The Natural Course of Radiographic Progression in Ankylosing Spondylitis — Evidence for Major Individual Variations in a Large Proportion of Patients

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ABSTRACT. ***Objective.*** To describe the natural course of radiographic progression and to differentiate rates of progression in patients with ankylosing spondylitis (AS).

Methods. Overall, 146 patients with AS who had never received anti-tumor necrosis factor therapy were analyzed in this retrospective cohort study. The main inclusion criterion was the availability of complete sets of cervical and lumbar radiographs from at least 2 timepoints within 6 years. Using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), we quantified the structural changes and assessed different rates of radiographic progression based on development of new syndesmophytes/year.

Results. The mean followup time was 3.8 ± 1.7 years (range 1–6) and the mean number of consecutive radiographs was 2.7 (range 2–6) per patient. The mean mSASSS change/year was 1.3 ± 2.5 units. Radiographic progression showed much variability, since 43% of patients showed a 4-fold greater rate of progression than the mean, and 23% had no progression. The data-based definition for "fast progression" was calculated as a change > 5 mSASSS units or > 2 new syndesmophytes; for "moderate progression" as change of 2.0–5.0 mSASSS units or < 2 new syndesmophytes; and for "slow progression" as change of < 2 mSASSS units or no more than 1 new syndesmophyte within 2 years. The only factor to predict future radiographic progression was the number of syndesmophytes at baseline.

Conclusion. Radiographic progression in AS is rather variable and many patients show high rates of progression. On the basis of this retrospective dataset we propose to differentiate patients on an individual level according to their progression rates: patients with fast, moderate, and slow radiographic progression, assessed by counting new syndesmophytes. Predicting radiographic progression remains difficult; only the prevalence of syndesmophytes at baseline is predictive of future damage. (J Rheumatol First Release April 1 2009; doi:10.3899/jrheum.080871)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS   SYNDESMOPHYTES
MODIFIED STOKE ANKYLOSING SPONDYLITIS SPINE SCORE
RADIOGRAPHIC PROGRESSION   PREDICTIVE FACTORS

Ankylosing spondylitis (AS) is a frequent chronic inflammatory rheumatic disease that affects the axial skeleton even in young persons[1], starting in the sacroiliac joints and spreading to the spine in most patients[2]. New bone formation, such as syndesmophytes and ankylosis of the vertebral column, is pathognomonic for AS. Conventional radiographs of the spine are considered the gold standard for assessment of chronic structural spinal changes in patients with AS[3,4]. The modified Stokes AS Spine Score (mSASSS), a well validated scoring system for quantification of chronic spinal changes detected by conventional radiographs[5], is currently considered the best method. For an acceptable sensitivity to change, a minimum followup time of 2 years was shown to be required[6]. Changes in mSASSS scores over time are mainly due to the growth of syndesmophytes and ankylosis, which are the most frequent radiographic features of progression in AS[7]. Differentiation between AS-specific and nonspecific changes, for example by separating syndesmophytes from spondylophytes, was shown not to have a major effect on mSASS scores[7].

Therapy with anti-tumor necrosis factor-α (TNF-α) agents has recently been shown to significantly improve signs, symptoms, and function of patients with AS[8-11]. Further, the inflammatory spinal lesions due to AS, as detected by magnetic resonance imaging (MRI) in short and longterm followup examinations, were shown to regress to a

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large degree[12-14]. In contrast, conclusions about the effect of anti-TNF treatment on radiographic progression in patients with AS remain inconsistent. Some studies have demonstrated a reduction in rate of progression[15,16], but others[17,18] showed no differences in radiographic progression between patients treated with and without TNF-α blockers. One major drawback in the methodology of studies performed to date has been that there are no and probably will be no prospective randomized placebo-controlled trials to compare AS patients with and without anti-TNF therapy. Therefore, the current approach has been to systematically compare the data from new AS cohorts with historical cohorts[15,19,20]. To compare the rate of radiographic progression in AS between studies is difficult[7], since there are different ways of reading radiographs[21], e.g., in the time order and the reader's knowledge about the time sequence of the images, in differences in the readers' experience, and also in the number of patients included in the studies[5,19-21].

