

Review

Modified stoke ankylosing spondylitis spinal score as an outcome measure to assess the impact of treatment on structural progression in ankylosing spondylitis

Désirée van der Heijde¹, Jürgen Braun², Atul Deodhar³, Xenofon Baraliakos², Robert Landewé⁴, Hanno B. Richards⁵, Brian Porter⁶ and Aimee Readie⁶

Abstract

In ankylosing spondylitis (AS), structural damage that occurs as a result of syndesmophyte formation and ankylosis of the vertebral column is irreversible. Structural damage is currently assessed by conventional radiography and scoring systems that reliably assess radiographic structural damage are needed to capture the differential effects of drugs on structural damage progression. The validity of the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) as a primary outcome measure in evaluating the effect of AS treatments on radiographic progression rates was assessed in this review. The mSASSS has not been used, to date, as a primary outcome measure in a prospective randomized controlled clinical trial of biologic therapy in AS. This review of the medical literature confirmed that the mSASSS is the most validated and widely used method for assessing radiographic progression in AS, correlating with worsening measures of disease signs and symptoms, spinal mobility and physical function, with a 2-year interval being required to ensure sufficient sensitivity to change.

Key words: ankylosing spondylitis, imaging, mSASSS, radiography, scoring, spondyloarthritis, radiograph

Rheumatology key messages

- In AS, structural damage occurring because of syndesmophyte formation and ankylosis is irreversible.
- Scoring systems that reliably assess radiographic structural damage in AS are needed to assess drugs' effects.
- The mSASSS is the most validated and widely used measure for assessing AS radiographic progression.

Background

AS is a chronic inflammatory disease that typically affects the axial skeleton and the entheses. The hallmark clinical manifestations of AS include inflammatory back pain and stiffness, with syndesmophytes and spinal ankylosis being the most characteristic features. Spinal ossification may

lead to reduced physical function and quality of life. Disability (limitation of physical function and spinal mobility) related to disease activity or inflammation may be reversible, and controlling inflammation or disease activity may not only have direct effects on patient-reported outcomes but also prevent further progression of structural damage. Structural damage can cause permanent limitation in spinal mobility and physical function [1]. Thus, drugs that are effective in both treating spinal inflammation and protecting against radiographic progression may have a beneficial impact on long-term physical function.

The aim of this scoping review is to describe the validity of the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) as a primary outcome measure in evaluating the efficacy of treatments for AS in terms of structural damage progression; a systematic review was not conducted. In brief, a literature search was conducted in PubMed, using the key search terms AS, structural

¹Department of Rheumatology, Leiden University Medical Centre, Leiden, The Netherlands, ²Rheumazentrum Ruhrgebiet, Herne, and Ruhr University Bochum, Germany, ³Division of Arthritis and Rheumatic Diseases, Oregon Health and Science University, Portland, OR, USA, ⁴Department of Clinical Immunology and Rheumatology, Amsterdam Rheumatology and Immunology Center, Academic Medical Center/University of Amsterdam, Amsterdam, The Netherlands, ⁵Novartis Pharma AG, Basel, Switzerland and ⁶Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

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Correspondence to: Aimee Readie, Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936-1080, USA. E-mail: aimee.readie@novartis.com

progression and associated terms intended to identify publications relating to radiographic outcome measures, such as the mSASSS, that are used to assess the impact of treatment on radiographic structural progression in patients with AS. Additionally, authors made suggestions regarding pertinent publications for potential inclusion in the review. The search demonstrated that the mSASSS has been used in a large number of AS studies to assess structural damage progression on spinal radiographs with different therapeutic interventions, including NSAIDs and biologic agents, in either retrospective cohort comparisons, prospective controlled trials of non-biologic therapies or prospective trials of biologic agents with no controlled comparison for long-term radiographic endpoints. However, the mSASSS has never been used as a primary outcome measure in a prospective randomized clinical study of a biologic therapy that includes a comparator.

Natural history and disease progression

Syndesmophyte formation and ankylosis of the vertebral column are pathognomonic structural changes in AS and are currently best visualized by conventional radiography of the axial skeleton, including the SI joints and the whole vertebral spine [2, 3]. Osteodestructive changes occur less frequently and may include erosions [2]. Erosions and sclerosis are early signs of radiographic progression that may precede the development of syndesmophytes, which can eventually grow and bridge adjacent vertebrae, ultimately leading to spinal fusion or the characteristic bamboo spine in some patients [3, 4].

