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Biologic therapy and spinal radiographic progression in patients with axial spondyloarthritis: A structured literature review

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***Abstract*:**
We aimed to perform a structured literature review of spinal radiographic progression, as assessed by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS), in patients with ankylosing spondylitis (AS) or nonradiographic axial spondyloarthritis (nr-axSpA) treated with biologic therapy. Searches were limited to English language manuscripts published in the 11 years prior to 9 July 2019. Randomized controlled trials, open-label extensions (OLEs) and observational studies reporting mSASSS progression in patients with AS or nr-axSpA treated with biologics were eligible for inclusion. Bias was assessed using the methodological index for nonrandomized studies (MINORS) tool. Among the 322 studies identified in the literature search, 23 (11 OLEs and 12 cohort studies) met the eligibility criteria and were selected for inclusion. Most studies reported mSASSS progression in patients with AS receiving tumor necrosis factor inhibitor (TNFi) treatment. One study reported mSASSS progression in patients with AS treated with secukinumab, an interleukin-17A inhibitor. The mean (range) MINORS score was 11.3 (7–15) for the 15 noncomparative studies and 15 (12–22) for the 8 comparative studies. Although results of the individual studies were variable, mSASSS progression in patients with AS was generally minimal and slow with long-term TNFi therapy. Moreover, odds ratios for the likelihood of mSASSS progression with/without TNFi favoured TNFi therapy in several of the cohort studies. The rate of mSASSS progression following continuous secukinumab treatment was low and remained stable over 4 years. Of two studies reporting progression in patients with nr-axSpA treated with TNFis, one showed no mSASSS progression; however, the lack of control limited comparative conclusions.

Keywords: ankylosing spondylitis, biologic therapy, interleukin-17A inhibitor, radiography, tumor necrosis factor inhibitor

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Introduction

Spondyloarthritis, characterized by inflammation of the spine and peripheral joints, includes a range of diseases such as axial spondyloarthritis (axSpA), psoriatic arthritis, reactive arthritis and enteropathic arthritis.[1,2] AxSpA is a chronic inflammatory disease with a heterogeneous clinical phenotype that primarily affects the sacroiliac joints and spine. It represents a spectrum of disease, including ankylosing spondylitis (AS, also known as radiographic axSpA) and nonradiographic axial spondyloarthritis (nr-axSpA).[3,4] According to the 1984 modified New York criteria, definitive radiographic sacroiliitis is required for the classification of AS.[5] However, it has become apparent that this occurs late in the disease course for many patients and signs of inflammation in the sacroiliac joints and spine can be

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detected much earlier using magnetic resonance imaging (MRI). Patients with nr-axSpA may also show some evidence of spinal radiographic damage although the extent of damage is less than that reported in patients with AS.[6]

Initial pharmacological treatment for patients with symptomatic axSpA and predominantly axial involvement consists of nonsteroidal anti-inflammatory drugs (NSAIDs), with tumor necrosis factor inhibitor (TNFi) treatment recommended as standard practice for those patients with persistently high disease activity despite NSAID treatment.[7,8] Five TNFis are indicated for patients with AS: adalimumab, certolizumab pegol, etanercept, golimumab and infliximab. A number of these agents are also approved for nr-axSpA, though this differs by country/region. In Europe, for example, all except infliximab are indicated for nr-axSpA but only certolizumab pegol is approved for nr-axSpA in the USA.[9,10] In addition, interleukin (IL)-17A inhibitors are approved for the treatment of patients with AS: secukinumab in both Europe and the USA[11,12] and ixekizumab in the USA;[13] as yet, no efficacy data are available in patients with nr-axSpA.

Prevention of structural damage is one of the key treatment goals for patients with axSpA[7] and spinal radiographic damage is shown to be an important determinant of spinal mobility and functional impairment.[14,15] However, although the clinical efficacy of biologic treatment has been established in terms of reducing inflammation and disease activity and improving patients' function,[16–18] the relatively slow rate of syndesmophyte formation and limited sensitivity of conventional radiography has made it difficult to determine the impact of biologics on spinal radiographic progression.[17,19] It is thought that inflammation of subchondral bone marrow leads to local repair processes and subsequent new bone formation, suggesting that early anti-inflammatory treatment may not only be able to halt inflammation but also prevent subsequent new bone formation and radiographic progression.[20]

A minimum follow-up period of 2 years is required to assess spinal progression on plain radiographs and, because TNFis have proven clinical efficacy, a 2-year placebo-controlled trial would not be ethical.[21] As such, several early open-label extension (OLE) studies compared spinal radiographic progression during TNFi treatment (infliximab, etanercept and adalimumab) with progression in the historical Outcome in Ankylosing Spondylitis International Study (OASIS) cohort, as measured by the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).[21–23]

Several scoring methods for the measurement of radiographic progression in clinical trials of AS are available. The mSASSS has demonstrated several advantages over items such as the Bath Ankylosing Spondylitis Radiology Index (BASRI) and the unmodified SASSS,[24] with changes in the mSASSS having been shown to accurately reflect deterioration in the signs and symptoms of AS, spinal mobility and physical function.[25] The mSASSS can be considered the most validated and widely used tool for assessing radiographic progression in AS,[26] having been endorsed by OMERACT (Outcome Measures in Rheumatology) and Assessment of SpondyloArthritis international Society (ASAS) experts as an appropriate clinical research outcome measure, given its reliability, sensitivity to change and proven feasibility for use.[27]

Patients in the OASIS cohort were treated according to clinical practice at the time and did not receive TNFi therapy during the 2-year follow-up period. The results of these earlier studies suggested that TNFi treatment had no effect on spinal radiographic progression at 2 years compared with standard of care; however, the studies were not designed to control for characteristics such as smoking status or baseline disease activity assessed by Ankylosing Spondylitis Disease Activity Score (ASDAS). A prospective observational study reported that TNFi treatment was associated with a 50% reduction in the odds of mSASSS progression compared with no TNFi treatment (70% after propensity score matching), with patients treated within 10 years of disease onset less likely to show progression compared with patients treated later.[19] These results suggested that there may be a role for early and long-term biologic therapy in slowing down spinal radiographic progression in patients with AS. Because most studies in this area have only included patients with AS, the effect of biologic therapy on spinal radiographic progression in patients with nr-axSpA is not fully defined.

Our objective was to perform a structured literature review of spinal radiographic progression, as assessed by mSASSS, in patients with AS or nr-axSpA treated with biologic therapy.

