Efficacy and safety of biological DMARDs: a systematic literature review informing the 2022 update of the ASAS-EULAR recommendations for the management of axial spondyloarthritis

Webers, C.; Ortolan, A.; Sepriano, A.; Falzon, L.; Baraliakos, X.; Landewe, R.B.M.; ... ; Nikiphorou, E.

Efficacy and safety of biological DMARDs: a systematic literature review informing the 2022 update of the ASAS-EULAR recommendations for the management of axial spondyloarthritis

Casper Webers ,[1,2] Augusta Ortolan ,[3,4] Alexandre Sepriano ,[4,5] Louise Falzon ,[6] Xenofon Baraliakos ,[7] Robert B M Landewé ,[8,9] Sofia Ramiro ,[4,9] Désirée van der Heijde ,[4] Elena Nikiphorou [4,10,11]

Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ard-2022-223298).

For numbered affiliations see end of article.

Correspondence to
Dr Casper Webers, Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Centre+, Postbus 5800, 6202AZ Maastricht, Limburg, The Netherlands;
casper.webers@mumc.nl

Received 31 August 2022
Accepted 3 October 2022
Published Online First 21 October 2022

To cite: Webers C, Ortolan A, Sepriano A, *et al*. *Ann Rheum Dis* 2023;**82**:130–141.

ABSTRACT

Objective To update the evidence on efficacy and safety of biological disease-modifying antirheumatic drugs (bDMARDs) in patients with axial spondyloarthritis (axSpA) to inform the 2022 update of the Assessment of SpondyloArthritis international Society/European Alliance of Associations for Rheumatology (ASAS-EULAR) recommendations for the management of axSpA.

Methods Systematic literature review (2016–2021) on efficacy and safety of bDMARDs in axSpA (radiographic axSpA (r-axSpA)/non-radiographic axSpA (nr-axSpA)). Eligible study designs included randomised controlled trials (RCTs), strategy trials and observational studies (the latter only for safety and extra-musculoskeletal manifestations). All relevant efficacy/safety outcomes were included.

Results In total, 148 publications were included. Efficacy of golimumab and certolizumab was confirmed. Tumour necrosis factor inhibitor (TNFi) biosimilar-originator equivalence was demonstrated. RCT (n=15) data on efficacy of interleukin-17 inhibitors (IL-17i) demonstrated clinically relevant effects (risk ratio vs placebo to achieve ASAS40 response 1.3–15.3 (r-axSpA, n=9), 1.4–2.1 (nr-axSpA, n=2)). Efficacy of secukinumab/ixekizumab was demonstrated in TNFi-naïve and TNFi-inadequate responders. IL-23 and IL-12/23 inhibitors (risankizumab/ustekinumab) failed to show relevant benefits. Tapering of TNFi by spacing was non-inferior to standard-dose treatment. The first axSpA treat-to-target trial did not meet its primary endpoint, but showed improvements in secondary outcomes. No new risks were identified with TNFi use in observational studies (data lacking for IL-17i). Secukinumab (n=1) and etanercept (n=2) were associated with increased risk of uveitis in observational studies compared to monoclonal TNFi.

Conclusions New evidence supports the efficacy and safety of TNFi (originators/biosimilars) and IL-17i in r-axSpA and nr-axSpA, while IL-23i failed to show relevant effects. Observational studies are needed to confirm long-term IL-17i safety.

PROSPERO registration number CRD42021257588

Key messages

What is already known on this topic

⇒ Since the 2016 update of the management recommendations for axial spondyloarthritis (axSpA), new evidence has emerged on the efficacy and safety of biological disease-modifying antirheumatic drugs (bDMARDs) in axSpA. This systematic literature review was conducted to inform the taskforce of the 2022 update of the Assessment of SpondyloArthritis international Society/European Alliance of Associations for Rheumatology (ASAS-EULAR) recommendations for the management of axSpA on this topic.

What this study adds

⇒ The efficacy of several interleukin-17 inhibitors (IL-17i) is confirmed in both radiographic axSpA and non-radiographic axSpA.

⇒ Interleukin-23 and Interleukin-12/23 inhibitors have not been found to be efficacious in axSpA.

⇒ Tapering of tumour necrosis factor inhibitors (TNFi) by spacing is not inferior to standard-dose treatment in patients with sustained remission.

⇒ Monoclonal TNFi are associated with reduced risk of anterior uveitis, compared to TNF receptor protein (etanercept) and IL-17i (secukinumab).

How this study might affect research, practice or policy

⇒ This review informed the 2022 ASAS-EULAR management recommendations for axSpA, highlighting new evidence on efficacy and safety of existing and new bDMARDs.

INTRODUCTION

The primary goal of treatment of axial spondyloarthritis (axSpA) is to maximise health-related quality of life.[1] Biological disease-modifying antirheumatic drugs (bDMARDs) play an important role in achieving this goal.[2] The introduction of tumour necrosis factor inhibitors (TNFi), as the first bDMARDs in axSpA, signalled a new era in the management of this disease. Until then, pharmacological treatment of axSpA had been limited mostly to non-steroidal anti-inflammatory drugs (NSAIDs), which remained limited in their effectiveness.[3] TNFi showed efficacy in patients with radiographic axSpA (r-axSpA), who failed to respond or were intolerant to NSAIDs. However, they are costly and

not without harm. Thus, guidance on their use was essential. The first consensus statement on the use of TNFi in r-axSpA was published by the Assessment of SpondyloArthritis international Society (ASAS) in 2003.[4] Subsequently, these recommendations were updated regularly,[5 6] as were the ASAS-European Alliance of Associations for Rheumatology (EULAR) recommendations for management of r-axSpA.[7 8] In 2016, all aspects of management were incorporated in a single set of recommendations for the entire spectrum of axSpA.[1]

Since the publication of the systematic literature review (SLR) informing the 2016 update of these management recommendations,[9] a substantial number of studies on bDMARD therapy in axSpA have been published. Large, international trials of new drugs have been conducted, expanding the number of therapeutic possibilities, including new interleukin-17 inhibitors (IL-17i). Also, we have witnessed the first trial on a treat-to-target (T2T) intervention in axSpA. In addition, more studies on biosimilar TNFi were carried out as well as on tapering strategies for bDMARDs. Finally, additional observational studies were performed to assess the safety of bDMARDs in axSpA, as well as their effect on extra-musculoskeletal manifestations (EMMs). The latter takes particular relevance as it represents a distinguishing factor in disease manifestations and one that impacts on disease assessment, treatment and outcomes.[10]

In this manuscript, we present an SLR investigating the evidence on the efficacy and safety of bDMARDs in the entire spectrum of axSpA (r-axSpA and non-radiographic axSpA (nr-axSpA)). This SLR was undertaken in parallel with an SLR on non-pharmacological and non-biological (including targeted synthetic DMARDs) interventions (presented in a review by Ortolan *et al*),[11] to inform the 2022 update of the ASAS-EULAR management recommendations for axSpA.[12]

