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Radiographic damage and progression of the cervical spine in ankylosing spondylitis patients treated with TNF-α inhibitors: Facet joints vs. vertebral bodies☆,☆☆

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ABSTRACT

Objectives: To investigate radiographic damage and 4-year progression of the cervical facet joints in a prospective observational cohort of AS patients treated with TNF-α inhibitors, to compare this with damage and progression of the cervical vertebral bodies, and to study the relation with patient characteristics and clinical outcome.
Methods: Patients from the Groningen Leeuwarden AS (GLAS) cohort starting TNF-α inhibitors with baseline and 4-year radiographs were included. Cervical facet joints and vertebral bodies were scored by two independent readers according to the method of de Vlam and mSASSS, respectively.
Results: At baseline, 25 of 99 (25%) AS patients had partial or complete ankylosis of the cervical facet joints, whereas 51 (52%) patients had non-bridging or bridging syndesmophytes of cervical vertebral bodies. During 4 years, 13 (13%) patients developed new (partial) ankylosis of the facet joints, whereas 26 (26%) developed new (bridging) syndesmophytes. Facet joint damage and progression without involvement of the vertebral bodies were seen in 5 (5%) and 8 (8%) patients, respectively. Damage of facet joints was associated with longer disease duration, history of IBD/uveitis/psoriasis, higher disease activity, larger occiput-to-wall distance, higher mSASSS, and presence of syndesmophytes. Progression of the facet joints was associated with larger occiput-to-wall distance and more facet joint damage at baseline.
Conclusions: Cervical facet joints were frequently involved in AS. During 4 years of TNF-α blocking therapy, 13% of the patients showed radiographic progression of cervical facet joints of which the majority did not show progression of vertebral bodies.

Introduction

Ankylosing spondylitis is a chronic rheumatic disease characterized by inflammation and structural changes in the axial skeleton [1]. Radiographic damage of the spine is an important outcome for monitoring structural changes in AS [2]. Sacroiliitis and syndesmophyte formation, especially bridging syndesmophytes, are considered as the most characteristic structural changes in AS [1]. The prevalence of syndesmophytes is approximately 60% in AS patients with advanced disease [3–6]. Presence of syndesmophytes has been found to be the strongest predictor for the development of more spinal radiographic damage [3,6,7].

Besides structural changes at the vertebral bodies, facet (zygapophyseal) joints of the spine are also affected in AS [8,9]. Previous cross-sectional studies in AS patients with longstanding disease have shown that 20–50% of the patients had facet joint ankylosis in the cervical and/or lumbar spine [9–12]. A cross-sectional study in 50 AS patients noted that 8% of cervical facet

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joints were ankylosed without the presence of bridging syndesmophytes. Presence of facet joint ankylosis was associated with impaired spinal mobility, including less cervical rotation and lower (modified) Schober index [9]. This can hamper patients in their daily activities, for example, sports and car driving. Therefore, scoring the facet joints might be of additional value in evaluating structural outcome in AS.

However, facet joints are not included in the most commonly used scoring method to evaluate spinal radiographic damage and progression in AS, the modified Stoke AS spine score (mSASSS) [13,14]. As a consequence, radiographic progression of facet joints has never been reported in longitudinal observational studies or randomized controlled trials evaluating the effect of treatment.

Our aim was to investigate radiographic damage and 4-year progression of the cervical facet joints in a prospective observational cohort of AS patients who were treated with TNF-α inhibitors. Secondly, to compare this with damage and progression of the cervical vertebral bodies and to study the relation with patient characteristics and clinical outcome.

Methods

The present analysis was based on consecutive AS patients from the Groningen Leeuwarden AS (GLAS) cohort who started treatment with TNF-α inhibitors because of active disease between 2004 and 2008 and had lateral radiographs of the cervical spine available at baseline and after 4 years of follow-up.

The GLAS cohort is an ongoing prospective longitudinal observational cohort study that started in November 2004 [6,15]. Included patients were 18 years or older, fulfilled the modified New York criteria for AS and the ASAS criteria to start treatment with TNF-α inhibitors [16].