Materials and methods

Structured literature search and study selection

'Structured reviews' are literature reviews that, while highly structured in approach, are not as rigorous as a full systematic review.[28–30] This approach was selected over a systematic review to evaluate the research question within a relatively short timeframe, while providing a comprehensive overview of the published literature on spinal radiographic progression with biologic therapy in patients with AS/nr-axSpA. This structured review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Search strategies were based on the objective for the structured review, as outlined in the introduction. Search terms were developed by reviewing the background literature for terms related to the research question; the full search strategy is shown in Table A1. Searches were conducted in PubMed (incorporating MEDLINE), EMBASE and the Cochrane library; the final search was conducted on 9 July 2019. Searches were limited to English language manuscripts that were published in the preceding 11 years, reflecting when data about spinal radiographic progression with TNFi treatment became available. Abstracts from conferences and meetings were excluded because they do not provide sufficient information for an assessment of bias. Review articles (with the exception of systematic reviews), commentaries, letters and editorials were also excluded from the search because these publications do not provide sufficient information required to answer the research question. Randomized controlled trials (RCTs) and OLEs were eligible for inclusion, as were relevant observational studies. Citations were downloaded into the reference management software EndNote X7 (Clarivate Analytics, Philadelphia, USA) to check for duplicates; deduplication was replicated with a manual search in Microsoft Excel. Citations and abstracts were screened for inclusion in Excel according to the eligibility criteria defined using the PICOS approach (population, intervention, comparator group, outcome and study design).[31] Per PICOS, the patient population was defined as patients with axSpA, including AS and nr-axSpA. The intervention was defined as any biologic, and the comparator as placebo, NSAIDs, other medications, usual standard of care or no comparator. The outcome was defined as spinal radiographic progression as determined by the mSASSS. The study design was limited to RCTs and their OLEs and relevant observational studies. Full manuscripts were obtained for any abstracts judged eligible for inclusion using PICOS, and their relevance assessed. Searches were screened and assessed for eligibility by one reviewer.

Data extraction and assessment

Data relating to study design, population and mSASSS results were extracted by one reviewer using a standardized extraction form. An assessment of bias for the outcome of interest was made using the methodological index for nonrandomized studies (MINORS) measure. The MINORS measure was selected because it is designed to assess the methodological quality of both noncomparative and comparative nonrandomized studies; furthermore, it is a validated instrument shown to have good reliability, internal consistency and validity.[32] The MINORS measure comprises an eight-item checklist of methodological criteria for nonrandomized studies, with four additional criteria specifically for comparative studies. For each criterion, the study is scored as 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The maximum possible score is 16 for noncomparative studies and 24 for comparative studies. As a statistical meta-analysis was not conducted, an overall assessment of quality across studies (such as heterogeneity or publication bias) was not performed.

The primary assessment was the reported likelihood of spinal radiographic progression by mSASSS in patients with AS or nr-axSpA treated with biologics. The results of this assessment are presented in tables and figures and narratively described.

Results

Literature search and selected studies

Among the 322 publications identified in the initial literature search, 23 met the eligibility criteria and were selected for inclusion (Figure A1). No RCTs were identified for inclusion; 11 studies were OLEs and the remaining 12 were cohort studies. A total of 20 studies looked at the effect of TNFi treatment on spinal radiographic progression; 12 of those examined the effect of multiple TNFis or TNFis as a class, and 8 examined the effect of specific TNFis (certolizumab pegol and golimumab were each assessed in one study, while adalimumab, etanercept and infliximab

were each assessed in two studies). Three publications looked at the effect of an IL-17A inhibitor, secukinumab, on spinal radiographic progression. Four studies (all cohort studies) assessed spinal radiographic progression in patients treated with TNFis compared with patients not treated with TNFis. Five studies (three OLEs and two cohort studies) compared spinal radiographic progression in patients treated with TNFis with historical cohorts of patients not treated with TNFis (the Herne, OASIS and Effects of Non-Steroidal Anti-Inflammatory Drugs on RAdiographic Damage in Ankylosing Spondylitis [ENRADAS] cohorts). The remaining 14 studies did not include any comparator group for the mSASSS assessment, although one of these compared prior TNFi use *versus* no prior TNFi use in a multivariate analysis. Most studies reported mSASSS progression in patients with AS (Tables 1 and 2); only two of the 23 eligible publications reported this specifically in patients with nr-axSpA (Table 1). The mean MINORS score for the 15 noncomparative studies was 11.3 (range 7–15) out of a possible score of 16. The mean MINORS score for the eight comparative studies was 15 (range 12–22) out of a possible score of 24, indicating that overall these studies were of lower methodological quality. The MINORS score for each study is reported alongside the respective mSASSS outcomes in Tables 1 and 2.

Effect of biologics on spinal radiographic progression in patients with AS

The studies reporting mSASSS outcomes in patients with AS were heterogeneous in terms of follow-up time and reported outcomes. Follow-up time ranged from 46 weeks to 10 years, with most studies reporting outcomes over a 2–4-year follow-up period. The majority of studies reported mSASSS at baseline and follow-up (Tables 1 and 2; Figure 1), with several studies reporting a statistic for the likelihood of progression in TNFi-treated patients compared with patients not treated with TNFis (Table 2).

Tumor necrosis factor inhibitors. The following studies are grouped according to design (OLE and cohort studies). Within each group, studies are reported chronologically, with the earlier studies presented first (Tables 1 and 2; Figure 1).

OLE studies. Three OLEs (1.8–2 years' follow-up) showed no significant difference in mSASSS progression between patients treated with TNFis (adalimumab, etanercept and infliximab) and the OASIS historical cohort of TNFi-untreated patients.[21–23] In the OLE of infliximab, 80.1% of patients had not progressed at 2 years (<2-point increase in mSASSS) compared with 82.4% of patients in the OASIS cohort. None of these three studies scored highly on the MINORS measure (Table 1). One short-term OLE study reported minimal mSASSS progression after 60 weeks of etanercept treatment.[33] In an OLE of the GO-RAISE golimumab study, 4-year mSASSS progression was low [mean ± standard deviation (SD): 50 mg, 1.3 ± 4.1; 100 mg, 2.0 ± 5.6].[34] The rate of mSASSS progression remained stable at years 2 and 4, and, after 2 years, 73.9% of patients randomized to golimumab 50 mg had not progressed (<2-point increase in mSASSS). An analysis of two long-term OLE studies of patients treated with infliximab or etanercept showed continuous slow mSASSS progression (about 1.2 mSASSS points every 2 years) over time;[35] however, this study scored lowest on the MINORS tool (7/16), indicating poor methodological quality. More recently, an OLE of the RAPID-axSpA study of certolizumab pegol demonstrated minimal mSASSS progression after 4 years, with a mean mSASSS change in patients with AS of 0.98 [95% confidence interval (CI) 0.34, 1.63].[37] The majority of progression was observed during the first 2 years of certolizumab pegol treatment (0.67), with a decrease in progression observed between years 2 and 4 (0.31; Table 1; Figure 1); at week 204, 80.6% of patients had not progressed (<2-point increase in mSASSS). Most recently, a 5-year study of 33 patients receiving TNFis (22 infliximab, 5 etanercept and 6 adalimumab)[39] showed mSASSS progression (⩾1 unit) in 19 patients, with 14 not progressing.