Our aim was to quantify and characterize the natural course of radiographic progression in a cohort of patients with AS who presented to our specialized hospital, and to define the different progression rates in those patients.

MATERIALS AND METHODS

Patients and study protocol. Overall, 146 patients with AS were retrospectively included in this study. All patients were hospitalized in our clinic between 1993 and 2005 for different reasons. Usual reasons for admission were high levels of pain, increased disease activity, and also disability and peripheral symptomatic inflammation associated with functional decline. The major inclusion criteria into this retrospective study were (1) established AS according to the modified New York criteria[22], and (2) the availability of complete sets of conventional radiographs of the cervical and the lumbar spine in the lateral view.

Radiographic assessment of chronic spinal changes using the mSASSS. All radiographic examinations were conducted using the same standardized examination protocol. All images were blinded for personal details and for time order of imaging and were scored by 2 readers (XB, AR) using the mSASSS[21]. Then mean scores of the 2 readers were calculated. "Agreement" between readers was defined as no difference in the same mSASSS change scores between timepoints. "Some disagreement" was defined as a small difference of ≤ 2 mSASSS units and "major disagreement" as disagreement > 2 mSASSS units of change (development of new syndesmophyte/ankylosis; see below) between 2 assessment timepoints. In case of major disagreement discrepancies between 2 readers (difference > 2 mSASSS units), a senior reader (JB) would reevaluate the image and give the final score.

According to recent proposals[5,15], patients were excluded from the evaluation if more than 3 vertebral sites were missing, for example due to missing segments. In cases with ≤ 3 vertebral sites missing, missing scores were substituted by the mean score of the vertebra from the same spinal segment of the patient[5,15].

In accord with a recent proposal[7], definite ("AS-specific") radiographic damage at baseline (taken here as first visit with radiographs available) was defined as a score of at least 2 (appearance in the patient of at least one syndesmophyte in at least one vertebral edge) in the mSASSS. Similar to this definition, definite radiographic progression was defined as the development of a new syndesmophyte between 2 visits with radiographs available.

Evaluation of scoring for definition of rate of progression. After scoring of all available images, sets of image pairs were assembled for each possible combination of followup time on the basis of individual patients. Thus up to 6 followup sets were allowed for the evaluation of radiographic progression based on the availability of radiographs starting from baseline up to 6 years of followup. The radiographic progression was then analyzed for each available pair of images in order to assess increase in mSASSS units, and also the number of new syndesmophytes per year within all possible time periods. On the basis of these data, calculation of 25th percentiles was performed in order to define subgroups with different rates of radiographic progression.

Statistical analysis. The paired Wilcoxon rank-sum test was used to compare readings at different timepoints. The associations between patients' baseline characteristics and the degree of radiographic progression (defined by percentiles of radiographic deterioration per year, as above) were investigated by means of the nonparametric Jonckheere-Terpstra trend test. Generalized linear models for ordinal data were applied to estimate the predicted probability of no, slow, moderate, or fast progression based on the number of syndesmophytes[23]. Further, Mann-Whitney U test was used to compare subgroups of patients. Reliability and agreement between readers was determined by comparison of individual radiographs and analysis of "agreement," "some disagreement," and "major disagreement," as described above.