METHODS

The study protocol for this SLR was preregistered in PROSPERO.[13]

Eligibility criteria and literature search

The scope of the SLR and eligibility criteria for studies were defined using the PICO (Population/Intervention/Comparator/Outcome) framework. The target population was adults with a clinical diagnosis of axSpA (r-axSpA or nr-axSpA). If a study also included other diagnoses, it was eligible only if results were reported separately for axSpA. Eligible interventions were any bDMARD therapy (bio-originator or biosimilar), including TNFi, IL-17i, interleukin-23 and interleukin-12/23 inhibitors (IL-23i and IL-12/23i), in any formulation and duration. Strategy studies that involved bDMARDs were also eligible. Comparators were defined as the same bDMARD in a different dose/regimen, another bDMARD, any non-bDMARD drug treatment, combination of bDMARD with non-bDMARD treatment, placebo or none (for safety only, if population-based incidence rates were reported).

Outcomes focused on (a) efficacy and (b) safety. For efficacy, the following outcomes were included: ASAS response criteria (ASAS20, ASAS40, ASAS5/6 and partial remission), disease activity (Ankylosing Spondylitis Disease Activity Score: absolute change, response criteria (clinically important improvement ($\Delta \geq 1.1$), major improvement ($\Delta \geq 2.0$)), states (inactive disease (<1.3), low disease activity (<2.1)); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI): absolute change, response (≥50% improvement); patient's global assessment of disease activity), day/night pain, spinal mobility (Bath Ankylosing Spondylitis Metrology Index; individual spinal mobility measures), physical function (Bath Ankylosing Spondylitis Functional Index), peripheral manifestations (enthesitis; swollen/tender joint count), functioning and health (ASAS Health Index (ASAS HI)), radiographic damage (modified Stoke AS Spine Score; radiographic sacroiliitis according to modified New York criteria), inflammation on MRI (active sacroiliitis according to ASAS/Outcome Measures in Rheumatology (OMERACT) definition; Spondyloarthritis Research Consortium of Canada (SPARCC) for sacroiliac joints and spine), work disability and productivity. In addition, EMMs (psoriasis, acute anterior uveitis (AAU), inflammatory bowel disease (IBD)) were added as an efficacy outcome for the current SLR. For safety, the following outcomes were included: serious adverse events (AEs), withdrawals due to AEs, deaths, infections, malignancies, congestive heart failure, cardiovascular disease, infusion/injection-site reactions, lipid levels, renal function, hepatic effects, haematological abnormalities, gastrointestinal effects and demyelinating disease.

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) were considered for both efficacy and safety. Open-label/long-term extensions of RCTs (OLE/LTEs), and observational cohort studies were considered for safety but not efficacy (except EMMs, see below). Cohort studies were eligible if they had a comparator group or reported population-based standardised incidence rates, and included at least 50 participants per group (observational studies with less than 50 participants per group were considered if they provided relevant evidence). Cohort studies were also considered for EMMs, as the effect of drugs on EMMs is often investigated in observational designs and it was felt that relevant evidence would be excluded otherwise. SLRs and meta-analyses were not included, with the exception of Cochrane reviews. Studies with a qualitative design were eligible for efficacy and safety, provided they made some form of comparison between treatments.

The search was conducted by an experienced librarian (LF) in the relevant electronic databases (MEDLINE, Embase, The Cochrane Database of Systematic Reviews, The Cochrane CENTRAL Register of Controlled Trials, Epistemonikos) for the period from 1 January 2016 to 31 December 2021. EULAR and American College of Rheumatology (ACR) conference abstract databases from the last 2 years (2020 and 2021) were also searched. The primary search strategy focused on bDMARDs (online supplemental text S1). In addition, separate searches on non-bDMARD therapies for axSpA were carried out for a related SLR (online supplemental text S2–S4).[11] If these separate searches yielded any records that were relevant for the current review, these were included. No restrictions in language were applied.

Study selection, data extraction and risk of bias assessment

Screening, data extraction and risk of bias (RoB) assessment were each conducted by two reviewers (CW/AO) for 20% of the records, and agreement between them was checked. As agreement was sufficient (kappa >predefined threshold of 0.90), a single reviewer (CW) carried out the screening, data extraction and RoB assessment for the remaining titles and abstracts. Any disagreement between reviewers was discussed for consensus, and resolved with the methodologists (EN and AS) if necessary.

After screening of titles and abstracts, definitive inclusion was confirmed by full-text review. Data were extracted using a predefined data extraction sheet. Data were extracted on general study characteristics, inclusion and exclusion criteria,

Table 1 Effect of TNFi on ASAS20, ASAS40, ASDAS and BASFI in patients with axSpA in placebo-controlled RCTs

Dichotomous outcome									
Drug*	Study	Population	N	Time point (weeks)	Response treatment (%)	Response placebo (%)	RR (95% CI)	NNT	Risk of bias
ASAS20									
Adalimumab	ASIM[18]	axSpA	49	6	52	17	3.1 (1.2 to 8.2)	2.8	Unclear
Golimumab	GO-ALIVE[17]	r-axSpA	208	16	73	26	2.8 (2.0 to 3.9)	2.1	Low
Certolizumab	C-axSpAnd[19]	nr-axSpA	317	52	-	-	-	-	Low
Etanercept	PrevAS[20]	Suspected axSpA†	80	16	17	11	1.5 (0.5 to 4.9)	18.0	Unclear
ASAS40									
Adalimumab	ASIM[18]	axSpA	49	6	48	4	11.5 (1.6 to 81.9)	2.3	Unclear
Golimumab	GO-ALIVE[17]	r-axSpA	208	16	48	9	5.4 (2.8 to 10.5)	2.6	Low
Certolizumab	C-axSpAnd[19]	nr-axSpA	317	52	57	16	3.6 (2.4 to 5.3)	2.5	Low
Etanercept	PrevAS[20]	Suspected axSpA†	80	16	8	8	1.0 (0.2 to 4.6)	‡	Unclear

