Arthritis Care & Research
Vol. 73, No. 2, February 2021, pp 275–281
DOI 10.1002/acr.24104

American College of Rheumatology
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Factors Predictive of Radiographic Progression in Ankylosing Spondylitis

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Objective. Using a longitudinal observational cohort of ankylosing spondylitis (AS) patients, we sought to identify progression rates and factors predictive of spinal progression. As a secondary aim, we analyzed the effect of tumor necrosis factor inhibitor (TNFi) treatment on radiographic progression.

Methods. AS patients who had baseline and follow-up cervical and lumbar radiographs were included in the study. Radiographic damage was assessed by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). A change of 2 mSASSS units in 2 years was defined as progression. The characteristics of the study group such as demographic, clinical, laboratory, and treatment history were collected.

Results. There were 350 patients in the study. The mean ± SD mSASSS increased from 9.3 ± 15.8 units at baseline to 17.7 ± 21.7 units by the sixth year. Mean ± SD changes in mSASSS between the years 0 to 2, 2 to 4, and 4 to 6 were 1.23 ± 2.68, 1.47 ± 2.86, and 1.52 ± 3.7 units, respectively. Overall, 24.3% of the group progressed over 2 years. Male sex (hazard ratio [HR] 2.46 [95% confidence interval (95% CI) 1.05, 5.76]), the presence of baseline damage (HR 7.98 [95% CI 3.98, 16]), increased inflammatory markers (log C-reactive protein level HR 1.35 [95% CI 1.07, 1.70]), and TNFi use (HR 0.82 [95% CI 0.70, 0.96]) were predictive of radiographic progression. There was a 20% reduction in the rate of progression with TNFi.

Conclusion. Male sex, the presence of baseline damage, active disease state, and higher inflammatory markers confer a high risk for disease progression. Treatment with TNFi showed a disease-modifying effect by slowing the rate of radiographic progression.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the spine and sacroiliac joints with an unknown etiology. The cardinal symptom is the presence of chronic inflammatory back pain, which is seen in up to 80% of patients (1). Aside from spinal pain, other clinical features such as peripheral arthritis, uveitis, and psoriasis may accompany the clinical course of AS (1). Structural spinal damage is a well-known feature of AS, which is characterized by new bone formation (syndesmophytes) in the spine. Currently, conventional radiography is the gold standard for assessment of the extent and severity of spinal disease caused by AS (2). Nearly 20–50% of AS patients have been reported to show some degree of spinal progression in 2 years of follow-up (3–5). Pain and stiffness due to disease activity and structural damage are the main contributors for physical function impairment in AS (6). A number of predictors of spinal disease progression have been described, including baseline structural damage, higher inflammatory burden, male sex, positivity for HLA–B27, and smoking (3–5,7,8). Nonsteroidal antiinflammatory drugs (NSAIDs) and tumor necrosis factor inhibitor (TNFi) treatments are the cornerstone therapies in the management of AS (9). Aside from being clinically effective, some reports suggest a beneficial effect on structural damage in AS, particularly with the use of TNFi (10–14).

The assessment of AS-related structural changes longitudinally is essential for understanding the natural course of progression and its underlying factors. This assessment could help identify the mechanisms responsible for progression and thereby aid in personalizing treatment. In this study, by using a longitudinal observational cohort of patients with AS, we sought to identify

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No potential conflicts of interest relevant to this article were reported.

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Submitted for publication September 26, 2018; accepted in revised form October 29, 2019.

SIGNIFICANCE & INNOVATIONS

- Nearly 25–50% of ankylosing spondylitis patients show spinal radiographic progression in 2 years.
- Male sex, baseline spinal damage, high disease activity, and increased inflammation markers confer a high risk for spinal radiographic progression.
- At least 1 year of treatment with tumor necrosis factor inhibitor therapy is associated with a 20% reduction in the rate of spinal radiographic progression.

progression rates and factors predictive of spinal progression. As a secondary aim, we analyzed the effect of TNFi on radiographic progression in AS.

PATIENTS AND METHODS

Study population. The Toronto Western Hospital Spondylitis Clinic is a longitudinal observational cohort that includes consecutive patients with axial spondyloarthritis (SpA) seen at this tertiary center. Using a standardized protocol, adult patients with axial SpA (age ≥18 years) are followed on an annual basis, and their data are systematically collected, including clinical (e.g., disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS)] [15,16] and functional parameters [Bath Ankylosing Spondylitis Functional Index (BASFI)]) (17), medication history (e.g., TNFi and disease-modifying antirheumatic drugs [DMARDs] treatment), and laboratory studies. Conventional radiographs are performed at 2-year intervals. Inclusion criteria for the current study were classification of AS based on the modified New York criteria (18) and the availability of the lateral views of cervical and lumbar radiographs from at least 2 time points, with a minimum interval of 18 months.