According to the GLAS study protocol, the following baseline characteristics were collected: gender, age, symptom duration, time since diagnosis, HLA-B27 status, body mass index (BMI), current smoking status (no/previous smoker vs. current smoker), smoking duration of current and past smokers in years, history of extra-articular manifestations [inflammatory bowel disease (IBD), uveitis, psoriasis], presence of peripheral arthritis (≥ 1 swollen joint; range: 0–44), use of non-steroidal anti-inflammatory drugs (NSAIDs; yes/no), and/or disease-modifying anti-rheumatic drugs (DMARDs; yes/no). Disease status was assessed using the Bath AS disease activity index (BASDAI), C-reactive protein (CRP), AS disease activity score ($ASDAS_{CRP}$), and Bath AS functional index (BASFI). Spinal kyphosis was measured using the occiput-to-wall distance. Cervical rotation to assess cervical spine mobility was introduced to our research protocol in 2009 and, therefore, only available at 4 years of follow-up.

The GLAS cohort was approved by the local ethics committees of the Medical Center Leeuwarden (MCL) and the University Medical Center Groningen (UMCG). All patients gave written informed consent according to the Declaration of Helsinki.

Radiological assessment of facet joints

Baseline and 4-year lateral radiographs of the cervical spine were scored by two trained and independent readers (F.M. and R.C.). Readers were blinded to patient characteristics and time sequence by removing all identifying information and performance date from the radiographs.

Readers scored the facet joints of C2–C3 up to C6–C7 on the lateral view of the cervical spine according to the method of de Vlam et al. [9]: 0 = normal, 1 = joint space narrowing or erosion, 2 = partial blurring or ankylosis, and 3 = complete blurring or ankylosis. Using this method, the left and right facet joints are scored simultaneously since they are projected over each other on the lateral radiograph. Facet joints not visible on spinal radiographs or difficult to score due to degenerative changes were scored as missing. C6–C7 level was missing in 4 (4%) patients at baseline and in 3 (3%) patients at 4 years. The remaining levels (C2–C3 to C5–C6) could be assessed in all patients. In a facet joint could not be scored, the missing score was substituted by the mean score of remaining facet joints. The facet joint total score was calculated as the sum of the 5 cervical facet joints (range: 0–15). For the analysis, the average of the total scores of the two readers was used.

Definite damage or definite progression of facet joints was defined as the presence or development of partial/complete blurring or ankylosis (score $\geq$ 2) in one or more facet joints, respectively. When there was discrepancy between readers regarding definite damage or progression (score 2 and 3), facet joints were reassessed by the same readers. A third independent reader (A.S.) scored the facet joints when discrepancy persisted after reassessment. The score of the primary reader closest to the third reader was used.

Inter-observer reliability for definite damage and definite progression was good with Cohen's κ of 0.81 and 0.60, respectively, with high percentages of absolute agreement ($\geq$92%). Inter-observer reliability for the total facet joint score was very good with an intra-class correlation coefficient (ICC: two-way mixed effects model, single measures, absolute agreement) of 0.95 (95% CI: 0.92–0.97) and moderate for progression with an ICC of 0.58 (95% CI: 0.43–0.70).

Radiological assessment of vertebral bodies

The same two readers scored the anterior corners of the vertebral bodies (lower C2 until upper Th1) on the lateral view of the cervical spine according to the mSASSS: 0 = no damage, 1 = presence of erosions, sclerosis, and/or squaring, 2 = non-bridging syndesmophyte, and 3 = bridging syndesmophyte [13,14]. Vertebral corners not visible on spinal radiographs or difficult to score due to degenerative changes were scored as missing. Lower C2 up to upper C6 was missing in 0–1% of the patients, lower C6 and upper C7 was missing in 10%, and lower C7 and upper Th1 was missing in 50% of the patients. The cervical mSASSS total score was calculated as the sum of the scores of all individual cervical vertebral corners (range: 0–36). For this calculation, the method of Wanders et al. was used, that is, $\leq$3 missing scores were substituted by the mean score of the remaining vertebral corners of the cervical spine. Total cervical mSASSS was not calculated if $>$3 scores were missing (in 2% of the patients) [14]. For the analysis, the average of the total scores of the two readers was used.

Definite damage or definite progression of vertebral bodies was defined as the presence or development of $\geq$1 non-bridging or bridging syndesmophyte (score $\geq$2) at one or more vertebral corners, respectively. In case of discrepancy between readers regarding definite damage or progression (scores 2 and 3), the same procedure of reassessment was followed as described for the facet joints.

