7 (4.6–24.0)    | 10.9 (4.6–25.5) | 15.0 (5.6–32.1)| 14.8 (7.9–32.8)|
| Progression  | 0–2 year (n = 151)| 2–4 year (n = 75)| 4–6 year (n = 42)|
| Mean change mSASSS | 1.3 ± 3.2 | 1.4 ± 2.8 | 1.3 ± 2.0 |
| Median change mSASSS | 0.8 (0.5–2.1) | 1.2 (0.6–2.8) | 1.0 (0.1–2.8) |
| <2 mSASSS units/2 years (slow) | 106 (70) | 44 (59) | 27 (64) |
| 2–5 mSASSS units/2 years (moderate) | 27 (18) | 25 (33) | 13 (31) |
| >5 mSASSS units/2 years (fast) | 18 (12) | 6 (8) | 2 (5) |

Values are presented as number of patients (%), mean ± SD or median (IQR). mSASSS: modified Stoke AS Spine Score.

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during long-term follow-up (data not shown). Mean BMI showed a small increase during follow-up, from 26.4 at baseline to 26.6 at 6 years (p < 0.05). NSAID use decreased significantly from 74% at baseline to 41%, 37%, and 25% at 2, 4, and 6 years, respectively (p < 0.001). Mean cumulative NSAID intake according to the ASAS-NSAID index decreased from 24.3 during the first 2 years to 14.4 and 9.2 during the 2–4 and 4–6 years time intervals, respectively (p < 0.001).

During TNF-α blocking therapy, no significant longitudinal associations were found between spinal radiographic progression and disease activity, BMI, or NSAID use over time (Table 4). Also the change in disease activity during the first 3 to 6 months, remission at 6 months (e.g. ASDAS < 1.3), prolonged remission (ASDAS < 1.3 for at least 2 consecutive visits), and change in NSAID use during the first 2 years were not significantly associated with spinal radiographic progression (data not shown). Only a trend was observed for the longitudinal association of CRP and ESR levels with radiographic progression (Table 4).

**Discussion**

This observational longitudinal cohort study prospectively investigated spinal radiographic damage over time and the associations of radiographic progression with patient characteristics.
and clinical assessments including disease activity in 176 AS patients treated with TNF-α blocking therapy in daily clinical practice. Spinal radiographic progression was linear at the group level with a mean progression rate of 1.3 mSASSS units per 2 years. This indicates that, on average, AS patients treated with TNF-α blocking therapy showed slow radiographic progression according to the definitions of Baraliakos et al. (<2 mSASSS units per 2 years) [24].

Radiographic progression was also linear during 12 years of follow-up in a large cohort of AS patients mainly treated with NSAIDs. In this cohort, the mean progression rate was estimated

### Table 3. Effect of time and time interactions with baseline characteristics on spinal radiographic progression.

|                                | β (95% CI) | p-value | Intervals | n  |
|--------------------------------|------------|---------|-----------|----|
| Time                           | 1.25 (1.10–1.40) | <0.001  | 475       | 176|
| Time*gender                    | 0.104      |         | 475       | 176|
| Time*age                       | 0.045      |         | 475       | 176|
| Age ≤40 years                  | 0.68 (0.49–0.90) |         | 206       | 75 |
| Age >40 years                  | 1.78 (1.64–1.93) |         | 269       | 101|
| Time*symptom duration          | 0.565      |         | 448       | 166|
| Time*time since diagnosis      | 0.516      |         | 465       | 171|
| Time*HLA-B27                   | 0.855      |         | 473       | 175|
| Time*BMI                       | 0.221      |         | 360       | 141|
| Time*smoking                   | 0.117      |         | 362       | 133|
| Time*NSAID use                 | 0.246      |         | 475       | 176|
| Time*ASAS-NSAID index          | 0.668      |         | 381       | 130|
| Time*BASDAI                    | 0.526      |         | 475       | 176|
| Time*ASDAS                     | 0.764      |         | 467       | 173|
| Time*Physician’s GDA           | 0.123      |         | 466       | 172|
| Time*Patient’s GDA             | 0.506      |         | 473       | 175|
| Time*CRP                       | 0.375      |         | 469       | 174|
| Time*ESR                       | 0.339      |         | 466       | 173|
| Time*syndesmophytes            | 0.022      |         | 475       | 176|
| Without syndesmophytes         | 0.52 (0.39–0.66) |         | 203       | 74 |
| With syndesmophytes            | 2.02 (1.88–2.17) |         | 272       | 102|

See Table 1 for abbreviations.