Scoring of the radiographs. A study coordinator identified 354 patients who fulfilled the inclusion criteria. The radiographs were anonymized and 2 experienced readers (IS and SL) scored the spinal radiographs independently but in chronologic order, using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) (19). Squaring in the cervical spine was not scored because of normal anatomical variation and previously defined measurement error (20,21). Radiographs with >3 missing vertebral corners (either cervical or lumbar) were excluded from the analysis. If ≤3 scores of vertebral corners were missing, imputation was carried out using a previously suggested technique (7). In case of disagreement, defined as ≥2 mSASSS units of difference between 2 assessments, a consensus reading was done by both readers. For all other patients, the mean of the 2 readers' scores was used. Starting from baseline, up to 5 follow-up sets, corresponding to 10 years of follow-up, were available. Total, cervical, and lumbar mSASSS scores were assembled for each period. A change of 2 mSASSS units in 2 years was defined as progression (3,10,14,22).

Other variables. The characteristics of the study group, such as demographics, clinical (e.g., the presence of extraspinal manifestations), laboratory (erythrocyte sedimentation rate and C-reactive protein [CRP] level), and medication history were collected. The following ASDAS cutoffs were used for disease activity: inactive disease (<1.3), low disease activity (≥1.3 to <2.1), high disease activity (≥2.1 to ≤3.5), and very high disease activity (>3.5) (23). In patients receiving TNFi, total exposure and exposure between radiographic intervals were calculated. For the assessment of TNFi effect, change and progression rates in the following 2-year radiographic interval were calculated (e.g., in a patient receiving TNFi in the radiographic interval 0 to 2 years, change in mSASSS was calculated for the years 2 to 4). Approval for this study was obtained from the hospital's Research Ethics Board. All subjects provided informed written consent.

Statistical analysis. Continuous variables were presented as mean ± SD. Nominal and ordinal data were expressed as percentages. Intraclass correlation coefficient (ICC) values and kappa statistics were used to analyze observer reliability. Radiographic progression over time was investigated using generalized estimating equations (GEE). For analysis, the linear model was selected. We specified participant ID as the "subject" variable and follow-up time as the "within-subject" variables. Based on the goodness-of-fit statistics, the smaller

Table 1. Baseline characteristics of the study group (n = 350)*

Characteristics	Values
Age, mean ± SD years	38.4 ± 13.7
Male	266 (76)
Symptom duration, mean ± SD years	14.9 ± 11.1
HLA–B27 positivity	263 (75.1)
Syndesmophytes	165 (47.1)
mSASSS, mean ± SD	9.3 ± 15.8
CRP, mean ± SD mg/liter	14.5 ± 21.7
ESR, mean ± SD mm/hour	15.6 ± 16.9
BASDAI, mean ± SD	4.7 ± 2.5
ASDAS-CRP, mean ± SD	2.9 ± 1.2
BASFI, mean ± SD	3.6 ± 2.8
Smoking ever	89 (25.4)
Uveitis ever	78 (22.3)
Psoriasis ever	27 (7.7)
Inflammatory bowel disease ever	25 (7.1)
Arthritis ever	118 (33.7)
TNFi ever	93 (26.6)
DMARD ever	42 (12)
NSAID ever	148 (42.3)

* Values are the number (%) unless indicated otherwise. ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; mSASSS = modified Stoke Ankylosing Spondylitis Spine Score; NSAIDs = nonsteroidal antiinflammatory drugs; TNFi = tumor necrosis factor inhibitor.

Table 2. Mean change in mSASSS over the years in the study*

	Baseline		2nd year		4th year		6th year	
	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD
Total	350	9.3 ± 15.8	252	10.5 ± 16.8	197	10.9 ± 17.7	116	17.7 ± 21.7
Cervical	350	5.1 ± 9.4	252	5.6 ± 9.8	197	6.1 ± 10.5	120	10.1 ± 12.9
Lumbar	350	4.2 ± 8.6	252	4.9 ± 9.4	198	4.7 ± 8.9	117	7.5 ± 10.8

* Some data are missing for cervical or lumbar modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), which means that the average of the cervical and the lumbar values is not necessarily equal to the total score.