Continuous Outcome								
Drug*	Study	Population	N	Time point (weeks)	Impr. treatment mean (SD)	Impr. placebo mean (SD)	SMD (95% CI)	Risk of bias
ΔASDAS§								
Adalimumab	ASIM[18]	axSpA	49	6	-	-	-	Unclear
Golimumab	GO-ALIVE[17]	r-axSpA	208	16	2.0 (1.0)	0.4 (0.8)	1.77 (1.44 to 2.08)	Low
Certolizumab	C-axSpAnd[19]	nr-axSpA	317	52	-	-	-	Low
Etanercept	PrevAS[20]	Suspected axSpA†	80	16	0.3 (0.9)	0.6 (1.5)	−0.24 (−0.70 to 0.22)	Unclear
ΔBASFI§								
Adalimumab	ASIM[18]	axSpA	49	6	2.3 (1.9)	0.2 (1.3)	1.29 (0.65 to 1.88)	Unclear
Golimumab	GO-ALIVE[17]	r-axSpA	208	16	2.4 (2.1)	0.5 (2.0)	0.93 (0.64 to 1.21)	Low
Certolizumab	C-axSpAnd[19]	nr-axSpA	317	52	-	-	-	Low
Etanercept	PrevAS[20]	Suspected axSpA†	80	16	-	-	-	Unclear

Some studies did not report on the outcomes presented above (indicated with a '-').
*Dose for each study: adalimumab 40 mg Q2W (ASIM), golimumab 2 mg/kg Q8W intravenously (GO-ALIVE), certolizumab pegol 200 mg Q2W (C-axSpAnd) and etanercept 25 mg TW (PrevAS).
†Suspicion of nr-axSpA, no objective sign of inflammation (positive MRI of sacroiliac joints or increased C-reactive protein) required.
‡NNT could not be estimated (no treatment difference).
§Mean improvement compared to baseline.
ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASFI, Bath Ankylosing Spondylitis Functional Index; Impr, improvement; NNT, number needed to treat; nr-axSpA, non-radiographic axSpA; Q2W, every 2 weeks; r-axSpA, radiographic axSpA; RCTs, randomised controlled trials; RR, risk ratio; SMD, standardised mean difference; TNFi, tumour necrosis factor inhibitor; TW, twice a week.

key methodological aspects around study design, study population demographics and disease characteristics, intervention and comparator characteristics and relevant outcomes. For EMMs, this included the history of EMMs at baseline and the number or incidence of (new-onset/recurrent) EMMs during follow-up.

RoB was assessed using V.2 of the Cochrane RoB tool (RoB 2) for RCTs and the Quality In Prognosis Studies tool for observational studies.[14–16] Overall RoB for each study was expressed as 'low', 'unclear' or 'high'. Conference abstracts were considered as 'unknown' RoB due to lack of information.

Data synthesis

For quantitative synthesis, descriptive statistics were generated on extracted data. No meta-analyses were conducted due to clinical and methodological heterogeneity. As measures of treatment effects, standardised mean difference (mean difference between intervention and comparator divided by pooled SD) with 95% CI were calculated for continuous outcomes, while risk ratios (RR) and number needed to treat (NNT) were calculated for dichotomous outcomes. For readability purposes, tables in this report only present new evidence (published from 2016). For a comprehensive overview of bDMARD efficacy and safety in axSpA, this manuscript should be read together with the previous SLR from 2016.[9]

RESULTS

The search yielded 17 480 records after de-duplication, of which 502 were selected for detailed review. Finally, 91 articles and 57 conference abstracts were included (146 from the search and 2 from reference checks) (online supplemental figure S1). These included 36 RCTs that were first published after the previous SLR, of which 16 (44%) assessed TNFi (10 originator, 6 biosimilar; including 3 trials on discontinuation and 2 on tapering), 15 (42%) IL-17i (including 1 trial on discontinuation), 4 (11%) IL-12/23i and 1 trial with any bDMARD (online supplemental table S2.1). From these, 18 trials included patients with r-axSpA (50%), while 7 (19%) and 11 (31%) included patients with nr-axSpA and axSpA (r-axSpA + nr-axSpA), respectively (online supplemental table S2.2). OLE/LTE results were available for nine RCTs that were already included in the previous SLR (online supplemental table S2.3). Altogether, 121 records provided data on RCTs and OLE/LTE. In addition, 27 observational studies (16 on safety, 9 on EMMs and 2 on both) were included (online supplemental tables S2.4–S2.6). No qualitative studies met the inclusion criteria.