Inter-observer reliability for definite damage and definite progression was very good with Cohen's κ of 0.94 and 0.92, respectively, with high percentages of absolute agreement (both 97%). Inter-observer reliability for cervical mSASSS status and progression scores was very good with ICC of 0.99 (95% CI: 0.98–0.99) and 0.79 (95% CI: 0.69–0.85), respectively.

Statistical analysis

Descriptive statistics were used to express the proportion of AS patients with radiographic damage and progression of facet joints

and vertebral bodies. Chi-square or Fisher exact test, Independent samples *t*-test, and Mann–Whitney *U* test were used as appropriate to compare patient characteristics and clinical outcome between groups. Univariable and multivariable logistic regression analysis (conditional stepwise forward method) were performed to investigate independent predictors for facet joint involvement. In case variables were highly correlated, the variable with the highest predicted value was included in the multivariable model.

Multivariable logistic regression analysis was also used to explore the association of facet joint involvement with physical function and spinal mobility after correcting for known confounding variables (cervical mSASSS and disease activity).

Descriptive statistics using cross-tabs were used to compare damage and progression of facet joints with damage and progression of vertebral bodies at the group level and at the single inter-vertebral level. At the group level, all evaluated cervical facet joints (C2–C3 up to C6–C7) and cervical vertebral bodies (C2–C3 up to C7–Th1) were compared. A sensitivity analysis was performed after exclusion of C7–Th1 level from the cervical mSASSS in order to include the same vertebral levels as the scored facet joints. At the single inter-vertebral level, facet joints and vertebral bodies of C2–C3 up to C6–C7 level were compared. The correlation between total scores was calculated using Spearman's correlation coefficient. $p \leq 0.05$ was considered as statistically significant. Statistical analysis was performed with IBM SPSS Statistics 22 (SPSS, Chicago, IL).

Results

A total of 173 AS patients were included in the GLAS cohort and started with TNF-α blocking therapy between 2004 and 2008. Altogether, 30 (17%) patients were excluded because they dropped out from the GLAS cohort or discontinued TNF-α inhibitors within the 4 years period, and 44 (25%) patients had no cervical radiographs available at baseline and/or 4 years of follow-up. The 30 patients who discontinued the cohort or TNF-α inhibitors had comparable baseline characteristics as the 143 patients who continued the cohort, except for a lower presence of peripheral arthritis (3% vs. 21%, $p < 0.05$). The 44 patients without cervical radiographs had comparable baseline characteristics as the 99 patients who were included in this study, except they were less frequently male (57% vs. 76%, $p < 0.05$), had higher BASDAI (mean: 6.5 vs. 5.9, $p < 0.05$), and higher BASFI (median: 6.4 vs. 5.7, $p < 0.05$).

The mean follow-up of the 99 included AS patients was 4.1 ± 0.4 years. As shown in Table 1, patients had active disease at baseline; 19 (19%) patients started with infliximab, 63 (64%) with etanercept, and 17 (17%) with adalimumab. During 4 years of follow-up, 20 (21%) switched to another TNF-α inhibitor. These 20 patients had comparable baseline characteristics as the 79 patients who stayed on the first TNF-α inhibitor (data not shown). Patients were exposed to TNF-α inhibitors for 3.8 ± 0.5 years.

Baseline damage

Facet joints

At baseline, 25 (25%) patients had definite damage (score ≥ 2) of at least one cervical facet joint; 21 patients showed complete ankylosis (score 3) of at least one cervical facet joint. On average, 3.4 facet joints per patient were involved. Complete ankylosis of all cervical facet joints (score 15) was present in 2 (2%) patients. The mean cervical total facet joint score was 2.6 ± 4.4, median score was 0 (IQR: 0–4). Definite damage (score ≥ 2) was seen at all inter-vertebral levels (Fig. A). Ankylosis was mainly seen at C2–C3 level (Fig. B).