RESULTS

Baseline characteristics. The mean age of all 146 patients was 54.2 ± 12.3 years (range 29–79 yrs). The mean time since first symptom was 23.6 ± 11.2 years (range 5–58 yrs) and mean time since diagnosis was 22.6 ± 12.1 years (range 2–55 yrs). Overall, 81% of patients were male and 78% were HLA-B27-positive; this information was available in 86/146 patients (59%). The mean C-reactive protein (CRP) was 2.0 ± 2.8 mg/dl (available in 76/146 patients, 52%), and 58.6% of those patients had elevated CRP levels (normal < 6 mg/dl). The mean Bath AS Disease Activity Index (BASDAI) was 4.4 ± 1.9 (range 0.5–7.3) and 58.3% of patients had BASDAI values > 4. The mean Bath AS Functional Index (BASFI) was 3.8 ± 2.6 (range 1.0–8.4). Information about intake of nonsteroidal antiinflammatory drugs (NSAID) and disease-modifying antirheumatic drugs (DMARD) was available in 81/146 patients. Of those, 74 patients (80.2%) were currently receiving NSAID and 17 (21%) took DMARD at baseline. No patient had been treated with biologic agents before baseline or during the entire observation period of the study.

Baseline demographic data of our cohort were largely comparable to those of other cohorts such as OASIS[5]. This includes patients of the OASIS cohort whose data were taken for comparison with patients treated with anti-TNF-α agents in clinical trials[19,20].

Reliability and agreement between readers. Both readers were in agreement in the change scores of the mSASSS in 82/146 patients (56.2%), while there was some disagreement in 53 patients (36.3%) and major disagreement in 11 patients (7.5%). Agreement was higher in those patients who had an mSASSS score of zero at baseline (as scored by both readers, data not shown).

Radiographic progression by assessment of the mSASSS. The mean followup time was 3.8 ± 1.7 years (range 1–6 yrs)

and the mean number of consecutive followup visits with radiographs was 2.7 (range 2–6). Within this period, the mean mSASSS of all 146 patients increased from 20.5 ± 14.4 to 24.6 ± 15.9 mSASSS units (p < 0.001). Overall, 112/146 patients (77.5%) showed radiographic progression at followup. The mean radiographic progression of the entire cohort was 1.3 ± 2.5 mSASSS units per year. However, the individual ranges of mSASSS changes varied between zero and 22.8 mSASSS units, and the mean progression rate was not similar for all 112 patients with any radiographic change. A rather large proportion of 48/112 patients (42.9%) showed progression rates faster than the mean: their rate was 4-fold higher than the mean mSASSS change (Figure 1). Similarly, 43/112 patients (38.4%) had a progression rate that was 2 standard deviations higher than the mean (Figure 1).

According to the calculation used to define different subgroups, the cutoff for the 25th percentile was 0.6 mSASSS units and for the 75th percentile 2.6 mSASSS units of change per year. On this basis, the cutoff for "slow" radiographic progression could be defined at 0.1–0.6 mSASSS units per patient and per year, the cutoff for "moderate" progression at 0.7–2.5 mSASSS units, and the cutoff for "fast" progression 2.6–72 mSASSS units. Since the minimum time to depict radiographic progression in AS is 2 years, these results are given on this basis (Table 1).

Stratification to subgroups for baseline characteristics such as NSAID or DMARD intake at baseline, BASDAI or BASFI values, age, sex, HLA-B27 status, symptom duration, and CRP or ESR revealed no differences related to radiographic progression or to classification according to rate of progression. Further, there were no differences in mSASSS status and change scores between the cervical and the lumbar spine (data not shown).

Table 1. Definition of radiographic progression in patients with ankylosing spondylitis. Stratification to different groups of progression rates is according to change of mSASSS or development of new syndesmophytes within a 2-year period.

Definition of Progression	mSASSS Change	Development of New Syndesmophytes
Slow	< 2 mSASSS units within 2 yrs	Not more than 1 syndesmophyte within 2 yrs
Moderate	2.0–5.0 mSASSS units within 2 yrs	Not more than 2 syndesmophytes within 2 yrs
Fast	> 5 mSASSS units within 2 yrs	More than 2 syndesmophytes within 2 yrs

mSASSS: modified Stoke Ankylosing Spondylitis Spine Score.