Table 2 Effect of IL-17i on ASAS20 and ASAS40 in patients with axSpA

Outcome / Drug	Study	Population	N	Time point (weeks)	Dose	Response treatment (%)	Response placebo (%)	RR (95% CI)	NNT	Risk of bias
ASAS20										
Secukinumab	SKIPPAIN[32]	axSpA	375	8	150 mg Q4W LD	-	-	-	-	Low
	ACHILLES[29]	axSpA*	76	24	150 mg Q4W LD	-	-	-	-	Low
	MEASURE 3[26]	r-axSpA	226	16	300 mg Q4W LD	61	37	1.6 (1.2 to 2.3)	4.2	Unclear
					150 mg Q4W LD	58		1.6 (1.1 to 2.2)	4.7	
	MEASURE 4[27]	r-axSpA	350	16	150 mg Q4W LD	59	47	1.3 (1.0 to 1.6)	8.0	Low
					150 mg Q4W NL	62		1.3 (1.0 to 1.7)	6.9	
	MEASURE 5[28]	r-axSpA	448	16	150 mg Q4W LD	58	37	1.6 (1.3 to 2.0)	4.6	Low
	ASTRUM[31]†	r-axSpA	211	12	150 mg Q4W W0‡	51 (pooled)	44	1.2 (0.8 to 1.6)	14.8	Unknown
					150 mg Q4W W4‡	-		-	-	
	PREVENT[30]	nr-axSpA	555	16	150 mg Q4W LD	57	46	1.2 (1.0 to 1.5)	9.0	Low
					150 mg Q4W NL	58		1.3 (1.0 to 1.6)	8.0	
Ixekizumab	COAST-V[33]§	r-axSpA	251	16	80mg Q2W	69	40	1.7 (1.3 to 2.3)	3.5	Low
					80 mg Q4W	64		1.6 (1.2 to 2.2)	4.2	
	COAST-W[34]	r-axSpA¶	316	16	80 mg Q2W	47	30	1.6 (1.1 to 2.3)	5.8	Low
					80 mg Q4W	48		1.6 (1.1 to 2.3)	5.4	
	COAST-X[35]	nr-axSpA	303	16	80 mg Q2W	-	-	-	-	Low
					80 mg Q4W	-		-	-	
Bimekizumab	BE-AGILE[38]	r-axSpA	303	12	16 mg Q4W	41	28	1.4 (0.9 to 2.4)	7.9	Low
					64 mg Q4W	62		2.2 (1.4 to 3.4)	2.9	
					160 mg Q4W	58		2.1 (1.3 to 3.2)	3.3	
					320 mg Q4W	72		2.5 (1.7 to 3.9)	2.3	
Netakimab	AILAS[36]	r-axSpA	88	16	40mg Q2W	73	43	1.8 (1.0 to 3.1)	3.1	Unclear
					80 mg Q2W	82		2.0 (1.2 to 3.4)	2.4	
					120mg Q2W	91		2.2 (1.3 to 3.7)	2.0	
	ASTERA[37]	r-axSpA	228	16	120 mg Q2W	61	3	23.0 (7.5 to 70.9)	1.7	Unclear
Brodalumab	Wei *et al*[39]	axSpA	159	16	210 mg Q2W	68	42	1.6 (1.2 to 2.2)	3.9	Low
ASAS40										
Secukinumab	SKIPPAIN[32]	axSpA	375	8	150 mg Q4W LD	-	-	-	-	Low
	ACHILLES[29]	axSpA*	76	24	150 mg Q4W LD	-	-	-	-	Low
	MEASURE 3[26]	r-axSpA	226	16	300 mg Q4W LD	42	21	2.0 (1.2 to 3.3)	4.8	Unclear
					150 mg Q4W LD	41		1.9 (1.2 to 3.2)	5.1	
	MEASURE 4[27]	r-axSpA	350	16	150 mg Q4W LD	39	28	1.4 (1.0 to 2.0)	9.4	Low
					150 mg Q4W NL	36		1.3 (0.9 to 1.9)	13.0	
	MEASURE 5[28]	r-axSpA	448	16	150mg Q4W LD	44	17	2.6 (1.8 to 3.8)	3.7	Low
	ASTRUM[31]†	r-axSpA	211	16	150 mg Q4W W0‡	44	21	2.0 (1.2 to 3.4)	4.5	Unknown
					150 mg Q4W W4‡	33		1.5 (0.9 to 2.7)	8.8	
	PREVENT[30]	nr-axSpA	555	16	150 mg Q4W LD	40	28	1.4 (1.1 to 1.9)	8.3	Low
					150 mg Q4W NL	41		1.5 (1.1 to 1.9)	7.8	
Ixekizumab	COAST-V[33]§	r-axSpA	251	16	80 mg Q2W	52	18	2.8 (1.7 to 4.6)	3.0	Low
					80 mg Q4W	48		2.6 (1.6 to 4.3)	3.4	
	COAST-W[34]	r-axSpA¶	316	16	80 mg Q2W	31	13	2.4 (1.4 to 4.4)	5.5	Low
					80 mg Q4W	25		2.0 (1.1 to 3.7)	7.7	
	COAST-X[35]	nr-axSpA	303	16	80 mg Q2W	40	19	2.1 (1.3 to 3.3)	4.7	Low
					80 mg Q4W	35		1.9 (1.2 to 3.0)	6.1	
Bimekizumab	BE-AGILE[38]	r-axSpA	303	12	16 mg Q4W	30	13	2.2 (1.0 to 4.7)	6.2	Low
					64 mg Q4W	43		3.2 (1.6 to 6.5)	3.4	
					160 mg Q4W	47		3.5 (1.7 to 7.0)	3.0	
					320 mg Q4W	46		3.4 (1.7 to 6.9)	3.1	
Netakimab	AILAS[36]	r-axSpA	88	16	40 mg Q2W	41	14	3.0 (0.9 to 9.6)	3.7	Unclear
					80 mg Q2W	64		4.7 (1.6 to 14.0)	2.0	
					120 mg Q2W	73		5.3 (1.8 to 15.7)	1.7	
	ASTERA[37]	r-axSpA	228	16	120 mg Q2W	40	3	15.3 (4.9 to 47.9)	2.7	Unclear
Brodalumab	Wei *et al*[39]	axSpA	159	16	210 mg Q2W	44	24	1.8 (1.1 to 2.9)	5.1	Low

Continued

Table 2 Continued

Outcome / Drug	Study	Population	N	Time point (weeks)	Dose	Response treatment (%)	Response placebo (%)	RR (95% CI)	NNT	Risk of bias

Some studies did not report on the outcomes presented above (indicated with a '-').
*With heel enthesitis at time of inclusion.
†Secukinumab or placebo with an initial 4 week stable NSAID run-in period, followed by (optional) NSAID tapering from week 4.
‡Secukinumab initiated in week 0 (W0 → SEC initiated 4 weeks before optional NSAID tapering; 'delayed tapering') or week 4 (W4, after 4 weeks of placebo → SEC initiated at time of optional NSAID tapering; 'early tapering').
§Also included a treatment arm with adalimumab treatment (n=90, not included in sample size reported in table above), which served as in-study active reference for comparison with placebo to provide additional context to interpretation of the ixekizumab study results.
¶With inadequate response to at least one TNFi.
ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; IL-17i, interleukin-17 inhibitors; LD, loading dose; NL, no loading dose; NNT, number needed to treat; nr-axSpA, non-radiographic axSpA; NSAID, non-steroidal anti-inflammatory drug; Q4W, every 4 weeks; r-axSpA, radiographic axSpA; RR, risk ratio; TNFi, tumour necrosis factor inhibitor.

Efficacy of bDMARDs

Efficacy of TNFi

Four RCTs of originator TNFi versus placebo were included (table 1, online supplemental tables S3.1−S3.10).[17–20] Two studies with low RoB confirmed the efficacy of golimumab intravenously in r-axSpA and certolizumab in nr-axSpA (ASAS40 47.6% for golimumab vs 8.7 for placebo (NNT 2.6); 56.6% for certolizumab vs 15.8 for placebo (NNT 2.5)).[17 19] One study of adalimumab in axSpA with a focus on imaging outcomes partially met its primary outcome (whole-body MRI smallest detectable change of ≥2.3 units met (44% vs 13%); SPARCC spine improvement of ≥5 units not met (36% vs 17%) after 6 weeks) and met several secondary outcomes (eg, ASAS40 48% for adalimumab vs 4% for placebo).[18] Finally, a trial of etanercept versus placebo in patients with 'suspected axSpA' (no objective signs of inflammation required) was negative.[20] Only one small study at high risk of bias compared originator TNFi with an active control (online supplemental tables S3.11−S3.20).[21] No RCTs tested the efficacy of TNFi in TNFi-experienced patients or infliximab in nr-axSpA.