Cohort studies. In a 46-week cohort study of patients treated with TNFis, the rate of mSASSS progression was 0.94 ± 1.98 (mean ± SD).[40] In a study comparing radiographic progression in infliximab-treated patients *versus* the historical Herne cohort who had not previously received TNFis, the rate of mSASSS progression over 8 years was 0.9 ± 0.8 (mean ± SD) per year and 1.5 ± 1.4 per year, respectively;[34] however, this study had a low MINORS score (12/24). In a 4-year cohort study of patients treated with adalimumab or etanercept, mSASSS progression was reported at a rate of 0.90 per year.[42] No benefit of TNFi treatment was found in one cohort study: there was no significant difference in mSASSS change from baseline after a mean 5-year follow-up period in

Table 1. Studies of spinal radiographic progression over time in patients with AS or nr-axSpA treated with biologic therapies.

Study	Design	Therapy	mSASSS comparator	Duration of follow-up	N*	Baseline mSASSS#	Reported mSASSS outcomes#	Observed or modeled data†	MINORS score
OLE studies in AS									
van der Heijde *et al.* 2008[21]	OLE	Etanercept¶	Historical control (OASIS cohort)	96 weeks	432	- Etanercept (n=257), 16 ± 18.3 - OASIS (n=175), 14 ± 17.6 - OASIS matched** (n=76), 19 ± 20.8	mSASSS change from baseline at 96 wks - Etanercept, 0.91 ± 2.45 - OASIS 0.95 ± 3.18 - OASIS matched** 1.27 ± 3.64 p=1.0 for etanercept vs OASIS p=NS for etanercept vs OASIS matched**	Observed, adjusted, missing values imputed	12/24
ASSERT van der Heijde *et al.* 2008[22]	OLE	Infliximab	Historical control (OASIS cohort)	2 years	393	- ASSERT cohort (n=190), 17.7 ± 17.9 - OASIS (n=176), 15.8 ± 18.1 - OASIS matched** (n=65), 17.5 ± 19.1	mSASSS change from baseline - ASSERT (n=156), 0.9 ± 2.6 - OASIS (n=165), 1.0 ± 3.2 - OASIS matched** (n=61), 1.2 ± 3.9 p=0.541 for ASSERT vs OASIS p=0.683 for ASSERT vs OASIS matched** Non-progressors## - ASSERT, 80.1% - OASIS, 82.4%	Observed, adjusted	16/24
ATLAS, M03-606 (pooled analysis) van der Heijde *et al.* 2009[23]	OLE	Adalimumab¶	Historical control (OASIS cohort)	2 years	476	- Adalimumab (n=307), 19.8 ± 19.3 - OASIS cohort (n=169), 15.8 ± 17.6; p=0.028	mSASSS change from baseline to 2 years - Adalimumab, 0.8 (2.6) - OASIS, 0.9 ± 3.3 - OASIS matched (n=77), 0.9 ± 4.1 p=0.771 for adalimumab vs OASIS p=0.744 for adalimumab vs OASIS matched**	Observed, adjusted	14/24
Dijkmans *et al.* 2009[33]	OLE	Etanercept¶	None	60 weeks	67	- Placebo crossover (n=34), 11.95 ± 16.8 - Etanercept only (n=33), 18.27 ± 21	mSASSS at wk 60 - Placebo crossover, 11.79 ± 16.8 - Etanercept only, 18.63 ± 20.9 Change from baseline at wk 60 - Placebo crossover: -0.15 (96% CI -0.7, 0.4) - Etanercept only, 0.36 (95% CI -0.1, 0.8)	Observed	12/16
GO RAISE Braun *et al.* 2014[34]	OLE	Golimumab¶	None	208 weeks	299	- Placebo (n=66), 16.1 ± 18.7 - Golimumab 50 mg (n=111), 11.7 ± 16.4 - Golimumab 100 mg (n=122), 13.5 ± 18.9	mSASSS change from baseline to wk 104: - Placebo crossover, 1.6 ± 4.6 - Golimumab 50 mg, 0.9 ± 2.7 - Golimumab 100 mg, 0.9 ± 3.9 mSASSS change from baseline to wk 208 - Placebo crossover, 2.1 ± 5.2 - Golimumab 50 mg, 1.3 ± 4.1 - Golimumab 100 mg, 2.0 ± 5.6 Rate of mSASSS progression - At wk 104, 0.4 per year (both doses) - At wk 208, 0.4 (50 mg) and 0.5 (100 mg) per year	Observed Modeled	11/16

(Continued)

Table 1. (Continued)