"quasi-likelihood under independence model criterion" was obtained with the autoregressive working correlation matrix. Time-adjusted univariable analysis was performed. We then proceeded with a Cox proportional hazards regression analysis by setting progression (yes/no) as our dependent variable. In the first model, we included baseline damage, sex, disease duration, baseline CRP level, and BASDAI score as predictors. The BASDAI score was chosen over ASDAS-CRP in part because there were fewer missing values, and in part to avoid potential multicollinearity with the CRP level. In the second model, we included total TNFi exposure in years, and in the third model we changed total TNFi exposure to TNFi use before baseline radiographs. CRP levels were log transformed to improve the distribution of this variable. A double-tailed *P* value of less than 0.05 was considered statistically significant. The statistical analysis was carried out using SPSS software, version 22.

RESULTS

General characteristics of the study population. There were 763 AS patients in the total cohort. The mean ± SD age was 39.9 ± 19.9 years, 71.8% of the group were male, and 73.7% were positive for HLA–B27. A total of 413 patients (mean age 41.1 ± 23.8 years, 68.3% male, and 71.8% HLA–B27 positive) were excluded from the study due to the presence of complete ankylosis at baseline (total mSASSS of 72, n = 4) or due to the lack of follow-up radiographs. In total there were 350 patients (76% male, mean ± SD age 38.4 ± 13.7 years) in the study. Among them, 126 (78% male) had been included in a previously published study (10). The mean ± SD symptom duration at baseline was 14.9 ± 11.1 years, 75.1% were positive for HLA–B27, and syndesmophytes were present in 46.6% of the patients. The baseline characteristics of the patients are shown in Table 1.

Reliability. Agreement between readers was good on assessing change in mSASSS over time (ICC = 0.88 [95% confidence interval (95% CI) 0.84, 0.91]) and moderate for dichotomous discrimination of progressing and nonprogressing patients (κ = 0.61 [95% CI 0.52, 0.67]). Disagreement was present in a total of 54 patients (corresponding to 140 radiographs).

Radiographic progression. At the individual level, structural disease progression was not linear and was highly variable (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24104/abstract). At the group level, the mean ± SD mSASSS increased from 9.3 ± 15.8 units at baseline to 17.7 ± 21.7 units by the 6th year (Table 2). The same trend was observed for cervical and lumbar segments separately, with more progression in the cervical spine. Mean ± SD change in total mSASSS between the radiograph intervals 0 to 2 years, 2 to 4 years, and 4 to 6 years were 1.23 ± 2.68, 1.47 ± 2.86, and 1.52 ± 3.7 units, respectively. The corresponding progression rates for the given time periods were 24.3%, 26.9%, and 19.7%, respectively. When considering all time periods, the mean ± SD change in total mSASSS during 2 years was 1.34 ± 2.9 units. Overall, 24.3% of the group showed progression according to the defined criteria of ≥2 units over 2 years. Tables 3 and 4 summarize the change in mSASSS and progression rates over time. A cumulative probability plot of the mSASSS change between the radiographic intervals is shown in Figure 1 (total spine) and Supplementary Figures 2–4 (cervical and lumbar segments separately), available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24104/abstract (cervical and lumbar segments).

TNFi use and radiographic progression. A total of 230 patients (65.7%, mean ± SD age 38 ± 13.1 years, and 78.7% male) were treated with TNFi at some point during their follow-up. The mean ± SD duration of anti-TNF use was

Table 3. Mean change in mSASSS between time periods of the study*

	0–2 years		2–4 years		4–6 years		All 2-year intervals	
	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD
Total	247	1.23 ± 2.68	119	1.47 ± 2.86	66	1.52 ± 3.7	432	1.34 ± 2.9
Cervical	249	0.63 ± 1.87	119	0.72 ± 1.92	69	0.94 ± 2.45	437	0.7 ± 1.98
Lumbar	250	0.66 ± 1.63	119	0.77 ± 2.0	67	0.67 ± 1.69	436	0.69 ± 1.75

* Some data are missing for cervical or lumbar modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), which means that the average of the cervical and the lumbar values is not necessarily equal to the total score.