Comparable efficacy and safety of biosimilars and originators was confirmed in four trials of adalimumab, etanercept and infliximab biosimilars (online supplemental tableS S3.21−S3.36).[22–25]

Efficacy of IL-17i

In total, 14 placebo-controlled trials assessed the efficacy of IL-17i (table 2, online supplemental tables S3.37−S3.66).[26–39] Patients with r-axSpA on secukinumab showed greater improvement compared to placebo in two phase III trials (ASAS20 58.1–60.5% vs 36.6–36.8%, low/unclear RoB).[26 28] Another phase III trial at low RoB saw numerically higher response rates for secukinumab compared to placebo in patients with r-axSpA, although results were not statistically significant (ASAS20 59.5–61.5% vs 47.0%) (table 3).[27] For the first time, the efficacy of secukinumab was shown in nr-axSpA, both with loading dose (LD) (ASAS40 41.5% vs 29.2%) and without LD (39.8% vs 19.9%) (table 3).[30] In both r-axSpA and nr-axSpA, response to secukinumab was higher compared to placebo in patients who were TNFi-naïve and in patients with prior inadequate response to TNFi (TNFi-IR), with higher rates in the TNF-naïve (ASAS40 38.8–43.9% vs 28.1–36.8%) (table 3, online supplemental figure S2).[26–28 30]

Three phase III trials assessed the efficacy of ixekizumab, all at low RoB (table 2).[33–35] In two of these on patients with r-axSpA, one including TNFi-naïve and the other TNFi-IR patients, ixekizumab was superior to placebo after 16 weeks (ASAS40 48–52% vs 18% for TNFi-naïve; 25–31% versus 13% for TNFi-IR).[33 34] Similar results were seen in a trial of patients with nr-axSpA who were TNFi-naïve (ASAS40 35–40% for ixekizumab vs 19% for placebo).[35]

Evidence on several newer IL-17i has also emerged in the past couple of years (table 2).[38 39] In a phase III trial with low RoB, brodalumab was superior to placebo in axSpA after 16 weeks (ASAS40 43.8% vs 24.1%).[39] A phase II dose-ranging study of bimekizumab, which neutralises both IL-17A and IL-17F, found response rates higher than with placebo in r-axSpA (ASAS40 29.5–45.9% vs 13.3%, low RoB).[38] Finally, netakimab was found to be efficacious in two phase II/III trials with unclear RoB, in patients with r-axSpA (ASAS40 40.4–72.7% vs 2.6–14.3%).[36 37]

Efficacy of IL-23i and IL-12/23i

Four trials investigated the efficacy and safety of IL-23i (risankizumab) and IL-12/23i (ustekinumab), all with negative results (online supplemental tables S3.67−S3.76).[40 41] Risankizumab was not superior to placebo in r-axSpA in a phase II study with low RoB (ASAS40 15.0–25.0% for various risankizumab doses vs 17.5% for placebo).[40] Ustekinumab failed in TNFi-naïve patients with r-axSpA in a phase III study with low RoB (ASAS40 28.1–31.0% for ustekinumab vs 28.4% for placebo).[41] These findings led to discontinuation of this study, as well as premature discontinuation of two ongoing phase III trials of ustekinumab.[41]

Strategy trials including discontinuation or tapering of bDMARDs

One cluster-randomised RCT compared a tight-control (TC)/T2T intervention with usual care.[42] The primary endpoint was not met (≥30% improvement in ASAS HI; 47.3% for TC/T2T vs 36.1% for usual care), but several secondary outcomes, such as ASAS20 and ASAS40 response, were significantly better in the TC/T2T strategy group (online supplemental tables S4.1−S4.10).

In the previous SLR, studies that investigated discontinuation of TNFi did not include a comparator arm. Since then, three studies on TNFi discontinuation with a comparator were conducted (table 4, online supplemental tables S4.11−S4.21).[43–45] In these three trials with low or unknown RoB, discontinuation of certolizumab (axSpA), adalimumab or etanercept (both nr-axSpA) in patients who were in remission resulted in a substantially higher rates of flare after 40–48 weeks than continuation (52.9–79.8% vs 16.3–29.6%).

Two non-inferiority trials investigated tapering of TNFi in patients with axSpA (online supplemental tables S4.22−S4.31).[46 47] In line with the findings of the previous SLR, spacing of TNFi (adalimumab, certolizumab, etanercept, golimumab, infliximab) was non-inferior to standard-dose continuation with regard to maintaining low disease activity (BASDAI<4/10) after 1 year (88.0% vs 91.5%, respectively).[46] Similarly, a combination of spacing and dose reduction of TNFi (adalimumab, etanercept, golimumab, infliximab) resulted in comparable rates of low disease activity after 1 year (81.3% vs 83.6%, respectively).[47]

Table 3 Effect of IL-17i on ASAS20 and ASAS40 according to prior TNFi experience at baseline in patients with r-axSpA and nr-axSpA

Outcome					TNFi-naïve					TNFi-IR				
Drug	Study	Population	Time point (weeks)	Dose	N	Resp. Tx (%)	Resp. PBO (%)	RR (95% CI)	NNT	N	Resp. Tx (%)	Resp. PBO (%)	RR (95% CI)	NNT
ASAS20														
Secukinumab	MEASURE 3[26]	r-axSpA	16	300 mg Q4W LD	173	65	39	1.7 (1.1 to 2.4)	3.9	50	47	29	1.6 (0.7 to 3.9)	5.6
				150 mg Q4W LD		63		1.6 (1.1 to 2.4)	4.1		41		1.4 (0.6 to 3.5)	8.5
	MEASURE 4[27]	r-axSpA	16	150 mg Q4W LD	253	60	49	1.2 (0.9 to 1.6)	9.4	97	58	41	1.4 (0.9 to 2.3)	5.9
				150 mg Q4W NL		62		1.3 (1.0 to 1.7)	7.7		59		1.4 (0.9 to 2.4)	5.5
	MEASURE 5[28]	r-axSpA	16	150 mg Q4W LD	362	58	37	1.6 (1.2 to 2.0)	4.7	96	58	35	1.6 (1.0 to 2.8)	4.4
	PREVENT[30]	nr-axSpA	16	150 mg Q4W LD	501	-	-	-	-	54	-	-	-	-
				150 mg Q4W NL		-		-	-		-		-	
Ixekizumab	COAST-V/W[33 34] (indirect)*	r-axSpA	16	80mg Q2W	251†	69	40	1.7 (1.3 to 2.3)	3.5	316	47	30	1.6 (1.1 to 2.3)	5.8
				80 mg Q4W		64		1.6 (1.2 to 2.2)	4.2		48		1.6 (1.1 to 2.3)	5.4
	COAST-X[35]	nr-axSpA	16	80 mg Q2W	303	-	-	-	-	n/a‡			n/a‡	n/a‡
				80 mg Q4W		-		-	-					
ASAS40														
Secukinumab	MEASURE 3[26]	r-axSpA	16	300 mg Q4W LD	173	44	24	1.8 (1.1 to 3.2)	5	50	37	12	3.1 (0.8 to 13.1)	4.0
				150mg Q4W LD		44		1.8 (1.1 to 3.2)	5		29		2.5 (0.6 to 11.2)	5.7
	MEASURE 4[27]	r-axSpA	16	150mg Q4W LD	253	40	30	1.3 (0.9 to 2.0)	10.1	97	35	24	1.5 (0.7 to 3.3)	8.4
				150 mg Q4W NL		39		1.3 (0.8 to 2.0)	11.5		28		1.2 (0.5 to 2.7)	21.8
	MEASURE 5[28]	r-axSpA	16	150 mg Q4W LD	362	43	18	2.4 (1.6 to 3.5)	4.1	96	49	13	3.8 (1.5 to 9.8)	2.8
	PREVENT[30]	nr-axSpA	16	150 mg Q4W LD	501	41	29	1.4 (1.1 to 1.9)	8.2	54	29	13	2.1 (0.5 to 9.2)	6.6
				150 mg Q4W NL		42		1.4 (1.1 to 1.9)	7.7		28		2.1 (0.5 to 9.2)	6.9
Ixekizumab	COAST-V/W[33 34] (indirect)*	r-axSpA	16	80 mg Q2W	251	52	18	2.8 (1.7 to 4.6)	3	316	31	13	2.4 (1.4 to 4.4)	5.5
				80 mg Q4W		48		2.6 (1.6 to 4.3)	3.4		25		2.0 (1.1 to 3.7)	7.7
	COAST-X[35]	nr-axSpA	16	80 mg Q2W	303	40	19	2.1 (1.3 to 3.3)	4.7	n/a‡			n/a‡	n/a‡
				80mg Q4W		35		1.9 (1.2 to 3.0)	6.1					