It has been hypothesized that progression of AS, at least in part, involves inflammation that progresses to fatty degeneration, as assessed by MRI, and ultimately to new bone formation in the form of syndesmophytes [5–7]. The link between baseline levels of inflammation and the development of structural damage in the SI joints is supported by a study that explored the risk factors for progression of non-radiographic to radiographic axial SpA [8]. Longitudinal analysis of 12-year data from the Outcome in Ankylosing Spondylitis International Study (OASIS) cohort, which found that disease activity assessed by the Ankylosing Spondylitis Disease Activity Score (ASDAS) was longitudinally associated with radiographic progression, provides the strongest evidence to date that inflammation leads to new bone formation [9].

Radiographic scoring methods in AS

A number of scoring methods are available for assessing radiographic damage in AS. These include the BASRI, a grading system that evaluates radiographs of the anteroposterior view of the pelvis, the anteroposterior and lateral views of the lumbar spine and the lateral view of the cervical spine [10]; the Stoke Ankylosing Spondylitis Spinal Score (SASSS) that evaluates posterior and anterior corners of the lumbar spine for erosions, sclerosis, squaring, syndesmophytes and total bony bridging [11]; the mSASSS, which is a modification of the SASSS and

evaluates only the anterior edges of both the lumbar and cervical spine on a lateral view [12]; and the Radiographic Ankylosing Spondylitis Spinal Score (RASSS), a newer scoring method that includes vertebral segments assessed in the mSASSS and additionally the lower vertebrae of the thoracic spine (T10–T12), scoring structural damage entirely based on new bone formation [13].

A limitation of all the available radiographic scoring systems may be the inability to assess involvement of the facet joints [14, 15]. Furthermore, the thoracic spine is not assessed using the BASRI, SASSS or mSASSS scoring methods; this is largely due to technical reasons, such as superimposition of the lungs on the thoracic vertebrae in plain radiographs [10, 11]. As MRI studies have shown the lower half of the thoracic spine to be most frequently affected by active inflammation and structural changes in patients with AS [16], the sensitivity of these scoring systems is limited by the fact that radiographic changes in the thoracic spine are not measured. The RASSS scoring method tried to overcome this limitation by adding the three lower thoracic vertebrae to the score, and the original study describing the RASSS demonstrated that this method had an increased sensitivity to change, compared with mSASSS [13]. However, another study comparing the performance of the RASSS to the mSASSS concluded that the contribution of the thoracic spine was negligible and did not warrant the additional time that is required in scoring, especially given that thoracic spine radiographs are technically challenging to obtain routinely in the clinical setting and may not be of the quality needed for adequate assessment in a clinical trial [17].

A study comparing three of these methods (i.e. BASRI, SASSS and mSASSS) concluded that mSASSS is the most appropriate method by which to score radiographic progression in AS clinical trials. The BASRI and SASSS had lower sensitivity to change relative to mSASSS, and while the BASRI had the advantage of reduced scoring time, it yielded the highest radiation exposure to patients and lowest sensitivity to change [18]. Consequently, the Assessment of SpondyloArthritis international Society and OMERACT group have endorsed the mSASSS as the preferred scoring method for radiographic progression in AS [18, 19].

More recently, a published study of 98 patients with AS assessed a novel scoring method—the Combined Ankylosing Spondylitis Spine Score, which evaluates all vertebral bodies captured in the mSASSS along with the cervical facet joints from C2 to C7. Based on the OMERACT filter, the Combined Ankylosing Spondylitis Spine Score performed similarly to the mSASSS with respect to feasibility and discrimination, while demonstrating greater truth value (i.e. Is the measure truthful, and does it measure what is intended? How valid is the measure?) because of its ability to assess a broader range of structural changes and to capture an increased number of AS patients with progression [20].

Scoring of the mSASSS

The mSASSS is a well-validated scoring method for quantifying chronic structural changes on conventional

radiographs. The methodology originally described by Creemers *et al.* recommended scoring each upper and lower vertebral edge as follows (see sample diagram in Fig. 1): 0=no abnormality; 1=erosion and/or sclerosis and/or squaring; 2=syndesmophyte (non-bridging); 3=total bony bridging between upper and lower vertebral edges (ankylosis), with the exception that the third cervical vertebra C3 is not scored for squaring. The total mSASSS (range: 0–72) is the sum of scores calculated for the 24 vertebral edges included in the lumbar and cervical scoring system, based on lateral radiographic views of the vertebrae [12].