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### Table 4. Longitudinal analysis of the relationship between spinal radiographic progression and disease activity, BMI, and NSAID use.

|                                | β (95% CI) | p-value | Intervals | n  |
|--------------------------------|------------|---------|-----------|----|
| Previous mSASSS                | 1.02 (1.00–1.04) | <0.001  | 268       | 159|
| BASDAI                         | -0.02 (-0.15–0.10) | 0.737   | 259       | 159|
| ASDAS                          | 0.24 (-0.08–0.55) | 0.143   | 255       | 158|
| Physician’s GDA                | -0.05 (-0.19–0.09) | 0.497   | 264       | 156|
| Patient’s GDA                  | -0.03 (-0.16–0.10) | 0.637   | 267       | 159|
| CRP                            | 0.03 (0.00–0.06)  | 0.071   | 255       | 158|
| ESR                            | 0.03 (0.00–0.06)  | 0.056   | 252       | 158|
| BMI                            | -0.02 (-0.09–0.05) | 0.596   | 266       | 181|
| ASAS-NSAID index               | 0.00 (-0.01–0.01) | 0.905   | 196       | 87 |

See Table 1 for abbreviations.

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at 2.0 mSASSS units per 2 years [12,25]. Although the mean 2-year progression rate found in our patients treated with TNF-α blocking agents was lower, no conclusions can be made since a direct comparison between the two cohorts is lacking. Other studies in AS patients treated with TNF-α blocking therapy for 2–8 years showed variable mSASSS progression scores with a minimum of 0.4 and a maximum of 1.8 mSASSS units per 2 years [2–8].

Before start of TNF-α blocking therapy, all AS patients had high disease activity and more than half (58%) had syndesmophytes, which is comparable to the results of previous studies. In these previous studies, the proportion of patients with syndesmophytes at baseline varied from 30% in ‘early’ AS (≤10 years symptom duration) [11], 47–58% in AS patients with a variable disease activity status [25] to 55–61% in AS patients with active disease before start of TNF-α blocking therapy [7,8]. In accordance with earlier findings, we found that male gender, older age, elevated CRP levels, but also longer symptom and diagnosis duration, longer smoking duration, and ASDAS >3.5 were significantly associated with the presence of syndesmophytes at baseline [10,26]. Additionally, we found that patients with high disease activity and syndesmophytes at baseline had significantly higher BMI which suggests an association between disease activity, BMI, and radiographic damage. However, this could not be confirmed in the longitudinal analyses.

At the individual level, spinal radiographic progression was highly variable. The mean mSASSS progression rate was 4-fold higher in patients with syndesmophytes at baseline and 2.5-fold higher in patients >40 years of age. These findings indicate that radiographic progression during the treatment of TNF-α blocking therapy mainly occurs in older AS patients and in patients with more advanced disease. Previous studies with different treatment regimens also identified the presence of syndesmophytes at baseline as the most important predictor for the development of more radiographic damage in both ‘early’ axial SpA [11] and longstanding AS [2,10,24,27].

In our analyses, none of the disease activity assessments at baseline and over time were significantly associated with spinal radiographic progression. This is probably due to the low variability in disease activity since all patients had high disease activity before start of TNF-α blocking therapy and stable low disease activity during treatment. Moreover, the mean change in mSASSS at the group level was small, which makes it difficult to observe significant differences. This was also confirmed by the low observed regression coefficients of the time-lagged autoregressive GEE models. Historical longitudinal observational cohort studies in AS patients that have found significant relationships between disease activity and radiographic progression included patients with a high variability in disease activity status and treatment regimens [11,12]. In the Outcome in AS International Study (OASIS), patients with very high disease activity (ASDAS >3.5) over time showed an additional increase of 2.3 mSASSS units per 2 years compared to patients with inactive disease (ASDAS <1.3) [12]. In another analysis of the same cohort, ESR was significantly associated with the development of new syndesmophytes after 4 years of follow-up (OR 1.03, 95% CI: 1.00–1.07, p < 0.05) [10]. In 210 early axial SpA patients from the German Spondyloarthritis Inception Cohort (GESPIC), elevated ESR levels at baseline (>20 mm/hr) and time-averaged elevated CRP levels over 2 years (>6 mg/L) were significantly associated with spinal radiographic progression during 2 years of follow-up [11].

Previous studies in AS reported a positive effect of continuous use of NSAIDs on the reduction of radiographic progression [28,29]. In our study, NSAID use decreased rapidly over time resulting in very low ASAS-NSAID index scores, as expected in patients starting TNF-α blocking agents. Only 10% of the patients had a cumulative NSAID intake of ≥50 according to the ASAS-NSAID index and no effect on radiographic progression could be found. Furthermore, follow-up data on smoking was not available in this study and therefore we could not include
smoking in the longitudinal model to investigate this influence on spinal radiographic progression.