Some studies did not report on the outcomes presented above (indicated with a '-').
*Indirect comparison: COAST-V included TNFi-naïve patients with r-axSpA, while COAST-W included TNFi-IR patients with r-axSpA.
†COAST-V also included a treatment arm with adalimumab treatment (n=90, not included in sample size reported in table above), which served as in-study active reference for comparison with placebo to provide additional context to interpretation of the ixekizumab study results.
‡COAST-X only included TNFi-naïve patients.
ASAS, Assessment of SpondyloArthritis international Society; axSpA, axial spondyloarthritis; IL-17i, interleukin-17 inhibitors; LD, loading dose; n/a, not applicable; NL, no loading dose; NNT, number needed to treat; nr-axSpA, non-radiographic axSpA; PBO, placebo; Q4W, every 4 weeks; r-axSpA, radiographic axSpA; Resp, response; RR, risk ratio; TNFi, tumour necrosis factor inhibitor; TNFi-IR, inadequate response to TNFi; Tx, treatment.

Table 4 Effect of bDMARD discontinuation on risk of flare in patient with axSpA

Outcome									
Drug	**Study**	**Population**	**N**	**Time point (weeks)**	**Flare* stop (%)**	**Flare* continuation (%)**	**RR (95% CI)**	**NNT**	**Risk of bias**
TNFi									
Certolizumab	C-OPTIMISE[44]	axSpA	313	48	80	16 (full dose)† 21 (reduced dose)†	4.9 (3.1 to 7.6) 3.8 (2.6 to 5.6)	1.6 1.7	Low
Adalimumab	ABILITY-3[43]	nr-axSpA	305	40	53	30	1.8 (1.3 to 2.4)	4.3	Low
Etanercept	RE-EMBARK[45]	nr-axSpA	-‡	40	75	<25	§	§	Unknown
IL-17i									
Ixekizumab	COAST-Y[50]	axSpA	155	40	45	17	2.7 (1.6 to 4.6)	3.5	Low

*Definitions of flare: ASDAS≥2.1 at two consecutive visits or ASDAS>3.5 at any visit (C-OPTIMISE, COAST-Y); ASDAS≥2.1 at two consecutive visits (ABILITY-3); ASDAS-ESR≥2.1 (RE-EMBARK).
†After a 48-week open-label induction period with certolizumab 200 mg Q2W, patients were randomised to certolizumab 200 mg Q2W (full dose), 200 mg Q4W (reduced dose) or placebo.
‡Number of patients not reported.
§RR and NNT could not be estimated (flare rate in continuation group not reported).
axSpA, axial spondyloarthritis; bDMARD, biological disease-modifying antirheumatic drug; IL-17i, interleukin-17 inhibitors; NNT, number needed to treat; nr-axSpA, non-radiographic axSpA; Q2W, every 2 weeks; RR, risk ratio; TNFi, tumour necrosis factor inhibitor.

One phase IV study (NOR-DRUM) with low RoB investigated therapeutic drug monitoring (TDM) in six diseases, including axSpA (online supplemental tables S4.36−S4.45).[48 49] Infliximab with TDM was not superior compared to infliximab without TDM in the first 30 weeks after drug initiation.[48] In patients on stable treatment, however, addition of TDM was efficacious for maintaining disease control over 52 weeks (79.4% with TDM vs 58.6% without TDM (NNT 4.8)).[49]

Only one trial evaluated the discontinuation of IL-17i.[50] Similar to observations with TNFi, the risk of flare following discontinuation of ixekizumab was significantly higher compared to continuation after 40 weeks (46.3% vs 16.7%) (table 4).[50] No studies on tapering of IL-17i were available.

Effect on extra-musculoskeletal manifestations

The frequency of AAU, IBD and psoriasis in RCTs (and OLE/LTE) of patients treated with TNFi and IL-17i was overall low and comparable to those of the placebo arm (online supplemental tables S5.1−S5.9, S5.22−S5.30).[17 19 24 26–28 30 32–35 38 51–62] One observational study at low RoB conducted in a large Swedish registry (Swedish Rheumatology Quality Register, SRQ) found an increased risk of first on-treatment AAU with etanercept use compared to adalimumab (HR 3.89 (1.85–8.06)) and infliximab (HR 1.99 (1.23–3.22)) use in those without recent AAU.[63] These findings were confirmed in another observational study within the same registry.[64] Other observational studies of TNFi and AAU did not highlight any differences between TNFi or were at high RoB (online supplemental tables S5.10−S5.21). The risk of a first AAU was higher with secukinumab compared to adalimumab in one study, conducted in the same Swedish registry mentioned above (HR 2.32 (1.16–4.63), low RoB).[64] In this study, the incidence of any AAU episode, first or recurrent, with secukinumab was also higher than with adalimumab or infliximab. Observational studies of TNFi and IBD/psoriasis were all at unknown or high RoB with conflicting results (online supplemental tables S5.31−S5.34).[65–68] No observational studies were available on the risk of IBD or psoriasis in IL-17i users.

Safety of bDMARDs

The frequency of serious infections, malignancies and cardiovascular events in RCTs of patients treated with TNFi and IL-17i was low (online supplemental tables S6.1−S6.6).[27 28 38 52–62 69–72] Observational studies evaluating the safety of TNFi and IL-17i are reported in table 5. The risk of infections was similar across different TNFi, in two observational studies at high RoB (online supplemental tables S6.7−S6.10).[73 74] For malignancies, the risk in TNFi users was not increased compared to non-users in two large Scandinavian registries (incidence rate ratio (IRR) for any malignancy 0.8 (0.6–1.1)) and in one US cohort.[75 76] Incidence of neuroinflammatory events was higher in TNFi-experienced patients compared to naïve patients (incidence rate 78–88/100 000 person-years (PY) vs 13–50/100 000 PY).[77] Incidence of multiple sclerosis in TNFi (ever) users compared to the general population was increased (IRR 3.9 (1.5–10.4)), although it was unclear whether this was a drug or disease effect.[78] No observational studies on safety of IL-17i were available.