Progression of structural damage in AS patients may be presented as the absolute change in mSASSS, the proportion of patients with progression exceeding a particular cut-off value [e.g. an increase in mSASSS of >0 or >0.5 U if using the mean scores of two readers, or an increase above the smallest detectable change (SDC)] [21], or the proportion of patients with new syndesmophyte(s). It is important to present the data in cumulative probability plots to show the coherence of the data and to take the negative changes into account [22]. A 2-year interval has been established as the shortest follow-up time to detect progression in an acceptable number of patients based on the reliability and sensitivity to change of the mSASSS [19, 23], although some research has advocated an interval as short as 1 year [12].

Scoring radiographs in AS clinical trials

To avoid reader bias, readers should be blinded as to the patient, time point and treatment assignment. Typically, two or more independent readers evaluate radiographs separately, with an average score used in the analysis. Films may be grouped for each patient but presented with readers blinded to the time point of the radiographs (paired scoring) or in chronological order of the radiographs. While research has suggested that reading films chronologically increases the ability to detect changes in comparison with paired reading, this method has the potential to result in an over-estimation of progression based on the readers' expectation [24]. It is questionable whether this is a disadvantage, however, provided that readers remain blinded to patient and treatment information. Adjudication of discrepant change scores between two readers by a third reader is a method commonly used to reduce variability of the final overall mSASSS. An even better alternative would be to use three blinded readers, which increases the precision and obviates the need for adjudication.

A percentage of the radiographs may also be scored a second time by the same reader for use in determining intra-rater variability, while inter-reader variability may be determined from the two readers' scores of all radiographs. The reliability of scoring is assessed by calculating inter- and intra-observer correlations by the intraclass correlation coefficient; additional information may be obtained by calculating the SDC and using Bland and Altman analysis on the progression intervals of mSASSS [25, 26].

The SDC represents the smallest change that can be detected beyond measurement error and is calculated as $SDC = (1.96 * s.d.diff) / (\sqrt{k} * \sqrt{2})$, where s.d. diff is the standard deviation (s.d.) of the set of differences in change scores of two readers and k is the number of readers whose change scores are used [21]. The SDC can be used to determine whether the progression in an individual patient is larger than measurement error. The SDC values reported from studies that scored radiographs in a blinded manner range from 1.8 to 2.8 mSASSS units [2, 27]. Two studies that scored radiographs in chronological order reported SDC values of 2.3 and 2.9 U [26, 28]. An increase of 2 U may reflect the formation of at least one new syndesmophyte at any vertebral edge or the development of erosions, sclerosis, and/or squaring in at least two vertebral edges [12].

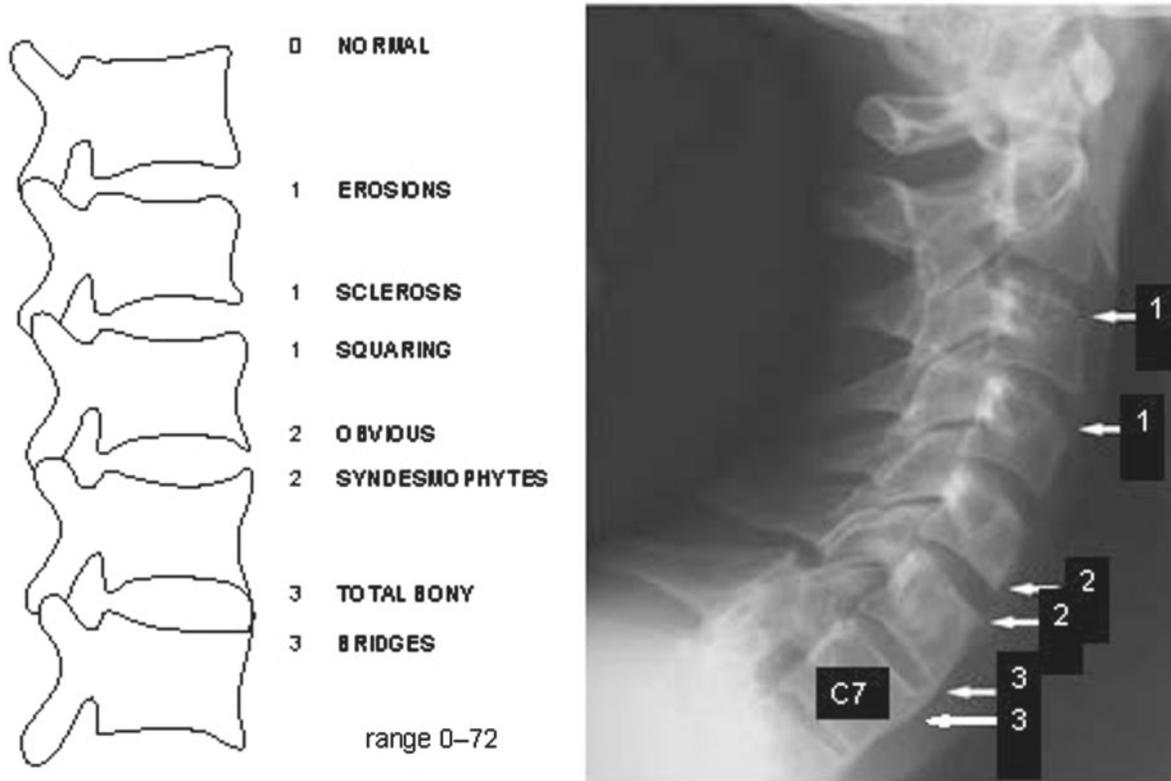
Use of mSASSS as an outcome measure in clinical studies