In the present study the reading of the radiographs was done without known time sequence which may lead to negative and smaller progression rates than when the reading was done in chronological time order [30]. Furthermore, it was not possible to draw conclusions about the effect of TNF-α blocking therapy on spinal radiographic progression, since AS patients without TNF-α blocking therapy were not included.

Conclusion

This large prospective observational cohort study in AS patients treated with TNF-α blocking therapy in daily clinical practice showed that spinal radiographic progression was overall slow and linear at the group level. At the individual level, radiographic progression was highly variable. Patients with syndesmophytes at baseline had a 4-fold increased radiographic progression rate and patients >40 years of age had a 2.5-fold increased radiographic progression rate. No longitudinal associations between radiographic progression and clinical assessments were found. A direct longitudinal comparison between cohorts with long-term follow-up and large study populations of AS patients treated with and without long-term TNF-α blocking therapy is required to evaluate the effect of this treatment and to further investigate the relationship between clinical assessment (e.g. disease activity) and spinal radiographic progression.

Supporting Information

S1 Fig. Bland-Altman plot representing the reliability of the mSASSS change scores. (TIF)

S1 Table. Baseline characteristics of AS patients with available 2, 4, or 6 years mSASSS data. (PDF)

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Author Contributions

Conceived and designed the experiments: AS EB EV SA. Performed the experiments: FM AS EB RB ME RC PO RW. Analyzed the data: FM. Contributed reagents/materials/analysis tools: FM AS NV EV SA. Wrote the paper: FM AS SA. Critically revised the manuscript: AS EB RB ME RC PO RW HB EV SA.

References

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007; 369: 1379–1390. PMID: 17448825
2. Baraliakos X, Listing J, Rudwaleit M, Brandt J, Sieper J, Braun J. Radiographic progression in patients with ankylosing spondylitis after 2 years of treatment with the tumour necrosis factor alpha antibody infliximab. Ann Rheum Dis. 2005; 64: 1462–1466. PMID: 15778240
3. van der Heijde D, Landewe R, Baraliakos X, Houben H, van Tubergen A, Williamson P, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis Rheum. 2008; 58: 3063–3070. doi: 10.1002/art.23901 PMID: 18821688
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4. van der Heijde D, Landewe R, Einstein S, Orty P, Vosse D, Ni L, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum. 2008; 58: 1324–1331. doi: 10.1002/art.23471 PMID: 18438853

5. van der Heijde D, Salonen D, Weissman BN, Landewé R, Maksymowych WP, Kupper H, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. Arthritis Res Ther. 2009; 11: R127. doi: 10.1186/ar2794 PMID: 19703304

6. Baraliakos X, Listing J, Brandt J, Haibel H, Rudwaleit M, Sieper J, et al. Radiographic progression in patients with ankylosing spondylitis after 4 yrs of treatment with the anti-TNF-alpha antibody infliximab. Rheumatology (Oxford). 2007; 46: 1450–1453. PMID: 17623745

7. Braun J, Baraliakos X, Hermann KG, Deodhar A, van der Heijde D, Inman R, et al. The effect of two golimumab doses on radiographic progression in ankylosing spondylitis: results through 4 years of the GO-RAISE trial. Ann Rheum Dis. 2014; 73: 1107–1113. doi: 10.1136/annrheumdis-2012-203075 PMID: 23644549

8. Baraliakos X, Haibel H, Listing J, Sieper J, Braun J. Continuous long-term anti-TNF therapy does not lead to an increase in the rate of new bone formation over 8 years in patients with ankylosing spondylitis. Ann Rheum Dis. 2014; 73: 710–715. doi: 10.1136/annrheumdis-2012-202698 PMID: 23505240

9. Haroon N, Inman RD, Leach TJ, Weisman MH, Lee M, Rahbar MH, et al. The impact of tumor necrosis factor α inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum. 2013; 65: 2645–2654. doi: 10.1002/art.38070 PMID: 23818109

10. van Tubergen A, Ramiro S, van der Heijde D, Dougados M, Mielants H, Landewé R. Development of new syndesmophytes and bridges in ankylosing spondylitis and their predictors: a longitudinal study. Ann Rheum Dis. 2012; 71: 518–523. doi: 10.1136/annrheumdis-2011-200411 PMID: 21895444

11. Poddubnyy D, Haibel H, Listing J, Märker-Hermann E, Zeidler H, Braun J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. Arthritis Rheum. 2012; 64: 1388–1398. doi: 10.1002/art.33465 PMID: 22127957