Table 1
Baseline characteristics of included AS patients

	All patients $n = 99$
Male gender	75 (76)
Age (years)	41.9 ± 11.1
Symptom duration (years)	16 (7–24)
Time since diagnosis (years)	7 (2–16)
HLA-B27+	83 (84)
BMI (kg/m^2)	26.2 ± 3.6
Current smoker	30 (37)
Total smoking duration (years)	12 (0–25)
History of IBD	9 (9)
History of uveitis	28 (29)
History of psoriasis	11 (11)
Peripheral arthritis	21 (21)
NSAID use	80 (85)
DMARD use	23 (23)
BASDAI (0–10)	5.9 ± 1.6
$ASDAS_{CRP}$	3.8 ± 0.8
CRP (mg/L)	15 (7–25)
BASFI (0–10)	5.7 (3.8–7.1)
Occiput-to-wall distance (cm)	5.0 (0.0–11.5)
Total mSASSS (0–72)	13.5 (5.5–35.2)
Cervical facet joint score (0–15)	0.0 (0.0–3.0)
Definite damage of ≥1 facet joint (score ≥ 2)	25 (25)
Complete ankylosis of ≥1 facet joint (score 3)	21 (21)
Complete ankylosis of all facet joints (score 15)	2 (2)
Cervical mSASSS (0–36)	6.6 (2.4–17.4)
Definite damage of ≥1 vertebral body (score ≥ 2)	51 (52)
Bridging syndesmophyte of ≥1 vertebral body (score 3)	36 (36)
Bridging syndesmophytes of all vertebral bodies (score 36)	8 (8)

Values are presented as number of patients (%), mean ± SD, or median (IQR).
Cervical rotation (average of left and right rotation) was only available at 4 years: median 65 (IQR: 38–80).
AS: ankylosing spondylitis; HLA: human leukocyte antigen; BMI: body mass index; NSAID: non-steroidal anti-inflammatory drug; DMARD: disease-modifying anti-rheumatic drug; BASDAI: Bath AS Disease Activity Index; ASDAS: AS Disease Activity Score; GDA: global disease activity; CRP: C-reactive protein; BASFI: Bath AS functional index; mSASSS: modified Stoke AS Spine Score.

Patients with definite damage of the facet joints had significantly longer symptom duration and time since diagnosis, more often a history of extra-articular manifestations (IBD, uveitis, and psoriasis), higher disease activity (ASDAS and CRP), larger occiput-to-wall distance, and more damage of the vertebral bodies at baseline (Table 2). Multivariable logistic regression analysis showed that time since diagnosis (OR = 1.09, 95% CI: 1.02–1.17) and cervical mSASSS (OR = 1.10, 95% CI: 1.05–1.16) were independently associated with definite facet joint damage at baseline.

Additional analysis at 4 years showed that patients with facet joint damage also had significantly worse cervical rotation than patients without facet joint damage (median 35° vs. 72°, $p < 0.001$). This association remained highly statistically significant after correcting for disease activity and cervical mSASSS at 4 years. Multivariable logistic regression analysis model showed that cervical rotation was the only independent risk factor for presence of cervical facet joint damage. Better cervical rotation was significantly associated with a reduced risk for facet joint damage (OR = 0.94, 95% CI: 0.92–0.98).

Vertebral bodies

At baseline, 51 (52%) patients had definite damage (score ≥ 2) of at least one cervical vertebral body; 36 patients showed at least one bridging syndesmophyte (score 3). Bridging syndesmophytes between all cervical vertebral bodies (score 36) were present in 8 (8%) patients. The mean cervical mSASSS was 11.3 ± 11.4, median score was 6.6 (IQR: 2.4–17.4).