Radiographic damage in AS generally takes several years to progress [23]. Highly variable rates of radiographic structural progression have been identified in individuals with AS [26, 29]. One longitudinal study of AS patients naïve to TNF inhibitors that scored radiographs in chronological order reported that ~25% of patients showed no progression, 25% showed a high level of progression (at least one 2-year interval with progression of ≥ 5 mSASSS units) and the remaining patients showed progression rates of ~2 mSASSS units over 2 years [26]. A constant rate of 0.98 mSASSS units/year was reported over the 12-year study period, with 60% of all AS patients developing at least one new syndesmophyte over that timeframe [26]. Another longitudinal study of the Groningen Leeuwarden AS cohort that includes TNF inhibitor-treated patients with severe AS and that also scored radiographs in chronological order estimated a mean progression rate of 1.7, 1.6 and 1.1 mSASSS units during time periods of 0–2, 2–4 and 4–6 years, respectively [30].

At a group level, mean changes in mSASSS from baseline to year 2 that have been reported in studies using a blinded approach to scoring radiographs range from 0.2 to 1.5 U in NSAID-treated AS patients [31–34] and 0.4–1.3 U in TNF inhibitor-treated patients (Table 1) [28, 34–38]. In a separate study that used a blinded approach to scoring radiographs and stratified patients according to whether they had syndesmophytes at baseline, the mSASSS from baseline to year 2 was 2.6 U in patients with syndesmophytes compared with 0.8 in patients without [2]. Using a chronological approach to reading radiographs, a mean change in mSASSS from baseline to year 2 of 1.6 has been reported for TNF inhibitor-treated patients [30].

The mean change in mSASSS may serve as a primary end point measure in randomized and controlled prospective studies comparing different interventions, but to date this has not been performed. There is no universally agreed upon mSASSS cut-off value defining radiographic progression and it is debatable whether choosing a high

Fig. 1 Sample mSASSS scoring (from 0 to 3) for spinal vertebral edges



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or low mSASSS threshold is preferable. While a number of studies have defined progression as an increase of ≥ 2 mSASSS units over 2 years [33, 35, 39], other studies have defined radiographic progression as any change in mSASSS of >0 U over time [31, 37]. Spinal radiographic progression over 2 years has been further classified, according to Baraliakos *et al.* [29], as slow (<2 mSASSS units), moderate (2–5 mSASSS units) or fast (>5 mSASSS units). Table 1 provides a summary of mSASSS changes after 2 years of treatment with NSAIDs and biologic therapies in studies assessing effects on progression of radiographic damage in patients with AS.

Nonsteroidal anti-inflammatory drugs and structural progression

The mSASSS has been used as an outcome measure to evaluate the ability of NSAIDs and biologic agents to inhibit structural progression in AS, with varying results (Table 1). There is some evidence from a randomized controlled trial (RCT) to suggest a potential benefit of NSAIDs in preventing structural progression in AS, with continuous use of celecoxib having an inhibitory effect on structural progression over a 2-year time period [31], although data from a more recent RCT with diclofenac failed to corroborate this [32]. *Post hoc* analysis of the celecoxib trial

demonstrated that patients with elevated vs normal levels of acute-phase reactants, including CRP, and ESR saw the most benefit from treatment with continuous celecoxib, in terms of radiographic progression [40]. Analysis of the German Spondyloarthritis Inception Cohort of patients with AS also provides support for NSAIDs retarding radiographic spinal progression, with high NSAID intake being associated with lower mSASSS progression over 2 years, as compared with low NSAID intake, particularly in those with syndesmophytes or abnormal CRP levels at baseline [41].