Summary of evidence

A summary of the level of evidence for all bDMARDs in axSpA is presented in figure 1. This summary is based on evidence included in the current SLR as well as the previous SLR from 2016.[9] In addition, a positive RCT of bimekizumab in nr-axSpA that was presented at EULAR 2022 (after conduct of the current SLR), was considered as well.[79]

DISCUSSION

The current SLR confirms the efficacy and safety of TNFi (originators and biosimilars) and IL-17i (in particular secukinumab and ixekizumab) in patients with axSpA. Several new IL-17i also showed promising effects in phase II and III trials. Discontinuation of TNFi or IL-17i was unsuccessful as it led to substantially more flares than continuing treatment. Tapering, however, and especially spacing, showed promising results in patients with sustained remission or low disease activity. IL-12/23i failed to show efficacy in multiple large trials in (r-)axSpA. The first T2T trial in axSpA did not meet its primary endpoint, but did show improvements in secondary outcomes. Finally, monoclonal TNFi were associated with reduced risk of uveitis compared to TNF receptor protein (etanercept) and IL-17i (secukinumab).

Several large, high-quality, trials have demonstrated the efficacy of secukinumab and ixekizumab in axSpA, including nr-axSpA and r-axSpA. For both drugs, efficacy was also assessed in patients who were TNFi-naïve or TNFi-IR. Of note, whereas the MEASURE programme included both types of patients in the same trials and stratified randomisation for prior TNFi exposure (allowing for a direct comparison between subgroups but

Table 5 Safety of bDMARDs in observational studies with a comparator group in patients with axSpA

Outcome / Study	Definition of outcome	Treatment/*comparator* group	N Patients	Exposure (PYs)	N Events	IR, per 100 PY	Effect size Ratio (95% CI)	Risk of bias
Serious infection								
Park *et al*[93]	Serious infection	Low-dose etanercept	100	441	–	0.5	IRR 0.44 (0.04 to 4.80)	Unclear
		Standard-dose etanercept	34	96	–	1	REF	
Moura *et al*[94]	Hospitalised infection	TNFi (±csDMARD) use	747 (overall)	948	20	2.1	HR 1.00 (0.47 to 2.11)*	Unclear
		TNFi non-use		380	10	2.6	REF	
Krabbe *et al*[95]	Serious infection	First bDMARD†	2958	–	81	2.7	HR 2.8 (2.2 to 3.6)	Unclear
		General population	29 579	–	292	1	REF	
Malignancies								
Hellgren *et al*[75]	First cancer diagnosis	TNFi initiated	3078	12 104	53	–	IRR 0.8 (0.6 to 1.1)‡	Unclear
		TNF-naïve	7023	45 903	310	–	REF	
Park *et al*[93]	Malignancy	Low-dose etanercept	100	441	–	0.5	HR 0.44 (0.04 to 4.80)‡	Unclear
		Standard-dose etanercept	34	96	–	1	REF	
Merjanah *et al*[76]	Malignant neoplasm	TNFi exposed	5370	–	530	–	OR – (p=0.20)	Unknown
		TNFi-naïve	7280	–	770	–	REF	
	Skin cancer§	TNFi exposed	5370	–	–	–	OR 0.9 (0.73 to 1.10)	
		TN*Fi-naïve*	7280	–	–	–	REF	
Cardiovascular								
Liew *et al*[96]	Incident hypertension	TNFi use	269	–	129 (overall)	–	HR 1.10 (0.83 to 1.37)¶	Unclear
		TNFi non-use	361	–		–	REF	
Neuroinflammatory								
Dreyer *et al*[78]	Multiple sclerosis	TNFi use, ever	1728	–	4	–	IRR 3.91 (1.47 to 10.42)**	Unclear
		General population	–	–	0	–	REF	
Kopp *et al*[77]	Neuroinflammatory events†† (cohort 1)	TNFi exposed	–	44 840	35	0.78/1000 PY	–‡‡	Unclear
		TNFi non-exposed	–	170 357	86	0.50/1000 PY	REF	
	Neuroinflammatory events†† (cohort 2)	TNFi exposed	–	14 697	13	0.88/1000 PY	–‡‡	
		TNFi non-exposed	–	7475	1	0.13/1000 PY	REF	

Only studies with a low/unclear/unknown RoB are presented.
*Adjusted for age, sex, socioeconomic status, number of outpatient visits/procedures 1 year before cohort entry, hospitalised infection 1 year before cohort entry, Charlson Comorbidity Index, IBD, ever use of NSAID/COXIB 1 year before cohort entry, glucocorticoid use).
†99.7% TNFi, 0.3% other bDMARD.
‡Age and sex standardised.
§Squamous cell carcinoma, malignant melanoma, basal cell carcinoma.
¶Adjusted for age, sex, race, study site, BMI, disease activity, NSAID use.
**Standardised for age, sex and calendar time period
††Demyelinating diseases of the central nervous system, multiple sclerosis, inflammatory polyneuropathies.
‡‡HR only reported for r-axSpA and psoriatic arthritis populations pooled (adjusted HR 1.50 (1.07–2.11) (cohort 1) and 3.41 (1.30–8.96) (cohort 2)).
axSpA, axial spondyloarthritis; bDMARD, biological disease-modifying antirheumatic drug; BMI, body mass index; csDMARD, conventional-synthetic DMARD; IBD, inflammatory bowel disease; IL-17i, interleukin-17 inhibitor; IR, incidence rate; IRR, incidence rate ratio; NSAID, non-steroidal anti-inflammatory drug; PY, patient-years; REF, reference group; TNFi, tumour necrosis factor inhibitor.

with a lower number of patients), the COAST trial programme conducted separate trials, one with TNFi-naïve patients and the other TNFi-IR patients (not allowing for a direct comparison, but with a large number of (TNFi-IR) patients). The confirmation that both drugs are efficacious in TNFi-naïve and TNFi-IR patients is clinically relevant, as it helps guide the position of these drugs in the management strategy for axSpA. In addition to secukinumab and ixekizumab, newer IL-17i also proved to be effective. For bimekizumab, only data from a phase II trial in r-axSpA were available at the time of our literature search. Since then, positive phase III trial results have been presented at EULAR 2022 in both r-axSpA and nr-axSpA.[79 80] Patients who fail TNFi have now valuable alternatives, which should bring new hope to those living with axSpA. Future trials should address the efficacy of TNFi in patients who failed a previous TNFi and in patients who failed an IL-17i.