Radiographic progression by assessment of new syndesmophytes. Development of new syndesmophytes was found in 85/146 patients (58.2%). This indicates that 85 out of 112 patients (76%) with any progression had definite AS-related changes. The mean number of new syndesmophytes per patient over the entire period of followup was 1.8 ± 2.6 (range 0–17 syndesmophytes). However, 20/85 patients (23.5%) had new syndesmophytes 2-fold more frequently than the mean, and 11/85 patients (12.9%) showed this more frequently than 2 standard deviations above the mean.

On the basis of percentiles used as cutoffs for the definition of different progression rates, the cutoff for the 25th percentile was calculated at 0.3 new syndesmophytes per patient and per year, and the cutoff for the 75th percentile was at 1.1 new syndesmophytes. This defines "slow" radiographic progression at 0.1–0.3 new syndesmophytes per patient per year. Similarly, "moderate" progression was defined by 0.4–1.0 new syndesmophytes and "fast" progression by 1.1–24 (derived theoretically from the 24 vertebral
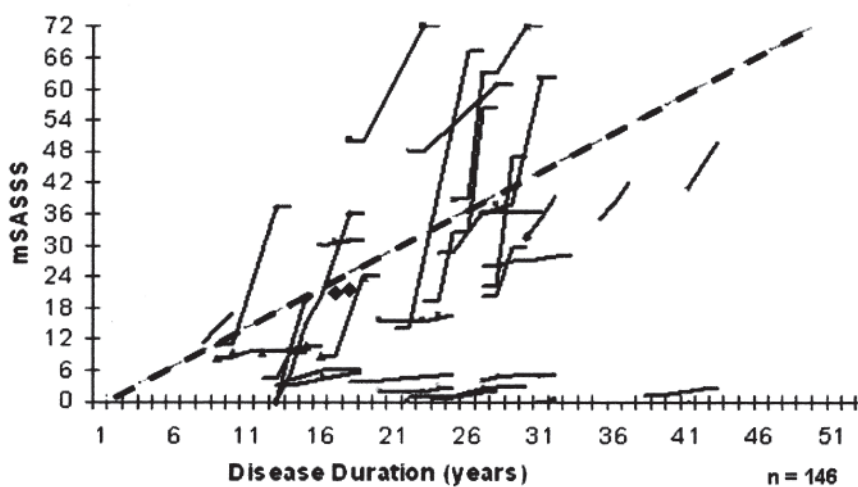

Figure 1. The natural course of radiographic progression in patients with AS is not always linear. Although the mean radiographic progression of the entire cohort (n = 146) was 1.3 mSASSS units per year (broken line), a large proportion of patients showed progression rates much faster or much slower than the mean (solid lines).

edges of cervical and lumbar spine) new syndesmophytes per patient per year. The 2-year data on the rate of radiographic progression are shown in Table 1.

There were no differences in progression of the mSASSS or occurrence of new syndesmophytes between cervical and lumbar spine, and as well no difference based on stratifications for any baseline characteristic was found in this analysis. The results were not different when applied to the scorings of each individual reader (data not shown).

Prediction of radiographic progression. Patients with definite radiographic damage at baseline also showed the greatest radiographic progression, with a change 6.9 ± 9.2 mSASSS units, as compared 4.8 ± 8.5 mSASSS units for patients with no definite baseline damage (p < 0.001). Based on the analysis of new syndesmophytes, patients with definite baseline damage showed a higher mean number of new syndesmophytes at followup, compared to patients with no definite baseline damage, with 2.1 ± 2.5 and 1.2 ± 2.6 new syndesmophytes per patient, respectively (p < 0.001).

Evaluation of all baseline measures showed that only the number of syndesmophytes at baseline was significantly predictive for future classification in one of the groups for rate of progression (Figure 2). None of the remaining measures (mSASSS units at baseline, occurrence or not of minor radiographic changes, clinical or baseline characteristics, NSAID intake at baseline) was predictive for future stratification in any progression group for future radiographic progression.