TNF-inhibitors and structural progression

While TNF-inhibitors have been reported to improve the signs and symptoms of AS [42], there are no data available to date from prospectively controlled and randomized studies to demonstrate a reduction in spinal radiographic progression in AS with anti-TNF treatment (Table 1). It is not considered ethical to expose patients with AS to ineffective treatment in a 2-year placebo-controlled trial. Thus, data on radiographic progression with different anti-TNF inhibitors have been compared with data from historical control cohorts, such as OASIS, whose participants are naïve to treatment with biologic agents. These historically controlled cohort comparisons have shown no significant benefit of

TABLE 1 Summary of mSASSS changes after 2 years of treatment in studies assessing effects on progression of radiographic damage in patients with AS

Baseline characteristics								
Clinical Study	Treatment/cohort	Number of patients ^a	Time since diagnosis, years ^b , mean (s.d.) or median (IQR)	mSASSS value, mean (s.d.)	Radiograph scoring approach	SDC, mSASSS units	% patients as reported with progression or non-progression (mSASSS cutoff, units) at year 2	Mean change in mSASSS from baseline to year 2, mean (s.d.) or 95% CI
NSAIDs								
Randomized trials								
Effects of NSAIDs on Radiographic Damage in Ankylosing Spondylitis (ENRADAS; NCT00715091) 2-year RCT (2016) [32]	Diclofenac (on-demand)	60	17.0 (12.6)*	16.4 (18.2)	Blinded	NR	Non-progression (≤ 0 U) in ~55% of both treatment groups ^c	0.8 (0.2, 1.4)
2-year RCT (2005) [31] and post hoc analysis (2012) [40]	Diclofenac (continuous) Celecoxib ^d (on-demand) Celecoxib ^d (continuous)	62 74 76	12.8 (11.3) 10.2 (9.3) 13.0 (10.2)	10.9 (15.5) 9.3 (15.2) 7.9 (14.7)	Blinded	NR	Progression (> 0 U) in 45% of on-demand vs 22% of continuous group Progression (≥ 3 U) in 23% of on-demand vs 11% of continuous group Progression (≥ 2 U) in 28% (low CRP) and 38% (high CRP) of on-demand vs 24% (low CRP) and 13% (high CRP) of continuous group	1.3 (0.7, 1.9) 1.5 (2.5)* 0.4 (1.7)
Observational studies								
Analysis of the German Spondyloarthritis Inception Cohort (GESPIC) Observational study (2012) [41]	Low intake NSAID (NSAID index < 50) High intake NSAID (NSAID index ≥ 50)	64 24	5.0 (2.9) 5.5 (2.7)	5.7 (11.6) 6.7 (7.7)	Blinded	NR	Progression (≥ 2 U) in 8.3% (high intake NSAID) vs 21.9% (low intake NSAID) of AS patients	1.0 (2.8)* 0.02 (1.39)
Analysis of German cohorts, including GESPIC, naive/not naive to TNF inhibitors (GESPIC; 2007) [2]	German cohorts	116	11.0 (8.2)	9.3 (14.0)	Blinded	2.0	Progression (> 0) in 42.2% Progression ($> \text{SDC}$) in 27.6%	2.6 (4.0) in patients with syndesmophyte at BL vs 0.8 (1.4) in patients without*

(continued)

TABLE 1 Continued

Baseline characteristics								
Clinical Study	Treatment/cohort	Number of patients ^a	Time since diagnosis, years ^b , mean (s.d.) or median (IQR)	mSASSS value, mean (s.d.)	Radiograph scoring approach	SDC, mSASSS units	% patients as reported with progression or non-progression (mSASSS cutoff, units) at year 2	Mean change in mSASSS from baseline to year 2, mean (s.d.) or 95% CI
TNF inhibitors								
Randomized trials (without radiographic control arm)								
GO-RAISE (NCT00265083) 4-year RCT (2014) [35]	Golimumab 50 mg Golimumab 100 mg	111 122	5.2 (1.6–11.6) ^e 5.2 (1.5–13.3) ^e	11.7 (16.4) 13.5 (18.9)	Blinded	NR	Progression (≥ 2 U) in 26.1% of golimumab 50 mg group vs 28.7% of golimumab 100 mg group at 4 years ^f	0.9 (2.7) 0.9 (3.9)
Historical control cohort comparison								
Comparison of 2-year pooled data from the ATLAS study (NCT00085644) and a Canadian AS study (M03-606; NCT00195819) vs an historic anti-TNF-naïve cohort (2009) [37]	Adalimumab OASIS	307 169	11.2 (9.3) 11.3 (8.7)	19.8 (19.3)* 15.8 (17.6)*	Blinded	NR	Non-progression (≤ 0 U) in ~55% of adalimumab group vs ~58% of OASIS cohort ^e	0.8 (2.6) 0.9 (3.3)
Comparison of 2-year data from RCT (NCT00356356) vs an historical cohort naïve to TNF inhibitors (2008) [34]	Etanercept OASIS	257 175	10.0 (8.5) 11.0 (8.5)	16.0 (18.3) 14.0 (17.6)	Blinded	NR	Non-progression (≤ 0 U) in ~55% of etanercept group vs ~55% of OASIS cohort ^c	0.9 (2.5) 1.0 (3.2)
Comparison of 2-year data from ASSERT, a double-blind RCT, vs an historic cohort naïve to TNF inhibitors (2008) [36]	Infliximab OASIS	156 165	10.2 (8.7) 11.3 (8.6)	17.7 (17.9) 15.8 (18.1)	Blinded	NR	Progression in infliximab group vs OASIS cohort: >1 U: 34% vs 35% >2 U: 20% vs 18% >3 U: 15% vs 10% >4 U: 11% vs 7%	0.9 (2.6) 1.0 (3.2)
Comparison of 2-year data from RCT vs a cohort naïve to TNF inhibitors (GESPIC; 2005) [38]	Infliximab GESPIC	41 41	15.5 (3–35) ^{e,*} 5.5 (1–10) ^{e,*}	12.2* 5.9*	Blinded	NR	Progression (≥ 1 U) in 17% of infliximab group vs 12% of GESPIC cohort	0.4 (2.7) 0.7 (2.8)