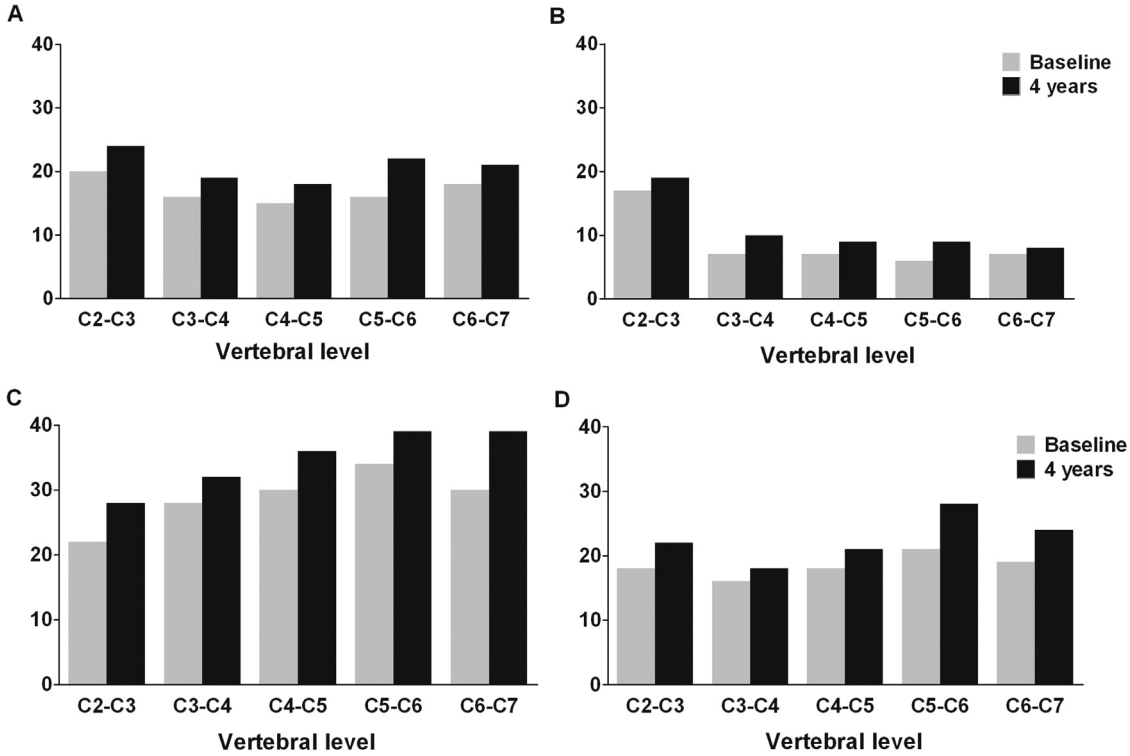

Fig. Location (C2–C7) and number of patients with definite damage of facet joints (A), complete ankylosis of facet joints (B), definite damage of vertebral bodies (C), and bridging syndesmophytes of vertebral bodies (D) at baseline and after 4 years of TNF-α treatment.

After exclusion of the C7–Th1 level in order to include the same vertebral levels as the scored facet joints, 49 (49%) patients had definite damage of vertebral bodies and 34 (34%) patients had bridging syndesmophytes. Non-bridging and bridging syndesmophytes occurred at all levels equally (Fig. C and D).

Table 2
Baseline characteristics of AS patients with and without definite damage (score ≥ 2) and with and without definite progression of facet joints (to score ≥ 2)