Study	Design	Therapy	mSASSS comparator	Duration of follow-up	N*	Baseline mSASSS#	Reported mSASSS outcomes#	Observed or modeled data†	MINORS score
							Non-progressors¶¶ - Placebo crossover, 71.2% - Golimumab 50 mg, 73.9% - Golimumab 100 mg, 71.3%		
Poddubnyy *et al*. 2016[35]	OLE	TNFis (etanercept or infliximab)	None	10 years	60	All, 11.1±16.1 - Infliximab, (n=43), 11.2 ± 16.4 - Etanercept, (n=17), 10.9 ± 15.5	mSASSS at follow-up - Year 2 (n=57), 12.9 ± 17.2 - Year 4 (n=41), 12.0 ± 2.3 - Year 6 (n=34), 14.6 ± 17.1 - Year 8 (n=23), 16.0 ± 17.5 - Year 10 (n=17), 17.2 ± 17.7	Observed	7/16
MEASURE-1 Braun *et al*. 2017[46]	OLE	Secukinumab¶	None	104 weeks	168	- 75 mg (n=82), 10.8 ± 16.7 - 150 mg (n=86), 9.6 ± 16.6 - Pooled dose cohort (n=168), 10.22 ± 16.62	mSASSS change from baseline at wk 104 - 75 mg, 0.31 ± 3.04 - 150 mg, 0.30 ± 1.94 - Pooled dose cohort, 0.30 ± 2.53 Non-progressors†† - Pooled dose cohort, >80%	Observed	12/16
RAPID-axSpA van der Heijde *et al*. 2018[36]	OLE	Certolizumab pegol¶	None	204 weeks	113	13.2	mSASSS change from baseline§ - At wk 96, 0.67 - At wk 204, 0.98 - Years 0–2, 0.67 (95% CI 0.21, 1.13) - Years 2–4, 0.31 (95% CI 0.02, 0.60) mSASSS change from baseline§ - At wk 96 (n=59), 0.76 - At wk 204 (n=59), 1.12 Non-progressors## - At wk 96, 84.2% - At wk 204, 80.6%	Modeled Observed	11/16
MEASURE-1 Braun *et al*. 2019[47]	OLE	Secukinumab	None	4 years	155	150 mg (n=71), 8.6 75 mg not uptitrated (n=61), 8.5 75 mg uptitrated (n=23), 15.7	mSASSS change from baseline at wk 208 150 mg 9.9; Δ1.2 ± 3.91 75 mg not uptitrated 10.3; Δ1.8 ± 4.32 75 mg uptitrated 17.3; Δ1.6 ± 5.67 Non-progressors: 75 mg: 78.6%, 150 mg: 78.9%	Observed	13/16
Pedersen *et al*. 2019[37]	OLE	TNFis	None	5 years	33	10.5 ± 12.5	15.5 ± 13.9 Non-progressors## 42.4%	Observed	15/16
Cohort studies in AS									
Pedersen *et al*. 2011[38]***	Cohort (BIO-SPA cohort)	TNFis	None	46 weeks	36	Median: 13 (IQR 6, 24)	mSASSS at wk 46 - Median 15 (IQR 6, 24) p=0.005 for wk 46 vs baseline	Observed	10/16

(Continued)

Table 1. (Continued)

Study	Design	Therapy	mSASSS comparator	Duration of follow-up	N*	Baseline mSASSS#	Reported mSASSS outcomes#	Observed or modeled data†	MINORS score
Haroon *et al*. 2013[19]	Cohort	TNFis	TNFi untreated patients	TNFi 2.9 ± 1.03 years No TNFi 2.8 ± 1.10 years	334	TNFi 10.6 ± 14.9 (n=201) No TNFi 8.2 ± 13.8 (n=133)	Prior anti-TNF vs no TNF: OR 0.52 (95% CI 0.30, 0.88); p=0.02	Observed	18/24
Baraliakos *et al*. 2014[34]	Cohort	Infliximab (DIKAS cohort)	Historical control (Herne cohort)	8 years	56	- DIKAS cohort (n=22), 13.2 ± 17.6 - Herne cohort (n=34), 14.2 ± 13.8	mSASSS at follow-up - DIKAS cohort, 20.2 ± 21.4 - Herne cohort, 25.9 ± 17.8 p=0.047 for comparison between cohorts Rate of mSASSS progression - DIKAS cohort, 0.9 ± 0.8 per year - Herne cohort, 1.5 ± 1.4 per year p=0.129	Modeled, adjusted	12/24
Kim *et al*. 2016[40]	Cohort (OSKAR cohort)	TNFis	TNFi untreated patients	TNFi treated: Mean 5.01 ± 1.24 years TNFi untreated: Mean 5.09 ± 1.07 years	610	- TNFi treated (n=269), 18.87 (17.96) - TNFi untreated (n=341), 15.68 ± 15.49	mSASSS change from baseline - TNFi treated, 6.14 (SE 2.0) - TNFi untreated, 4.73 (SE 1.01) p=0.54 for comparison	Observed, adjusted	12/24
Park *et al*. 2016[39]	Cohort (SNUH-biologics cohort)	TNFis (adalimumab or etanercept)	None	4 years	165	13.5 ± 16.6	Rate of mSASSS progression - 0.90 per year	Modeled	14/16
Maas *et al*. 2017[41]	Cohort (GLAS cohort)	TNFis	None	6 years	80	8.7 ± 13.3	Overall rate of mSASSS progression - 0–2 years: 1.7 (95% CI 1.1, 2.3) - 2–4 years: 1.5 (95% CI 0.8, 2.3) - 4–6 years: 1.0 (95% CI -0.1, 2.1) *In patients with risk factors for progression*: - 0–2 years: maximum 2.8 across risk factors - 4–6 years: minimum 0.9 across risk factors In patients without risk factors for progression: - ⩽1 per 2 years Non-progressors§§: 75%	Modeled	14/16
Maas *et al*. 2017[42]	Cohort (GLAS cohort)	TNFis	None	8 years	210	10.0 ± 15.5	mSASSS change from baseline - At 2 years (n=163), 1.6 ± 2.8 - At 4 years (n=132), 3.5 ± 4.6 - At 6 years (n=80), 4.2 ± 4.8 - At 8 years (n=41), 7.0 ± 6.3	Observed	14/16
Jeong *et al*. 2018[43]	Cohort	TNFis	None	Mean 102.9 ± 54.9 months	151	7.6 ± 10.8	Overall rate of mSASSS progression - 1.01 ± 1.23 per year *TNFi use ⩾84 months after symptom onset vs within 84 months*: 1.32 ± 0.16 vs 0.68 ± 0.10; p=0.001	Observed	8/16

(Continued)

Table 1. (Continued)