(continued)

TABLE 1 Continued

Clinical Study	Treatment/cohort	Baseline characteristics					SDC, mSASS units	% patients as reported with progression or non-progression (mSASSS cutoff, units) at year 2	Mean change in mSASSS from baseline to year 2, mean (s.d.) or 95% CI
		Number of patients ^a	Time since diagnosis, years ^b , mean (s.d.) or median (IQR)	mSASSS value, mean (s.d.)	Radiograph scoring approach	Progression (>SDC) in			
Observational studies									
Groningen Leeuwarden AS (GLAS) ^g	Infliximab, etanercept, or adalimumab	163	6 (1–15) ^g	10.0 (15.5) ^h	Chronological order	2.3	Progression (>SDC) in 25%	1.6 (2.8)	
Prospective longitudinal observational study (2016) [30]									
GLAS ^g	Infliximab, etanercept, or adalimumab	176	5 (1–14) ^e	11 (5–24) ^e	Blinded	NR	Progression: <2 U: 70% of patients 2–5 U: 18% of patients >5 U: 12%	1.3 (3.2)	
Prospective longitudinal observational study (2015) [28]									
IL-17 inhibitor									
Randomized trials (without radiographic control arm)									
MEASURE 1	Secukinumab iv-75 mg	82	7.8 (8.9)	10.8 (16.7)	Blinded	2.8	Non-progression (mSASSS-<SDC) in >80% of AS patients ⁱ	0.3 (3.0)	
(NCT01358175)	Secukinumab iv-150 mg	86	6.6 (7.0)	9.6 (16.6)				0.3 (1.9)	
2-year RCT (2016) [27]									

^aSignificant differences ($P < 0.05$) between treatment groups (after adjustment for radiographic status at baseline in GESPIC). ^bNumber of patients with baseline and year 2 radiographic images. ^cData for TNF inhibitors, with the exception of golimumab, are disease duration in years. ^dVisual estimation based on cumulative probability plots. ^ePatients who discontinued celecoxib (due to inefficiency or adverse event) were allowed to continue the study with any other NSAID, but were instructed to maintain the allocated dosing strategy (on-demand or continuous treatment only); ~73% of patients in both groups used celecoxib during the entire study period. ^fValues are median (interquartile range). ^gData unavailable at 2 years. ^hA different mSASSS scoring approach was performed in these studies using patients from the GLAS cohort. ⁱBaseline data for all patients in study ($n = 210$). ^jAs defined by SDC at 80% level of agreement (i.e. 1.838). **ASSERT**: Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy; **ATLAS**: Adalimumab Trial Evaluating Long-Term Efficacy and Safety for Ankylosing Spondylitis; **BL**: baseline; **GESPIC**: German AS cohort (GESPIC); **GLAS**: Groningen Leeuwarden AS; **IQR**: interquartile range; **mSASSS**: modified Stoke Ankylosing Spondylitis Spinal Score; **NR**: not reported; **OASIS**: Outcome in Ankylosing Spondylitis International Study; **OR**: odds ratio; **RCT**: randomized controlled trial; **SDC**: smallest detectable change.

anti-TNF therapies on structural progression after 2 years (Table 1) [34, 36, 37].