	Definite damage of facet joints			Definite progression of facet joints		
	Yes $n = 25$	No $n = 74$	p Value	Yes $n = 13$	No $n = 86$	p Value
Male gender	22 (88)	53 (72)	0.099	9 (69)	66 (77)	0.510
Age (years)	45.5 ± 9.3	40.7 ± 11.5	0.062	43.5 ± 14.2	41.7 ± 10.7	0.840
Symptom duration (years)	23 (18–30)	12 (6–22)	< **0.001**	23 (11–29)	16 (7–23)	0.145
Time since diagnosis (years)	15 (7–21)	4 (1–12)	< **0.001**	9 (5–21)	7 (1–15)	0.119
HLA-B27+	21 (84)	62 (84)	1.000	12 (92)	71 (83)	0.687
BMI (kg/m^2)	26.2 ± 3.0	26.1 ± 3.8	0.944	26.4 ± 2.9	26.1 ± 3.7	0.752
Current smoker	7 (35)	23 (37)	0.866	3 (30)	27 (38)	0.739
Total smoking duration (years)	3 (0–18)	14 (0–26)	0.089	7 (0–27)	12 (0–25)	0.657
History of IBD	5 (20)	4 (9)	**0.045**	2 (15)	7 (8)	0.341
History of uveitis	11 (44)	17 (23)	**0.048**	6 (46)	22 (26)	0.132
History of psoriasis	6 (24)	5 (7)	**0.018**	2 (15)	9 (11)	0.635
Peripheral arthritis	4 (16)	17 (23)	0.578	1 (7)	20 (23)	0.289
NSAID use	23 (96)	57 (81)	0.107	12 (100)	68 (83)	0.202
DMARD use	5 (20)	18 (24)	0.658	4 (31)	19 (22)	0.493
BASDAI (0–10)	5.9 ± 1.6	5.9 ± 1.7	0.993	5.6 ± 1.1	5.9 ± 1.7	0.317
$ASDAS_{CRP}$	4.0 ± 0.7	3.7 ± 0.8	**0.049**	4.0 ± 0.6	3.8 ± 0.8	0.186
CRP (mg/L)	17 (12–41)	14 (6–23)	**0.046**	20 (15–42)	14 (7–24)	0.088
BASFI (0–10)	6.3 (4.6–7.1)	5.3 (3.1–7.1)	0.072	6.5 (4.4–7.0)	5.5 (3.6–7.1)	0.291
Occiput-to-wall distance (cm)	12.7 (5.4–15.3)	3.8 (0.0–8.0)	< **0.001**	9.0 (5.8–13.0)	4.5 (0.0–10.0)	**0.027**
Total mSASSS (0–72)	35.7 (15.9–54.9)	9.6 (3.8–24.2)	< **0.001**	23.6 (7.7–47.2)	11.5 (5.4–30.0)	0.151
Cervical facet joint score (0–15)	11.0 (5.0–12.0)	0.0 (0.0–1.0)	–	6.0 (2.5–11.0)	0.0 (0.0–1.3)	< **0.001**
Definite damage (score ≥ 2)	25 (100)			10 (77)	15 (17)	< **0.001**
Complete ankylosis (score 3)	21 (84)			8 (62)	13 (15)	< **0.001**
Cervical mSASSS (0–36)	27.6 (9.2–33.7)	4.0 (1.7–10.0)	< **0.001**	12.6 (6.7–30.4)	5.9 (2.4–16.2)	0.085
Definite damage (score ≥ 2)	20 (80)	31 (42)	**0.001**	10 (77)	41 (48)	0.073
Bridging syndesmophyte (score 3)	18 (72)	18 (24)	< **0.001**	7 (54)	29 (34)	0.160

Values are presented as number of patients (%), mean ± SD, or median (IQR).
See Table 1 for abbreviations.
Values in bold represent statistically significant p-values ($p \leq 0.05$).

Table 3
Presence of definite damage (score ≥ 2) and complete ankylosis (score 3) of the cervical facet joints in comparison to damage of the cervical vertebral bodies

	Yes	No	Total
Definite damage of ≥1 facet joint			
Definite damage of ≥1 vertebral body			
Yes	20 (20)	31 (31)	51 (51)
No	5 (5)	43 (44)	48 (49)
Total	25 (25)	74 (75)	99 (100)
Complete ankylosis of ≥1 facet joint			
Bridging syndesmophytes of ≥1 vertebral body			
Yes	14 (14)	22 (22)	36 (36)
No	7 (7)	56 (57)	63 (64)
Total	21 (21)	78 (79)	99 (100)

Values are presented as number of patients (%).

Patients with definite damage of the vertebral bodies were more frequently male, older, had longer symptom duration, and time since diagnosis, higher BMI, worse physical function, larger occiput-to-wall distance, and more damage of the facet joints (Supplementary Table S1).

Facet joints vs. vertebral bodies

Definite damage of both cervical facet joints and cervical vertebral bodies was seen in 20 (20%) patients and in 9–14% of the individual inter-vertebral levels (Table 3 and Supplementary Table S2). Definite damage of cervical facet joints without involvement of cervical vertebral bodies was seen in 5 (5%) patients and in 4–8% of the individual inter-vertebral levels.

In comparison, definite damage of cervical vertebral bodies without involvement of cervical facet joints was seen in 31 (31%) patients and in 10–25% of the individual inter-vertebral levels. Comparable patterns were observed for ankylosis (Table 3 and Supplementary Table S2).

Total cervical facet joint score correlated moderately with cervical mSASSS ($\rho = 0.535$, $p < 0.001$).

Sensitivity analysis after exclusion of C7–Th1 level from the mSASSS revealed similar results (data not shown).