Study	Design	Therapy	mSASSS comparator	Duration of follow-up	N*	Baseline mSASSS#	Reported mSASSS outcomes#	Observed or modeled data†	MINORS score
							TNFi continued for <40.9% of disease duration vs greater than ⩾40.9%: 1.23 ± 0.16 vs 0.79 ± 0.11; p=0.026		
Molnar *et al.* 2018[6]	Cohort (SCQM cohort)	TNFis	TNFi untreated patients	10 years	432	6.6 ± 12.5	Change for whole population over 2 years: 0.9 ± 2.3 Prior anti-TNF vs no TNF: OR 0.50 (95% CI 0.28, 0.88); p=0.02	Observed	10/16
Park *et al.* 2019[44]	Cohort	TNFis	NSAIDs	2 years	215	TNFi cohort (n=135), 6.2 ± 9.9 NSAID cohort (n=80), 7.3 ± 10.8	Change for whole population over 2 years: 1.30 ± 2.97 TNFi group showed significantly slower radiographic progression over 2-year intervals vs NSAID group in model that included baseline age, CRP level, smoking status, and the presence of syndesmophytes β = −0.90 (95% CI −1.51, −0.29)†††	Observed	22/24
Beek *et al.* 2019[45]	Cohort	TNFis	None	Mean 4.5 years	135	Median 4.8 (range, 1.6–22.2)	Median 6.5 (IQR 2.1-22.9) i.e. median increase of 2.5 mSASSS points in 4 years	Observed	11/16
MEASURE-1 Braun *et al.* 2019[48]	Cohort (ENRADAS cohort)	Secukinumab	NSAIDs	2 years	237	Mean ± SD Sec (n=168), 9.6 ± 14.1 NSAIDs (n=69), 9.9 ± 13.8	LS mean change (SE) 0.55 (0.139) 0.89 (0.216) Δ −0.34 (0.257) p=0.1852	Observed	14/24
OLE and cohort studies in nr-axSpA									
Cantarini *et al.* 2015[49]	Cohort	Adalimumab	None	Mean 23.7 (range, 6–76) months	37	0.625 ± 0.518	mSASSS at follow-up 0.540 ± 0.576 p=ns for follow-up vs baseline	Observed	8/16
RAPID-axSpA van der Heijde *et al.* 2018[36]	OLE	Certolizumab pegol¶	None	204 weeks	83	4.42	Change from baseline§ - To wk 96, -0.01 - To wk 204, 0.06 Change from baseline§ - To wk 96 (n=34), -0.03 - To wk 204 (n=34), 0.04	Modeled Observed	11/16

*For mSASSS assessment; #Mean ± standard deviation, unless otherwise specified; †Refers to whether outcomes were based on observed data only or estimated using statistical modelling of observed data (e.g. generalized estimating equation, mixed model repeated measures); ¶Includes crossover from placebo; §Change in least squares mean; **Sub-set of OASIS cohort matched for TNFi RCT trial entry criteria; ##Progression defined as ⩾2 point increase in mSASSS; ††Defined by the smallest detectable change at the 80% level; ¶¶Progression defined as >2 units change in mSASSS; §§Defined by the smallest detectable change; ***All patients had axSpA according to Assessment of SpondyloArthritis International Society criteria and 90% had AS according to the modified New York criteria; †††Indicates difference in mSASSS change in 2-year radiographic interval between the 2 groups (dichotomous variable) or when a covariate increases by 1 unit (continuous variable).

AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; BIO-SPA, Biomarkers in Spondyloarthritis; CI, confidence interval; DIKAS, Deutsche Infliximab Kohorte für AS; ENRADAS, Effects of Non-Steroidal Anti-Inflammatory Drugs on RAdiographic Damage in Ankylosing Spondylitis; GLAS, Groningen Leeuwarden AS; IQR, interquartile range; MINORS, methodological index for non-randomized studies; mSASSS, modified Stokes Ankylosing Spondylitis Spine Score; ns, not significant; OASIS, Outcome in Ankylosing Spondylitis International Study; OLE, open-label extension; OSKAR, Observation Study of Korean SpondyloArthropathy Registry; SE, standard error; SNUH, Seoul National University Hospital; TNF, tumor necrosis factor; wk, week.

Table 2. Relationship between TNFi treatment and spinal radiographic progression in patients with AS.

Study	Design	Therapy	Length of follow-up	N*	Baseline mSASSS#	Likelihood of progression	Type of analysis	MINORS score
Haroon *et al.* 2013[19]	Cohort	TNFis	TNFi treated - Mean 2.9 ± 1.03 years TNFi untreated - Mean 2.8 ± 1.1 years	334	All, 9.6 ± 14.5 - TNFi treated (n=201), 10.6 ± 14.9 - TNFi untreated (n=133), 8.2 ± 13.8	TNFi treatment vs no TNFi treatment, OR 0.52 (95% CI 0.30, 0.88); p=0.02 TNFi treatment vs no TNFi treatment in 142 post-propensity score matched samples, OR 0.30 (95% CI 0.11, 0.78); p=0.01 TNFi treatment for >50% of disease duration vs ⩽50%,OR 0.2 (95% CI 0.04, 0.92); p=0.04 Delay in starting therapy of >10 years vs ⩽ 10 years,OR 2.4 (95% CI 1.09, 5.3); p=0.03	Univariate, adjusted for baseline mSASSS** Multivariate, adjusted† Univariate, adjusted for baseline mSASSS** Univariate, adjusted for baseline mSASSS**	18/24
Kim *et al.* 2016[40]	Cohort (OSKAR cohort)	TNFis	TNFi treated - Mean 5.01 ± 1.24 years TNFi untreated - Mean 5.09 ± 1.07 years	610	- TNFi treated (n=269), 18.87 ± 17.96 - TNFi untreated (n=341), 15.68 ± 15.49	TNFi treatment vs no TNFi treatment, OR 0.79 (95% CI 0.56, 1.11); p=0.17 TNFi treatment vs no TNFi treatment in 166 vs 166 post-propensity score matched samples, OR 0.69 (95% CI 0.29, 1.63); p=0.41	Univariate Multivariate, adjusted for disease duration, baseline mSASSS and TNFi exposure	12/24
Jeong *et al.* 2018[43]	Cohort	TNFis	Mean 102.9 ± 54.9 months	151	7.6 ± 10.8	Time to start TNFi, ß-coefficient 0.004 (SE 0.001); p=0.001 TNFi index§, ß-coefficient -0.007 (SE 0.004); p=0.077 Time to start TNFi, ß-coefficient 0.003 (SE 0.001); p=0.028 TNFi index§, ß-coefficient -0.008 (SE 0.004); p=0.048	Univariate Univariate Multivariate, adjusted for time to start TNFi Multivariate, adjusted for TNFi index§	8/16
Molnar *et al.* 2018[6]	Cohort (SCQM cohort)	TNFis	Up to 10 years	432	6.6 ± 12.5	TNFi use prior to a 2-year radiographic interval (yes vs no), OR 0.50 (95% CI 0.28, 0.88); p=0.02 TNFi use during a 2-year radiographic interval (yes vs no), OR 0.87 (95% CI 0.49, 1.56); p=0.64 Number of years of continuous TNFi use prior to a 2-year radiographic interval,¶ OR 0.79 (95% CI 0.66, 0.94); p=0.01	Multivariate, adjusted† Multivariate, adjusted† Multivariate, adjusted†	10/16

*For mSASSS assessment; #Mean ± standard deviation, unless otherwise specified; †Adjusted for multiple baseline clinical and demographic characteristics; ¶Estimated effect of TNFi per year of continuous TNFi use; §Ratio of period of TNFi use: entire period of disease; **Additional multivariate analysis and analyses in matched samples are also reported but have not been included here for simplicity.
CI, confidence interval; MINORS, methodological index for non-randomized studies; mSASSS, modified Stokes Ankylosing Spondylitis Spine Score; OR, odds ratio; OSKAR, Observation Study of the Korean SpondyloArthropathy Registry; SCQM, Swiss Clinical Quality Management; SE, standard error; TNF, tumor necrosis factor.