Multiple observational studies have suggested that TNF inhibitors have either no effect or a possible effect on structural progression; however, it is difficult to draw firm conclusions from these studies, since a comparison with similarly active but untreated patients was lacking [30, 35, 41]. Data from prospective longitudinal studies suggest that TNF inhibitors may have a delayed beneficial effect on, or deceleration of, radiographic progression, but it is unknown if this effect is attributable to confounding factors that may influence radiographic progression. These studies were observational and include follow-up data from the Groningen Leeuwarden AS cohort out to 8 years [30], a North American cohort out to 9 years [range 1.5–9 years; mean 2.87 (1.17)] [43], and from extension studies out to 4 years (GO-RAISE, RAPID-axSpA) [35, 44]. The findings of one such study [43] have been criticized over methodological concerns [45]. Two recent studies, one of which has been published as an abstract, adjusted for confounding by indication and provide circumstantial evidence that TNF inhibitors may have some inhibitory effect on radiographic progression; this effect appears to be mediated by reducing disease activity [46, 47].

IL-17A inhibitors

Recent radiographic results of biologic treatment that blocked a different cytokine pathway in patients with AS have been reported from the MEASURE 1 study, a randomized trial of secukinumab (an IL-17A inhibitor). Two-year data from the trial demonstrated a mean change in mSASSS of 0.3 U [27]. However, it is difficult to interpret the significance of the finding and the findings from other similarly designed studies of TNF inhibitors, due to the uncontrolled nature of the studies.

Risk factors for radiographic progression in AS

The most widely studied factor in relation to radiographic progression is the level of inflammation. An association between radiographic progression and higher baseline CRP levels has been demonstrated in several shorter-term studies [9, 33, 40]. It is only recently that a significant longitudinal association could be demonstrated between radiographic progression and disease activity in AS, with ASDAS being the most significant measure, in a 12-year follow-up of the OASIS cohort [9]. This was confirmed in an analysis of the German Spondyloarthritis Inception Cohort cohort [48]. However, the evidence for BASDAI alone as a risk factor for structural damage progression has been less consistent, with one study demonstrating an association [10], while others have not [33, 49].

Several baseline risk factors have been associated with the formation of new bone in the spine of patients with AS, the most significant of which appears to be the presence of radiographic damage at baseline, as assessed by mSASSS or by the number of syndesmophytes [9, 28, 29]. Results of a retrospective cohort study showed

syndesmophyte formation in 44% of patients with radiographically detectable damage (syndesmophytes or ankylosis) at baseline, compared with only 19% in patients without syndesmophytes at baseline [2]. A more recent prospective longitudinal cohort study indicated the risk of radiographic progression was 4-fold higher in patients with pre-existing syndesmophytes [28].

The presence of fatty lesions on MRI is also reported to be an important risk factor in the development of structural damage [5–7].

Younger age and shorter symptom duration have also been established as risk factors for radiographic progression [9]. Other risk factors for structural damage progression include male gender, smoking and having a physically demanding job [9, 26, 28, 43, 50].

When evaluating spinal radiographic progression, the risk factors above need to be borne in mind, as analyses should be adjusted for patient characteristics that have the potential to influence radiographic progression [30].

Relationship between mSASSS and spinal mobility/physical function in AS

According to the stratified model of health outcomes published by Machado *et al.* [51], spinal mobility is determined by structural damage and inflammation of the spine, while physical function is determined by spinal mobility and disease activity.

An association between structural damage, as measured using mSASSS, and impaired spinal mobility, as assessed by multiple disease outcomes, has been established at a group level in several studies (supplementary Table S1, available at *Rheumatology* online); however, at an individual patient level, the relationship between spinal radiographic findings and spinal mobility is variable [52–55]. An analysis of the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy cohort demonstrated that spinal mobility impairment in AS is independently determined both by reversible spinal inflammation, as measured by MRI, and irreversible spinal damage, as measured by mSASSS [56].

Analysis of the OASIS cohort has demonstrated that functional impairment in AS is independently associated with both patient-reported signs and symptoms of disease activity and the degree of structural damage in both the cervical and lumbar spine, as assessed by the mSASSS [9]. Radiographic abnormalities including syndesmophytes, in addition to erosions, sclerosis and squaring of vertebral edges, were found to contribute to impaired physical function [1].