Progression after 4 years of TNF-α inhibitors

Facet joints

After 4 years of follow-up, 13 (13%) patients developed definite progression (score ≥ 2) of at least one cervical facet joint; 8 patients developed complete ankylosis (score 3) of at least one cervical facet joint. The mean change in total facet joint score was 0.3 ± 1.0, median change was 0 (IQR: 0–0). Progression was seen at all inter-vertebral levels (Fig. A and B).

Patients with definite progression of the facet joints had significantly larger occiput-to-wall distance and more damage of facet joints at baseline (Table 2). Multivariable logistic regression analyses showed that baseline facet joint score was the independent predictor for definite progression of facet joints (OR = 1.21, 95% CI: 1.08–1.35).

Vertebral bodies

In comparison, 26 (26%) patients developed definite progression (score ≥ 2) of at least one cervical vertebral body; 16 patients developed at least one bridging syndesmophyte (score 3) between vertebral bodies. The mean change in cervical mSASSS was 1.6 ± 3.1, median change was 0.6 (IQR: 0.0–2.4).

Exclusion of C7–Th1 level resulted in the same patients with progression of vertebral bodies since no progression was observed at C7–Th1 level. Progression was seen at all other vertebral levels (Fig. C and D).

Patients with definite progression of vertebral bodies were significantly older, had longer symptom duration, higher BMI, and more damage of vertebral bodies at baseline (Supplementary Table S1).

Facet joints vs. vertebral bodies

Definite progression of cervical facet joints was not concurrent with definite progression of cervical vertebral bodies in 8 (8%) patients (Table 4). Of these 8 patients, 1 patient already had complete ankylosis of all vertebral bodies at baseline.

Progression to complete ankylosis of facet joints was not concurrent with progression to bridging syndesmophytes of vertebral bodies in 5 (5%) patients (Table 4).

The correlation between change in total cervical facet joint score and change in cervical mSASSS was low ($\rho = 0.187$, $p = 0.07$).

An additional analysis was performed in which the cervical facet joint scores were added to the total mSASSS. This analysis showed that 6 (6%) extra patients had definite progression according to this combined score than according to the mSASSS alone.

Discussion

This prospective longitudinal observational cohort study in AS patients with active disease showed that 25% of the patients had partial or complete ankylosis of cervical facet joints and 52% of the patients had non-bridging or bridging syndesmophytes of the cervical vertebral bodies. After 4 years of TNF-α blocking therapy, 13% developed new complete or partial ankylosis of cervical facet joints and 26% developed new non-bridging or bridging syndesmophytes of the vertebral bodies.

Although more patients had radiographic damage and progression of the cervical vertebral bodies, the present study showed that facet joints are frequently involved in AS and not always concurrent with damage or progression of vertebral bodies. Partial or complete ankylosis of the cervical facet joints without presence of syndesmophytes was seen in up to 7% of the patients and in up to 8% of the individual inter-vertebral levels. This pattern was also observed in a previous smaller cross-sectional study in 50 AS patients with comparable disease duration but with unknown disease activity and mSASSS status scores [9]. Scoring the cervical facet joint resulted in 8% and 6% more patients with definite progression in addition to the patients with definite progression according to the cervical and total mSASSS, respectively. Although this seems not a large percentage, this might be of additional relevance, not only at the group level but especially at individual patient level. AS is an overall slowly progressive disease in which

Table 4
Development of definite progression (to score ≥ 2) and progression to complete ankylosis (to score 3) of cervical facet joints in comparison to progression of vertebral bodies after 4 years of TNF-α treatment

	Yes	No	Total
Definite progression of ≥1 facet joint			
Definite progression of ≥1 vertebral body			
Yes	5 (5)	21 (21)	26 (26)
No	8 (8)	65 (66)	73 (74)
Total	13 (13)	86 (87)	99 (100)
Progression to complete ankylosis of ≥1 facet joint			
Progression to bridging syndesmophyte of ≥1 vertebral body			
Yes	3 (3)	13 (13)	16 (16)
No	5 (5)	78 (79)	83 (84)
Total	8 (8)	91 (92)	99 (100)

Values are presented as number of patients (%).

radiographic damage and progression is highly variable between individual patients.