12. Ramiro S, van der Heijde D, van Tubergen A, Stolwijk C, Dougados M, van den Bosch F, et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. Ann Rheum Dis. 2014; 73: 1455–1461. doi: 10.1136/annrheumdis-2014-201518 PMID: 24812292

13. Arends S, Spoorenberg A, Houtman PM, Leijisma MK, Bos R, Kallenberg CG, et al. The effect of three years of TNF-alpha blocking therapy on markers of bone turnover and their predictive value for treatment discontinuation in patients with ankylosing spondylitis: a prospective longitudinal observational cohort study. Arthritis Res Ther. 2012; 14: R98. doi: 10.1186/ar3823 PMID: 22546520

14. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984; 27: 361–368. PMID: 6231933

15. Braun J, Davis J, Dougados M, Sieper J, van der Linden S, van der Heijde D. First update of the international ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. Ann Rheum Dis. 2006; 65: 316–320. PMID: 16096329

16. Arends S, Brouwer E, van der Veer E, Groen H, Leijisma MK, Houtman PM, et al. Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. Arthritis Res Ther. 2011; 13: R94. doi: 10.1186/ar3369 PMID:21689401

17. Dougados M, Simon P, Braun J, Burgos-Vargas R, Maksymowych WP, Sieper J, et al. ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. Ann Rheum Dis. 2011; 70: 47–52. PMID: 21989544

18. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994; 21: 2286–2291. PMID: 7699630

19. Lukas C, Landewe R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis. 2009; 68: 18–24. doi: 10.1136/ard.2008.094870 PMID: 18625618

20. van der Heijde D, Lie E, Kvien TK, Sieper J, Van den Bosch F, Listing J, et al.; Assessment of SpondyloArthritis international Society (ASAS). ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis. 2009; 68: 1811–1818. doi: 10.1136/ard.2008.100826 PMID: 19060001

21. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis. 2011; 70: 47–53. doi: 10.1136/ard.2010.138594 PMID: 21068095
22. Spoorenberg A, de Vlam K, van der Linden S, Dougados M, Mielants H, van de Tempel H, et al. Radiological scoring methods in ankylosing spondylitis. Reliability and change over 1 and 2 years. J Rheumatol. 2004; 31: 125–132. PMID: 14705231

23. Wanders AJ, Landewe RB, Spoorenberg A, Dougados M, van der Linden S, Mielants H, et al. What is the most appropriate radiologic scoring method for ankylosing spondylitis? A comparison of the available methods based on the Outcome Measures in Rheumatology Clinical Trials filter. Arthritis Rheum. 2004; 50: 2622–2632. PMID: 15334477

24. Baraliakos X, Listing J, von der Recke A, Braun J. The natural course of radiographic progression in ankylosing spondylitis—evidence for major individual variations in a large proportion of patients. J Rheumatol. 2009; 36: 997–1002. doi: 10.3899/jrheum.080871 PMID: 19332632

25. Ramiro S, Stolwijk C, van Tubergen A, van der Heijde D, Dougados M, van den Bosch F, et al. Evolution of radiographic damage in ankylosing spondylitis: a 12 year prospective follow-up of the OASIS study. Ann Rheum Dis. 2015; 74: 52–59. doi: 10.1136/annrheumdis-2013-204055 PMID: 23956249

26. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Märker-Hermann E, Zeidler H, et al. The early disease stage in axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum. 2009; 60: 717–727. doi: 10.1002/art.24483 PMID: 19248087

27. Baraliakos X, Listing J, Rudwaleit M, Haibel H, Brandt J, Sieper J, et al. Progression of radiographic damage in patients with ankylosing spondylitis: defining the central role of syndesmophytes. Ann Rheum Dis. 2007; 66: 910–915. PMID: 17329306

28. Kroon F, Landewé R, Dougados M, van der Heijde D. Continuous NSAID use reverts the effects of inflammation on radiographic progression in patients with ankylosing spondylitis. Ann Rheum Dis. 2012; 71: 1623–1629. doi: 10.1136/annrheumdis-2012-201370 PMID: 22532639

29. Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Märker-Hermann E, Zeidler H, et al. Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Ann Rheum Dis. 2012; 71: 1616–1622. doi: 10.1136/annrheumdis-2011-201252 PMID: 22459541

30. van Tuyl LH, van der Heijde D, Knol DL, Boers M. Chronological reading of radiographs in rheumatoid arthritis increases efficiency and does not lead to bias. Ann Rheum Dis. 2014; 73: 391–395. doi: 10.1136/annrheumdis-2012-202876 PMID: 23349128