Other imaging techniques to monitor structural disease progression in AS

Although less validated, other imaging techniques can also prove useful in monitoring changes in AS patients (disease activity and/or structural damage), including MRI and CT; the strengths and weaknesses of these techniques are summarized in Table 2. MRI can be used to

TABLE 2 Strength and weaknesses of spinal imaging techniques in patients with AS

Imaging technique	Strengths	Weaknesses
Conventional radiography [3, 57]	Relatively less expensive and widely available Relatively rapid review	Unable to visualize the thoracic spine reliably Radiation exposure Long duration (≥ 2 years) required to detect structural progression, precluding placebo-controlled trials
MRI [3, 57]	Detects inflammatory changes in bone and soft tissue Does not use radiation Tomographic method Allows visualization of the thoracic spine	Long acquisition time Scoring of MR images can be time-consuming More expensive and less widely available than conventional radiography Value in detecting new bone formation is limited
CT [3, 57]	Rapid technique Tomographic method Excellent visualization of bone Allows visualization of thoracic spine Sensitive method for detection of new bone formation	Use of ionizing radiation More expensive and less widely available than conventional radiography

detect inflammatory changes in the spine [57, 58] and has been compared with radiography in the assessment of chronic structural changes in the spine [59] and SI joints [60]. There are several emerging MRI techniques that may prove useful in assessing mineralized bone and subsequent new bone formation; for example, using chemical shift-encoded MRI to map transverse relaxation rate ($R2^*$) as a potential marker of bone marrow composition and structure [61].

CT provides a sensitive method for assessing structural changes in the spine and has the advantage over conventional radiography of being able to detect structural changes in the thoracic spine [62]. At present, conventional radiography is considered the preferred method for detecting structural progression in AS [57], but this may change in the near future with the use of low-dose CT scanning, which may offer a more sensitive means than conventional radiography of assessing structural damage. This modality has the increased sensitivity of CT for structural changes in the spine, with a 10-fold lower radiation dose than conventional CT and, thus, has the potential for being more sensitive than conventional radiography in detecting structural changes in AS. However, the radiation dose is still 10-fold higher than with conventional radiographs, but with new imaging software this may be reduced. Future studies comparing assessments with low-dose CT vs mSASSS would be of interest.

A number of spine scoring systems have been developed for use with MRI in AS, such as the Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity score, the Berlin modification of the Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity and the Spondyloarthritis Research Consortium of Canada score, all of which assess spinal inflammation [63–65], as well as the Canada-Denmark scoring system, which can also be used to assess structural changes on MRI [66]. The CT syndesmophyte scoring

system is a validated method to assess bone formation on spinal CT scans of the spine [67]. Use of the currently available imaging measures to monitor structural damage progression may be challenging in clinical practice due to the paucity of experienced readers; thus, development of an automated means of assessing spinal structural damage may be of value.

Conclusions

Interventions that slow or halt the progression of irreversible structural damage in AS are expected to confer clinical benefits in terms of delaying loss of function and improving quality of life. Preventing the progression of structural damage in the spine is, therefore, an important goal in the treatment of AS [45]. This review explores the validity of the mSASSS as a primary outcome measure to evaluate the efficacy of treatments for AS in terms of structural damage progression.

A scoping review of the literature showed that there are a number of scoring methods available for assessing radiographic damage in AS, although the advantages of the mSASSS over other scoring methods such as the BASRI and SASSS to measure radiographic progression in AS clinical trials have been noted [18]. Moreover, multiple studies have demonstrated the association between the mSASSS and worsening measures of AS signs and symptoms, spinal mobility and physical function [9]. The inability of the mSASSS (and, similarly, the BASRI and SASSS) to monitor radiographic changes in the thoracic and other parts of the spine is a limitation that restricts sensitivity [38]. Nonetheless, the mSASSS is deemed the preferred scoring system of spinal radiographs in comparison to the newer RASSS method, which includes the thoracic spine [17], and the mSASSS has been endorsed by OMERACT and Assessment of SpondyloArthritis international Society experts as an

appropriate clinical research outcome measure, given its reliability, sensitivity to change and proven feasibility for use [19]. Although other imaging techniques such as MRI and CT can prove useful in detecting structural damage in patients with AS, and while several years are required to detect structural changes by conventional radiography, X-ray assessments are the most widely validated modality for monitoring structural progression in AS. Comparisons of structural assessments using X-rays to other imaging modalities, such as low-dose CT, would be of interest.

The mSASSS has never been used as a primary outcome measure in prospective, controlled and randomized clinical trials of biologics with a comparator arm out to 2 years. Despite the large number of completed and ongoing studies in AS that have used the mSASSS, there are no data from prospective studies that provide a long-term controlled comparison to confirm that treatment with any biologic is associated with a reduction in spinal structural progression in patients with AS [34, 36–38]. Therefore, well-designed head-to-head studies are needed to establish the role of biologic therapies in slowing the progression of structural damage in AS, for which the mSASSS can be used as a primary outcome measure.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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