Cervical facet joint damage was associated with longer disease duration and more severe disease, including higher disease activity, larger occiput-to-wall distance, and more damage of the vertebral bodies. Importantly, cervical rotation was independently associated with cervical facet joint damage. This underlines that cervical spinal function is influenced by radiographic damage of these joints. A very interesting additional finding was the association between facet joint damage and a history of IBD, uveitis, and psoriasis. This association was not present for damage of the vertebral bodies. Previous studies showed that complete facet joint ankylosis is common in psoriatic arthritis (PsA) with reported prevalence rates ranging between 11% and 29% [17,18]. The association with uveitis has also been found in the earlier mentioned, small cross-sectional study of 50 AS patients, in which 37% of patients with facet ankylosis had a history of uveitis [9]. A history of uveitis is strongly associated with disease duration since the proportion of patients with a history of uveitis becomes higher with increasing age and disease duration [19]. This could explain why disease duration instead of a history of uveitis was an independent risk factor for the presence of facet joint damage at baseline in our study.

Until now, predictors of radiographic progression of the facet joints have not been investigated. From previous studies evaluating predictors of radiographic progression of the vertebral bodies, it is known that the presence of baseline syndesmophytes is the most important prognostic factor [20]. Our longitudinal analysis showed that baseline syndesmophytes was indeed associated with radiographic progression of vertebral bodies, but not with progression of the facet joints. Interestingly, we found that baseline facet joint damage was the most important predictor of radiographic progression of these joints.

Previously, it has been suggested that facet joint damage is nonspecific for AS since these joints can be affected by degenerative changes [21]. To take this into account, we did not score abnormalities in combination with clear degenerative changes such as a decrease in disk space height and horizontal bone spurs in the present study. Additionally, we used a cut-off value of score ≥ 2 representing partial/complete ankylosis to define facet joint damage as a result of the AS disease process. We did not found a higher prevalence of facet joint damage at C4–C5 level, the level in which degenerative changes mainly occur according to a previous study in 58 patients with degenerative spondylolisthesis [22]. Interestingly, we found that 7 (28%) of the 25 patients with facet joint damage were younger than 40 years of age. Longer symptom duration, time since diagnosis, and higher disease activity (ASDAS and CRP), and not age, were significantly associated with facet joint damage. This is in line with previous findings [9]. Finally, an immunohistological analysis of bone marrow from facet joints from patients with advanced AS showed increased numbers of T and B cells demonstrating inflammation in these joints [23]. All these findings demonstrate that facet joint damage is AS specific.

This was the first longitudinal study that included cervical facet joints in the assessment of spinal radiographic damage during follow-up and after starting treatment with TNF-α inhibitors. We would like to emphasize that our goal was not to investigate the influence of treatment on radiographic progression. The design of this cohort study does not allow any conclusions on this subject. There are some additional limitations involved in this study. Radiographic involvement of both facet joints and vertebral bodies might be underestimated since patients with higher BASDAI and BASFI were excluded due to missing radiographs. Radiographic damage was assessed on the lateral view of the cervical spine according to the method of de Vlam et al. [9], the only investigated and validated scoring method to assess radiographic cervical facet joint damage in AS. Left and right cervical facet joints were scored simultaneously since both sides are projected over each other. Facet joints were clearly visible in $>95\%$ of the patients. It was not possible to assess differences between left and right cervical facet joints. However, de Vlam et al. [9] showed symmetrical involvement for facet joints on oblique radiographs of the lumbar spine, so symmetrical involvement of cervical facet joints can also be presumed. Finally, radiographs were scored with unknown time sequence instead of chronological time order which may result in negative and less progression. This method was used to diminish reader bias since all patients were treated with TNF-α inhibitors.

In conclusion, our prospective observational cohort study in AS patients starting TNF-α inhibitors in daily clinical practice showed that facet joints of the cervical spine are frequently (25%) involved in AS. Overall, 13% of the AS patients showed radiographic progression of facet joints during 4 years of TNF-α treatment. The majority of these patients did not show progression of the vertebral bodies. These results indicate that incorporating cervical facet joints in existing scoring methods may be of additional value to increase the sensitivity to change of scoring radiographic progression in AS. Radiographic damage of the cervical facet joints in individual AS patients may be of influence on treatment decisions since it is associated with longstanding and more severe disease, impaired spinal mobility, and extra-articular manifestations.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.semarthrit.2016.11.003.

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