DISCUSSION

The rate of the natural radiographic progression in patients with AS has been a matter of controversy for many years, but data on this subject have been limited until now. The accepted way of thinking is that the progression rate is rather linear in AS[24,25]. In a retrospective cohort study we examined the potential differences in the rates of radiographic progression between AS patients with established disease who had never been treated with biologic therapies. On this basis we are able, for the first time, to provide definitions for 3 different rates of structural progression in AS.

To carry out this analysis, patients with AS who were hospitalized in our department for different reasons (mainly but not only related to disease activity) were assessed with respect to their longterm radiographic progression. The scoring method for this analysis of radiographic progression has been validated recently: the modified SASSS is currently considered the best scoring system for quantification of chronic spinal changes in AS, based on a study using the OMERACT filter[5]. In a recent publication we confirmed the face validity of this method by showing that the growth of one syndesmophyte is the major contributor to progression of radiographic damage in patients with AS, and we also confirmed the limited but definite sensitivity to change of this method in a 2-year followup[7].

The issue of rapid radiographic progression has for some years been related to possible indications for anti-TNF therapy in AS[26], but the question of different rates of radio-
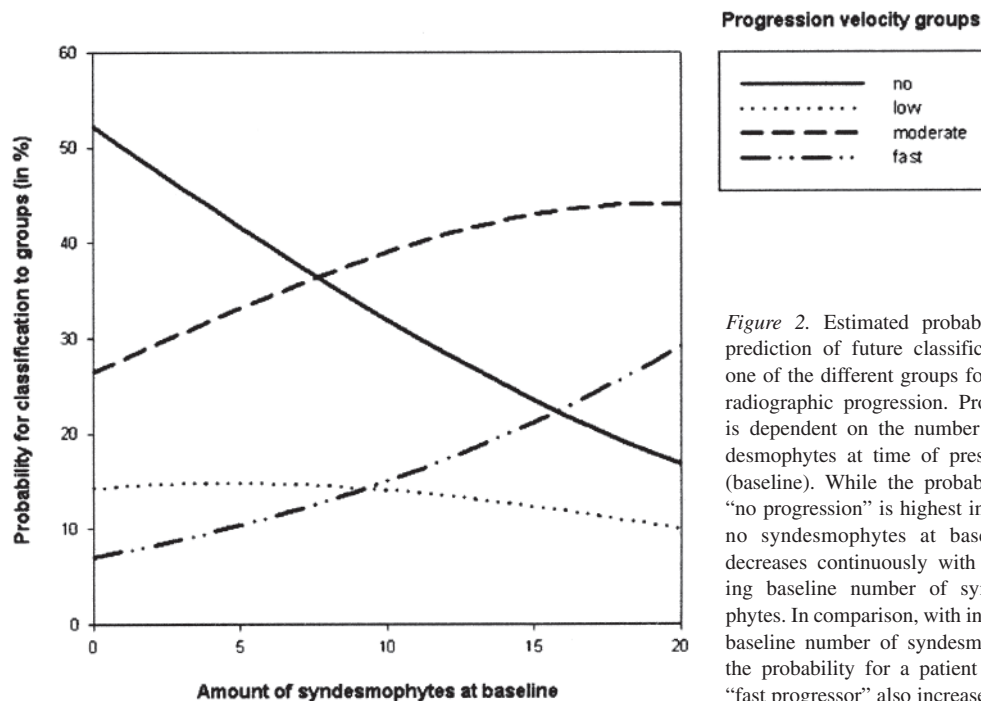

Figure 2. Estimated probability for prediction of future classification to one of the different groups for rate of radiographic progression. Probability is dependent on the number of syndesmophytes at time of presentation (baseline). While the probability for "no progression" is highest in case of no syndesmophytes at baseline, it decreases continuously with increasing baseline number of syndesmophytes. In comparison, with increasing baseline number of syndesmophytes, the probability for a patient to be a "fast progressor" also increases.

graphic progression in AS has not been investigated. The main issue turns out to be the difference between the mean and the individual and group rates of progression. In the cohort analyzed here, the mean radiographic progression rate per year was 1.3 mSASSS units. However, no radiographic change was seen in 23% of patients, and 13%–43% of patients had accelerated radiographic progression.