Table 4. Progression rate between time periods of the study*

	0–2 years		2–4 years		4–6 years		All 2-year intervals	
	No.	Rate (%)	No.	Rate (%)	No.	Rate (%)	No.	Rate (%)
Total	247	60 (24.3)	119	32 (26.9)	66	13 (19.7)	432	105 (24.3)
Cervical	249	36 (14.5)	119	21 (17.6)	69	12 (17.9)	437	69 (15.8)
Lumbar	250	41 (16.4)	119	16 (13.4)	67	12 (17.4)	436	69 (15.8)

* Some data are missing for cervical or lumbar modified Stoke Ankylosing Spondylitis Spine Score, which means that the average of the cervical and the lumbar values is not necessarily equal to the total score.

5.2 ± 3.4 years. For the calculation of radiographic progression, patients who were receiving anti-TNF for a period of at least 12 months were identified. The change in mSASSS and rate of progression over the following 2-year interval were calculated. A total of 67 patients had been treated with TNFi prior to their baseline radiographs (change in mSASSS calculated in the years 0 to 2), and 80 patients receiving TNFi in the interval 0 to 2 years (change in mSASSS calculated in the years 2 to 4). The same approach was used for conventional-treatment patients (prior baseline radiography [n = 186], and in the years 0 to 2 [n = 81]). Compared to conventional treatment, TNFi-treated patients had a lower mSASSS change in the spinal segments in the subsequent 2-year radiographic interval, but the differences were not statistically significant (Table 5).

Predictors of radiographic progression. In a time-adjusted univariable linear GEE analysis, male sex (β = 0.82, SE 0.39), the presence of baseline syndesmophytes (β = 1.05, SE 0.13), baseline CRP level (β = 0.18, SE 0.006), high (β = 1.64, SE 0.7) and very high (β = 1.52, SE 0.61) disease activity state according to ASDAS-CRP, and TNFi use (β = –0.24, SE 0.12) were significantly predictive of mSASSS change over time (Table 6). On the other hand, symptom duration, the presence of HLA–B27, smoking status, BASFI score, and clinical variables, including the presence of radiographic hip disease, uveitis, psoriasis, inflammatory bowel disease, and DMARD and NSAID use, showed no associations with mSASSS progression ($P > 0.05$) (Table 6 and Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24104/abstract). In Cox multiple regression analysis, aside from disease duration and BASDAI score, male sex (hazard ratio [HR] 2.46 [95% CI 1.05, 5.76]), the presence of baseline damage (HR 7.98 [95% CI 3.98, 16]), and log CRP level (HR 1.35 [95% CI 1.07, 1.70]) were predictive of radiographic progression. In the second model, after correcting for the aforementioned variables, total TNFi use in years (HR 0.82 [95% CI 0.70, 0.96]) was an independent predictor of progression. In the third model, prior TNFi use was included and found not to be associated with progression (Table 7).