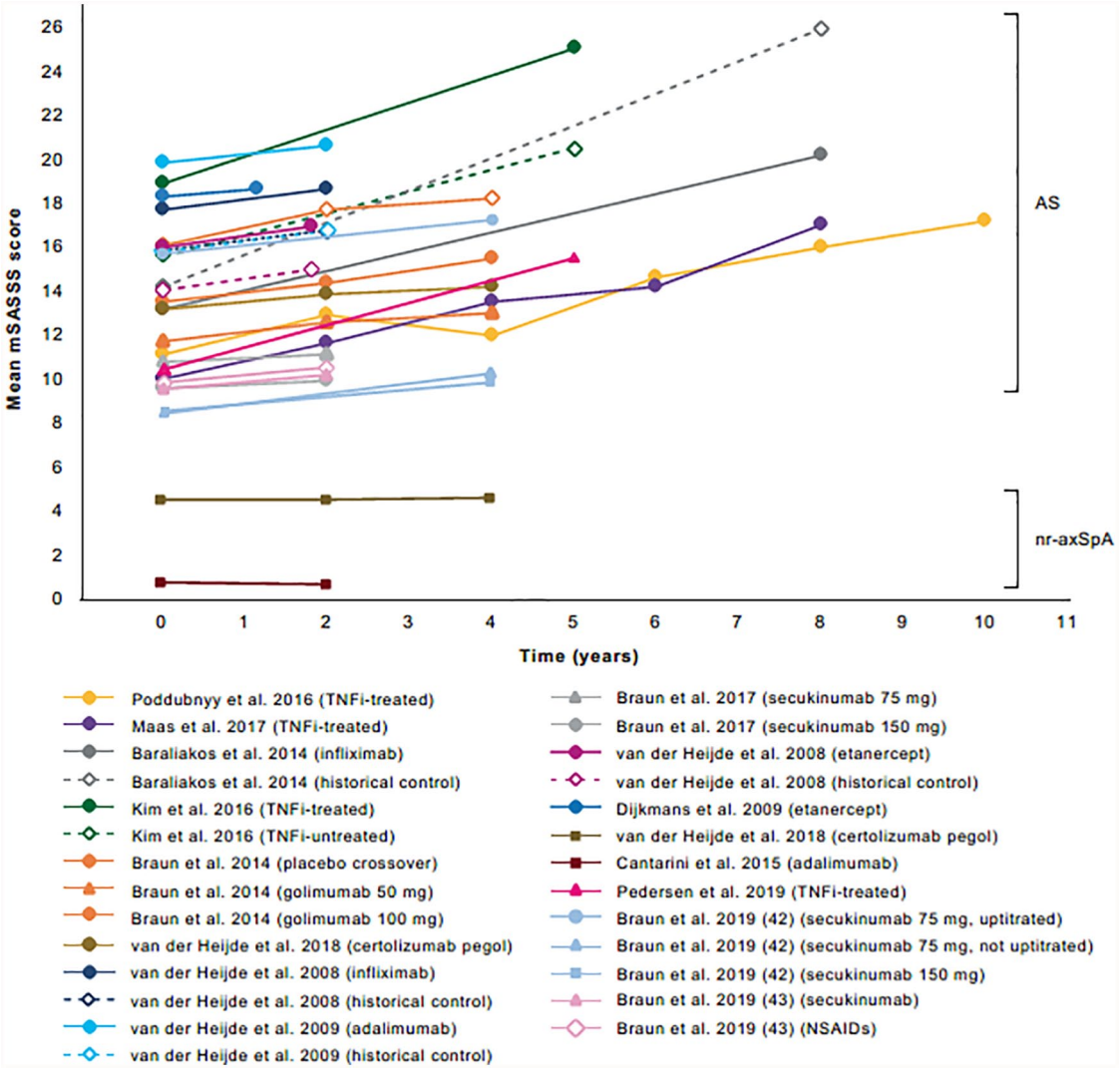

Figure 1. Spinal radiographic progression over time in patients with AS and nr-axSpA.
The figure shows mean mSASSS progression at baseline in TNFi-treated (solid lines) and TNFi-untreated (dashed lines) patients with AS and nr-axSpA. Reasons for excluding data from this figure were: median rather than mean mSASSS data were reported (Pedersen *et al.*;[40] Beek *et al.*[47]) or increases in mSASSS for individual populations were not reported (Molnar *et al.*;[6] Park *et al.*[46]). For studies that reported mSASSS change from baseline, absolute mSASSS at follow-up was calculated using the reported data. Both absolute and mean follow-up times are shown in the figure, depending on which were reported in the study. For further details on reported follow-up intervals, see Table 1.
AS, ankylosing spondylitis; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; nr-axSpA, nonradiographic axial spondyloarthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; TNFi, tumor necrosis factor inhibitor.