According to our observation that radiographic progression was not linear over time in the patients in our cohort, we propose to characterize patients as "slow," "moderate," or "fast" progressors by assessing the rate of radiographic deterioration in the most recent years. This can be measured by either quantifying radiographic change in mSASSS units or by simply counting the number of new syndesmophytes in the followup period (Table 1). However, a change of 2 mSASSS units in one patient does not necessarily mean that a syndesmophyte has grown, 2 minor changes of 1 mSASSS unit each would also be possible[7]. Thus, for the definition of radiographic progression more information is needed: for "slow" progression (mSASSS change < 2 units), "no new syndesmophyte" may have occurred within 2 years; for "moderate" progression (mSASSS change 2.0–5.0 units), syndesmophyte formation should not exceed 2 new cases; and finally, for "fast" progression (mSASSS change > 5 units), more than 2 new syndesmophytes should have occurred within the previous 2 years.

In our study, the occurrence of definite baseline damage as assessed by the number of syndesmophytes was the only significant predictive indicator for classification in any group by rate of radiographic progression. This result adds validity to the usefulness of the syndesmophyte as a disease-specific radiographic sign[7] in the assessment of radiographic deterioration in AS, for both clinical studies and daily clinical practice. None of the other radiographic, clinical, or laboratory measures could predict rate of future progression. Prospective studies will possibly add more information to this important issue.

There are some potential limitations of our study because of the retrospective design, which implies that the amount of available radiographs and timepoints was varied. However, the radiographs were indicated in daily routine situations without further selection. We cannot exclude that there was a tendency to include more severe patients in terms of disease activity and radiographic damage. In any case, these results represent the natural radiographic progression in a large cohort of AS patients seen in our hospital. Given the scarcity of data available on the natural course of AS we believe this cohort is of interest particularly for comparisons to biologics and other potential DMARD in AS.

Another limitation of the study is missing data, since some baseline variables, such as CRP, BASDAI, BASFI, and NSAID intake, were not available for all patients, because they were not clearly identified in the records. However, since our data are consistent with recent studies[7,15,16,19] that, for example, identified the number of baseline syndesmophytes as the only predictive factor for future radiographic progression, we do not think that missing data are of major relevance to the main conclusions of the study.

Our results may have implications for future studies on radiographic progression in AS. Recently, anti-TNF-α treatment has dramatically changed the therapeutic outcome in AS, revealing significant improvement of clinical signs and symptoms of disease activity after only a few weeks[8-11]. Anti-TNF-α therapy also showed a significant decrease of spinal inflammation, as assessed by MRI[12-14]. In contrast, conclusions about the effect of anti-TNF-α therapy on radiographic deterioration of the same patients cannot be drawn at this time, given the inconsistency of data from the available studies[15-18]. These findings have been a matter of debate, and the question has been raised whether the available scoring system is sensitive enough to depict all radiographic progression, for example, including the thoracic spine and the zygoapophyseal joints. Our data confirm that a period of 2 years is probably good enough to demonstrate changes and differences by the mSASSS, but a mean change of less than one syndesmophyte in 2 years is not very impressive. Thus, future studies may possibly concentrate on patients with syndesmophytes at baseline. As well, studies are needed to assess the efficacy of early treatment of patients with axial spondyloarthropathy before the onset of structural damage.

We show, for the first time, different rates of radiographic progression of patients with AS. We demonstrate that radiographic progression in AS is not linear over time in many patients. The progression rates proposed here may be useful for characterization of patients with AS in daily practice and for research purposes.

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