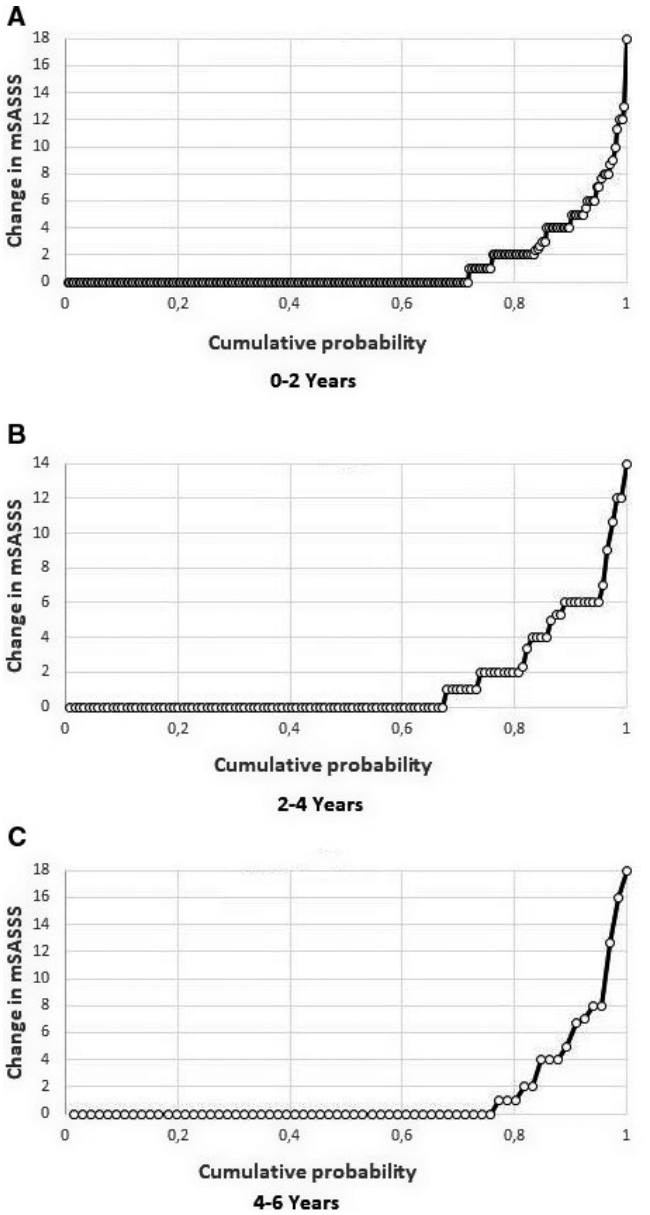

Figure 1. Cumulative probability plots of radiographic spinal progression between the years 0 to 2 (**A**), 2 to 4 (**B**), and 4 to 6 (**C**) for the total spine. mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score.

Table 5. Change in mSASSS and progression rates in the next 2-year radiography interval in TNFi and conventionally treated AS patients*

	Total		Cervical		Lumbar	
	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD
TNFi	147	1.12 ± 2.4	148	0.60 ± 1.8	147	0.52 ± 1.5
Conventional	260	1.61 ± 3.5	263	0.89 ± 2.5	264	0.80 ± 1.8

* No statistically significant differences were found between the TNFi versus conventional treatment groups. AS = ankylosing spondylitis; mSASSS = modified Stoke Ankylosing Spondylitis Spine Score; TNFi = tumor necrosis factor inhibitor.

DISCUSSION

In this study we demonstrated the following results in a longitudinal AS cohort: 1) a progressive increase in the mean mSASSS on average of 1.34 units/2 years; 2) 24.3% of the group progressed according to the criteria of mSASSS ≥2 units; 3) male sex, baseline spinal damage, high disease activity, increased inflammatory markers, and treatment with TNFi were predictors of progression; and 4) using TNFi therapy for at least 1 year was associated with a decreased progression rate in the next radiographic interval and a 20% reduction in the rate of spinal progression.

One of the hallmark clinical characteristics of AS is the development of structural spinal damage over time. A few longitudinal studies have reported 20–45% rates of radiographic progression at 2 years in AS (3–5,7,8,24). Several variables have been linked to spinal progression, including baseline spinal damage (3–5,7,8), male sex (7,8), positivity for HLA–B27 (7), higher inflammatory burden (3,25,26), and smoking (3). In the current study, patients had symptoms for an average of 15 years at baseline and nearly half of our patients had baseline damage. Progression rates were highly variable at the individual level, with a mean change in mSASSS of 1.34 units every 2 years, and one-fourth of patients progressed (change in mSASSS ≥2 in 2 years). There was a trend of greater progression in the cervical compared to lumbar spine, but the rate of progression was similar between the groups. Our results are consistent with the published literature. Baseline damage, male sex, and disease activity have previously been shown to predict spinal progression (24). After correcting for time, each unit increase in ASDAS-CRP resulted in a 0.45-unit increase in the yearly slope of mSASSS. Patients with high and very high disease activity states were more likely to progress over time.

Table 6. Univariable analysis investigating the relationship between mSASSS progression and different variables in a time-adjusted model*

	Beta	SE (95% CI)	*P*
Time	1.08	0.3 (0.5, 1.7)	<0.0001
Time × symptom duration	0.04	0.29 (–0.02, 0.96)	0.19
Time × sex (men)	0.82	0.39 (0.06, 1.6)	0.04
Time × HLA–B27 (positive)	–0.11	0.58 (–1.3, 1.03)	0.85
Time × baseline damage	1.05	0.13 (0.81, 1.29)	<0.0001
Time × total TNFi	0.12	0.72 (–0.13, 0.15)	0.86
Time × TNFi prior radiographic intervals	–0.24	0.12 (–0.48, –0.006)	0.04
Time × smoking	0.04	0.62 (–1.18, 1.25)	0.95
Time × CRP	0.18	0.006 (0.006, 0.03)	0.002
Time × ESR	–0.009	0.18 (–0.04, 0.03)	0.59
Time × BASFI	0.19	0.12 (–0.03, 0.42)	0.09
Time × BASDAI (≥4)	–0.29	0.58 (–1.43, 0.85)	0.61
Time × ASDAS-CRP			
Continuous	0.45	0.18 (0.09, 0.81)	0.01
Moderate	0.8	0.56 (–0.31, 1.91)	0.16
High	1.64	0.7 (0.27, 3)	0.02
Very high	1.52	0.61 (0.33, 2.71)	0.01

* 95% CI = 95% confidence interval; ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; mSASSS = modified Stoke Ankylosing Spondylitis Spine Score; TNFi = tumor necrosis factor inhibitor.