TNFi-treated *versus* TNFi-untreated patients.[41] The MINORS score was low, indicating poor methodological quality (12/24). In another cohort study, mSASSS progression in TNFi-treated patients with risk factors for spinal radiographic progression was found to be nonlinear, with a higher rate of progression observed over 0–2 years (maximum 2.8 across risk factors) compared with 4–6 years (minimum 0.9 across risk factors). In TNFi-treated patients without risk factors, progression was linear at a rate of ⩽1 per 2 years.[43] After 6 years, 75% of patients had not progressed (based on the smallest detectable change). In patients followed for up to 8 years in the same study, a reduction in the rate of mSASSS progression was observed after 4 years' follow-up.[44] The MINORS score was 14/16, indicating that, although nonrandomized, the study was of good methodological quality. In a long-term cohort study (mean follow-up, 102.9 months), a significantly lower rate of mSASSS progression was observed in patients treated with TNFis within 84 months of symptom onset *versus* ⩾84 months after symptom onset.[45] The rate of mSASSS

progression was also significantly lower in patients treated with TNFis for ⩾40.9% of disease duration *versus* <40.9% of disease duration.[45] A cohort study with a 4-year follow-up period showed that there was no significant difference between rate of progression in the first 2 years of treatment [1.36 (95% CI 0.82, 1.89)] compared with the second 2 years of treatment [1.25 (95% CI 0.82, 1.68) $p = 0.757$].[46] This study, which compared cohorts of patients treated with a TNFi with patients treated with NSAIDs, found that radiographic progression over 2-year intervals was significantly slower with TNFis than with NSAIDs [$\beta = -0.90$ (95% CI −1.51, −0.29) $p = 0.004$]. However, in another study, radiographic progression in patients receiving TNFi treatment over a 4-year period showed an increase in median mSASSS of 2.5 points ($p < 0.001$).[47]

Three cohort studies reported an odds ratio for the likelihood of mSASSS progression with *versus* without TNFi treatment.[6,19,41] The odds ratio reported in each of these studies favoured TNFi treatment, although one did not reach statistical significance (Table 2). Two studies reported an odds ratio after propensity score matching (a subgroup analysis of patients that could be matched one to one in the two arms based on propensity to receive TNFi); in each case, the risk of mSASSS progression with TNFi was further reduced in the post-propensity score-matched analysis compared with the overall analysis.[19,41] Several studies demonstrated an association between the length of TNFi therapy or time to start TNFi therapy and risk of progression,[6,19,45] with no effect of TNFis observed within a 2-year follow-up interval[6] (Table 2).

IL-17A inhibitors. Three papers reported mSASSS progression during treatment with the IL-17A inhibitor, secukinumab. All three papers reported mSASSS data from the OLE of the MEASURE-1 study over different follow-up periods or *versus* a historical cohort. Secukinumab was administered as a 10 mg/kg intravenous infusion at baseline and weeks 2 and 4, followed by subcutaneous injections of 150 mg or 75 mg every 4 weeks from week 8. Mean change in mSASSS after 2 years of treatment was 0.30 ± 2.53; as defined by the smallest detectable change, >80% of patients had not progressed at follow-up.[36] In another report after 4 years of continuous secukinumab treatment,[38] mean (± SD) mSASSS change from baseline to Week 208 was 1.2 ± 3.91 in patients receiving secukinumab 150 mg, indicating that the rate of mSASSS progression remained stable over 4 years of secukinumab treatment, with a numerically lower mSASSS change from baseline with secukinumab 150 mg *versus* 75 mg, regardless of uptitration. mSASSS progression was also reported from baseline to 2 years and from 2 years to 4 years; for secukinumab 150 mg, change from baseline to 2 years was 0.5 ± 1.69 and change from 2 years to 4 years was 0.7 ± 3.32.

mSASSS outcomes in the OLE of the MEASURE-1 study were also compared with the ENRADAS historical cohort of patients who did not receive biologics.[48] Change in mSASSS over 2 years was numerically, but not significantly, lower in MEASURE-1 *versus* the ENRADAS cohort (0.55 ± 0.139 *versus* 0.89 ± 0.216, $p = 0.1852$; least squares means ± standard errors). In the MEASURE-1 cohort, 82% of patients did not progress *versus* 73% of patients in the ENRADAS cohort. These findings were in agreement with published reports of mSASSS progression in TNFi-treated patients compared with progression in historical TNFi-untreated cohorts, with no significant differences observed between cohorts after 2 years of follow-up.

However, because MEASURE-1 did not include a comparator arm and contained relatively few patients, further studies are required to confirm if secukinumab is more effective than nonbiologic therapies in reducing the likelihood of spinal radiographic progression.

Effect of TNFis on spinal radiographic progression in patients with nr-axSpA

Two studies reported spinal radiographic outcomes with TNFis specifically in patients with nr-axSpA; no studies of IL-17A inhibitors in patients with nr-axSpA were identified. In a small cohort study of adalimumab ($n = 37$), no mSASSS progression was observed over a 2-year mean follow-up period (range 6–76 months).[49] The adalimumab study scored at the lower end of the MINORS score (8/16), indicating poor methodological quality. In an OLE of the RAPID-axSpA study of certolizumab pegol over a 4-year follow-up period, no mSASSS progression was observed in patients with nr-axSpA[37] (Table 1). A limitation of both studies is the lack of a control cohort; therefore, further information is needed to establish whether TNFis are more effective than nonbiologic therapy in reducing the likelihood of

spinal radiographic progression in patients with nr-axSpA.

Discussion

Clinical symptoms of axSpA may be accompanied by identifiable radiographic damage or the presence of human leucocyte antigen B27,[3,4] but diagnostic aspects for patients who lack the classical features of axSpA remain a matter of debate.[50] The underlying pathology of axSpA may be linked to an abnormal immune response to biomechanical stress on bones and joints, and changes of the intestinal microbiome leading to the activation of the innate immunity, which has, in turn, been associated with gut inflammation.[51] Current research is focusing on the relationship between the gut microbiome and systemic immune system, and its contribution to the induction and progression of autoimmune conditions, including axSpA.[2,52,53] Genetic analysis and preclinical research have highlighted the key roles of IL-17 and TNF in axSpA pathogenesis and clinical symptomatology.[51,54,55] IL-17 is known to promote osteoclastogenesis, while TNF triggers bone destruction and indirectly inhibits bone formation *via* suppression of the Wnt/β-catenin signalling pathway. This latter pathway regulates osteogenesis by promoting osteoblast formation and reducing osteoclastogenesis. IL-17 can therefore both promote bone formation in areas of inflammation and also, in action with TNF, bone destruction.[56] These findings have resulted in the development of targeted therapies aimed at inhibiting these inflammatory cytokines. However, although the clinical efficacy of biologic treatment has been established in patients with axSpA,[16–18] their impact on spinal radiographic progression has proven more difficult to establish.[17,19]

The duration of biologic treatment is an important factor in assessing its effect on spinal progression in axSpA. Conventional radiography can be an insensitive tool for evaluating progression with a relatively large measurement error[43] and a requirement for a radiographic interval of at least 2 years.[17,26,57] Hence, long-term treatment is necessary before radiographic progression can be detected using current techniques. A systematic literature review has recently been published on this topic, which supported this finding and determined that no significant difference in spinal radiographic progression was apparent between patients receiving and not receiving TNFi over the first 2 years; however, after 2 years, a potential protective effect of TNFi treatment was observed.[58]