The impact of TNFi treatments on radiographic progression is a topic of keen interest (10,13,27–32). Studying the disease modification potential of biologic response modifiers is not an easy task. Disease progression is slow and influenced by several factors, as seen here. The ideal scientific way to study this question would be to have a long-term randomized controlled trial stratified by relevant baseline variables and following patients for at least 4-6 years. Keeping 1 group of patients on placebo or NSAID alone for such a long period would be unethical, however, considering the proven significant benefits of biologic therapy on symptom control. Cohort studies have demonstrated lower radiographic progression in TNFi-treated patients. Haroon et al (10) showed that TNFi treatment in AS (n = 334) was associated with a 50% reduction in the odds of progression. That study also reported a higher progression rate in patients who delayed starting TNFi for >10 years compared to those who started earlier (10).

In another study (n = 432), patients who received continuous TNFi at least 2 years prior their baseline radiographs showed 50% less radiographic progression during the next 2-year interval compared to non-TNFi–treated patients (11). In a Dutch study (n = 210), TNFi treatment was associated with reduced progression beyond 4 years of treatment (12). In a recent study, axial SpA patients (n = 315) receiving certolizumab pegol had less progression rates in the years 2–4 compared to 0–2 (33). In this study, there were 230 patients (65.7%) who received TNFi during the follow-up period. At least 1 year of treatment with TNFi was associated with a 20% reduction in spinal progression during the next

Table 7. Cox proportional hazards regression analysis investigating predictive factors of spinal progression*

	Model 1	Model 2	Model 3
Men	2.46 (1.05, 5.76)†	2.45 (1.05, 5.74)†	2.43 (1.04, 5.69)†
Presence of baseline damage	7.98 (3.98, 16)†	7.93 (3.95, 15.9)†	7.98 (3.98, 16)†
Log CRP	1.35 (1.07, 1.7)†	1.37 (1.08, 1.74)†	1.32 (1.05, 1.67)†
BASDAI	1.06 (0.97, 1.16)	1.07 (0.97, 1.17)	1.06 (0.96, 1.16)
Symptom duration	0.85 (0.52, 1.39)	0.88 (0.54, 1.44)	0.85 (0.52, 1.39)
Total TNFi use	–	0.82 (0.7, 0.96)†	–
TNFi exposure before radiographs	–	–	0.87 (0.72, 1.04)

* Values are the hazard ratio (95% confidence interval). BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; CRP = C-reactive protein; TNFi = tumor necrosis factor inhibitor.
† Statistically significant change.

2-year interval compared to non-TNFi–treated patients. This effect remained significant even after correction of the well-established predictors of radiographic progression, including sex, baseline damage, disease activity, and inflammation markers.

In this study, radiographic progression and related measures were evaluated based on the total mSASSS. We did not analyze the development of syndesmophytes and bridging syndesmophytes separately, which can be considered a limitation of the study. We did not calculate an NSAID index that prevented more sensitive analysis related to the use of these medications on radiographic progression. We also acknowledge the limitations related to mSASSS scoring itself. In this scoring system only anterior vertebral corners of the cervical and lumbar spine were counted (14). Because the thoracic segment, posterior vertebral corners, and facet joints were not included, the true rate of radiographic progression is expected to be higher.

In summary, our study adds to the current knowledge on progression of spinal disease in AS. Nearly one-third of patients progress over time. At baseline, male sex, the presence of damage, active disease state, and higher CRP level confer a higher risk of disease progression. In addition, this study confirms the results of our earlier multicenter study, and other subsequent longer-term studies, that TNFi have a disease-modifying effect in AS (10–12,33).

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Haroon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Sari, Inman, Haroon.
Acquisition of data. Sari, Lee.
Analysis and interpretation of data. Sari, Tomlinson, Johnson, Inman, Haroon.

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