Despite most studies in our structured literature review lacking a contemporary control, our results are generally in agreement with those reported in the abovementioned systematic review by Boers and colleagues.[58] We found that prolonged biologic treatment appeared to minimize or stabilize spinal radiographic progression in patients with AS. Patients with AS who received long-term ($\geq$4 years) TNFi treatment generally had less continuous spinal radiographic progression than those not treated with TNFis. Spinal radiographic progression in patients with AS treated with secukinumab was also limited; however, this was reported in a single, unblinded short-term (2-year) study with no comparator arm, so additional controlled studies are required to confirm the outcome and to compare it with outcomes with other biologics. Patients with nr-axSpA treated with certolizumab pegol showed no spinal radiographic progression over a 4-year follow-up period. However, due to the lack of a control cohort of patients, further information is needed to establish whether TNFis are effective in reducing spinal radiographic progression in this patient population. Unfortunately, the scarcity of robust data reflects the ethical challenges inherent in performing adequately controlled clinical trials, in which no treatment or the use of placebo is not permissible due to the availability of effective therapies. Nevertheless, the results of an observational study that evaluated data from TNFi-treated and -untreated patients over 10 years of follow-up support the reduction in spinal progression with TNFi but also indicate that a minimum duration of treatment ($>$2 years) was required before this can be observed and measured.[6]

Our finding that prolonged TNFi therapy was required before an effect on mSASSS progression in patients with AS could be observed may explain why the results of early, short-term OLE studies showed no beneficial effect of TNFis on mSASSS progression. For example, in the cohort study reported by Haroon and coworkers, which found a significantly lower mSASSS change with TNFi *versus* no TNFi therapy (relative ratio 0.42, $p = 0.04$) for a radiographic interval $>$3.9 years, there was no significant difference when the radiographic interval was $\leq$3.9 years.[19] Only one long-term AS study (5 years' mean follow-up) did not find a positive impact of TNFi therapy on

mSASSS progression;[41] this may have been related to differences in patient characteristics between this Korean cohort compared with other studies, such as a higher prevalence of peripheral arthritis and hip joint involvement.[59] Previous publications have noted that variability among X-ray readings performed at different times, plus heterogeneous study designs and populations, may all contribute to confound study results and introduce bias into the subsequent inferences.[55]

Only one study (MEASURE-1) was identified that examined the rate of mSASSS progression in patients with AS treated with an IL-17A inhibitor.[36,38,48] Although the three analyses indicated a large proportion of patients had minimal radiographic progression (<2-point increase) over 4 years (~79%), and mSASSS increases were numerically lower than the ENRADAS cohort not receiving biologic therapy, further prospective studies are needed to confirm that the IL-17A inhibitor class is effective in reducing the likelihood of mSASSS progression.

Two eligible studies assessed mSASSS progression in patients with nr-axSpA.[37,49] Although Cantarini and colleagues[49] found no significant change in mSASSS in patients treated with adalimumab after a mean follow-up period of 2 years, the small sample size of the study ($n = 37$), short follow-up and poor MINORS score make drawing wider conclusions difficult. The RAPID-axSpA study represents, to our knowledge, the longest follow-up of spinal radiographic progression in patients with nr-axSpA treated with a TNFi, finding almost no mSASSS progression with certolizumab pegol to week 204 (mean change 0.06; 95% CI −0.17, 0.28).[37] However, neither of these studies incorporated a control cohort of patients, so the effect of biologics could not be precisely defined. In a cohort study of patients with nr-axSpA that was outside the scope of this review, mean change in mSASSS at 2 years was 0.74 ± 1.95 *versus* 0.51 ± 1.72 with high *versus* low NSAID use, respectively.[60] These rates are higher than those reported in either of the nr-axSpA studies included in this review;[37,49] however, cross-trial comparisons are not advised.

While the extended follow-up periods precluded a randomized placebo comparator, only three studies incorporated a contemporary control cohort with four studies including historical control cohorts. A limitation of nonrandomized studies is that potential confounding factors, such as smoking and concomitant NSAID exposure, may not be adequately addressed. A further limitation of the studies included in our review is that the mSASSS does not capture changes in the thoracic spine or facet joints.[61] Nevertheless, the mSASSS remains the most widely used, validated score, and is considered the gold standard for assessing spinal structural progression in patients with axSpA.[24,26,61] Due to the lack of studies including a randomized placebo comparator arm, and the heterogeneity of studies that addressed the objective for this review, no meta-analyses or formal synthesis of results could be performed; therefore, a structured literature review was considered to be the best approach to address our objective. Indeed, compared with a recently published systematic review,[58] our structured literature review included a more comprehensive evidence base covering the effect of biologic treatment on spinal radiographic progression in patients with axSpA. The results of the current structured review were summarized in tables and narratively described, in line with previous approaches.[29]

It may be possible to overcome some of the methodological challenges identified during the analysis of these studies, namely the lengthy study durations required to observe radiographic progression and the inability to use a placebo control over long trial durations, with the use of newer, more sensitive imaging modalities, such as functional MRI, single-photon emission computed tomography (SPECT), or SPECT in combination with low-dose computed tomography.[62,63] However, the use of such techniques generates new hurdles to surmount, including the standardization of protocols and cost implications.[64,65] Furthermore, the radiation exposure for patients may limit the use of several of these techniques in daily practice.[66] In the future, novel biomarkers involved in bone turnover, such as matrix metalloproteinase-3 and dickkopf-1, may prove to be more convenient and effective in predicting and monitoring spinal radiographic progression,[67,68] but again, results need to be confirmed over long durations in large-scale trials before such techniques can be translated into daily clinical practice.

Substantial heterogeneity existed between studies in terms of design, patient populations, outcome measures, duration of follow-up, and type of data (observed or modelled; univariate or multivariate). In addition, our analysis included a large number of cohort studies with their associated

confounders and biases; despite using the MINORS measure to account for bias, this represents a key limitation of our analysis. It will be important to revisit this research question once further long-term follow-up data are available from RCTs involving radiographic outcomes. In conclusion, the results of this structured literature review indicate a variable effect of biologic therapy on spinal radiographic progression in patients with AS. Spinal radiographic progression with TNFi or IL-17A-inhibitor therapy was generally minimized or stabilized with longer duration (>2 years) of treatment. Assessment of comparative efficacy of the various biologics would be facilitated by further studies incorporating comparative control arms.

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Supplemental material

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