On a related note, with the exception of the tapering and discontinuation trials, all efficacy trials in the current SLR were placebo-controlled. Although the results of the various drugs and drug classes seem somewhat comparable (NNT of TNFi and IL-17i mostly in the 3–6 range for ASAS40 response), differences between trials with regard to design, study populations and quality/RoB hamper indirect comparisons. The lack of formal head-to-head RCTs, which was already highlighted in the previous SLR from 2016, remains an ongoing unmet need.[9] Yet, one of the trials on ixekizumab did include (a small number of patients on) adalimumab as an 'in-study' active reference for comparison with placebo, to provide additional context to the interpretation of the study results.[33] Although no formal comparison between ixekizumab and adalimumab was made, perhaps this trial could encourage the undertaking of true head-to-head non-inferiority trials in axSpA in the near future.

In the case of ustekinumab, despite promising results in a proof-of-concept study, all four subsequent trials with IL-(12/)23i failed to show any clinically relevant effect leading to a premature termination of the ustekinumab trial programme.[40 41] This clear contrast with the trials in psoriatic arthritis and psoriasis, where IL-23i have shown substantial benefits, has sparked

Class	Intervention	r-axSpA	nr-axSpA
TNFi	Adalimumab	1a	1b
	Certolizumab	1b	1b
	Etanercept	1a	1b
	Golimumab	1a	1b
	Infliximab	1a	NA
IL-17i	Secukinumab	1b	1b
	Ixekizumab	1b	1b
	Bimekizumab	1b	*
	Brodalumab	1b†	1b†
	Netakimab	1b	NA
IL-(12/)23i	Ustekinumab	1b	1b
	Risankizumab	1b	NA
IL-6i	Tocilizumab	1b	NA
	Sarilumab	1b	NA
Other	Abatacept	4	NA
	Rituximab	4	NA

Supportive Unsupportive No data

Figure 1 Level of evidence and support for bDMARDs, by axSpA subtype. Colours provide information on whether the available evidence, as included in the current SLR and a previous SLR,[9] supports or does not support the use of each bDMARD in axSpA. The levels of evidence are based on the EULAR standardised operating procedures and the Oxford Centre for Evidence-based Medicine Levels of Evidence. *Judged as 'Supportive' based on a positive RCT presented at EULAR 2022,[79] after conduct of the current SLR. †Formally only tested in axSpA overall, not by subtype. axSpA, axial spondyloarthritis; bDMARDs, biological disease-modifying antirheumatic drugs; IL, interleukin; NA, not available; nr-axSpA, non-radiographic axSpA; RCT, randomised controlled trial; r-axSpA, radiographic axSpA; SLR, systematic literature review; TNFi, tumour necrosis factor inhibitor.

discussion on the precise role of IL-23 in the pathophysiology of axSpA.[81 82]

In new studies on biosimilars, efficacy and safety were comparable to originators in patients with active disease or when switching from originator to biosimilar in those with stable disease.[22–25] Together with previous evidence,[83] it is clear now that originators and biosimilars can be considered equivalent in terms of efficacy and safety in axSpA.

Another important update in the existing evidence base, has been the Tight Control in Spondyloarthritis (TICOSPA) study; the first trial investigating a T2T approach in axSpA. TICOSPA failed to meet its primary endpoint. Yet, the choice of outcome measure (ASAS HI improvement, instead of a direct 'disease activity-related' outcome) and the high level of expertise of the participating centres (usual care response was higher than expected)[42] may well explain the failure to meet the primary endpoint, rather than this being an indication that T2T is not a viable approach in axSpA. In this line, noting that most secondary efficacy outcomes were met, including ASAS20/40 responses, becomes relevant. Additional trials are needed to clarify whether T2T has benefits in axSpA, and which strategies and targets should be used to maximise patients' health.

Two new trials on tapering of TNFi, both with good results,[46 47] represent another valuable contribution to the literature. Taken together with two trials that were included in the previous SLR from 2016,[84 85] there are now three separate studies in axSpA that demonstrate spacing to be non-inferior to standard TNFi regimens,[46 47 85] and one study that found dose reduction to be inferior.[84] Altogether, these observations suggest that tapering of bDMARDs is feasible in axSpA and that spacing is the preferred option. Identifying the 'right' patients for spacing remains to be determined.

TDM was of added benefit in maintaining disease control in those already on stable infliximab (NOR-DRUM B), but not in those starting infliximab (NOR-DRUM A).[48 49] Recently published EULAR Points to Consider (PtC) on drug monitoring do not recommend proactive TDM in the management of inflammatory RMDs (of note, the positive results of NOR-DRUM B were unavailable when these PtC were formulated).[86] Additional studies are necessary to determine the role of (proactive) TDM in the management of axSpA.

As part of this SLR, we evaluated the effect of bDMARDs on EMMs, which was a change compared to the previous SLR. This change was prompted by clinical questions related to the preferred choice of bDMARDs in patients with EMMs. Most evidence in this area focuses on AAU. In two large studies within the same registry, etanercept (two studies) and secukinumab (one study) were associated with increased risk of AAU compared to adalimumab.[63 64] Although the RoB of both studies was judged as low and several sensitivity analyses were conducted, the risk of residual confounding and channelling bias cannot be entirely ruled out. Nonetheless, these findings suggest that in case of a history of AAU, monoclonal TNFi might be preferred. Observations from the C-VIEW and GO-EASY studies (not included in the current SLR due to the lack of a concurrent comparator) confirmed the effect of monoclonal TNFi on AAU.[87 88] For other EMMs, the evidence is still limited to data from RCTs and their LTEs. In RCTs of IL-17i, rates of IBD were low and in line with previous findings, although it should be noted that they pertain to selected populations, thus these findings need confirmation in long-term observational studies. Of note, results from RCTs in non-axSpA populations with IBD support preference for monoclonal TNFi (over etanercept and IL-17i) for patients with IBD, similar to uveitis.[89–92]

The evidence from observational studies evaluating the safety of bDMARDs in axSpA remains limited. Although the new evidence supports the findings of the previous SLR that TNFi are safe in axSpA, definitive conclusions are still challenging to make, primarily due to the majority of studies being at high risk of bias. In addition, there was a striking lack of studies evaluating the safety of IL-17i. Going forward, observational studies with good methodological quality are needed to confirm the long-term safety of bDMARDs in axSpA.

Bringing the evidence together, this SLR confirms the efficacy and safety of IL-17i in patients with both r-axSpA and nr-axSpA, while IL-23i and IL-12/23i have failed to show relevant benefits in axSpA. TNFi biosimilar-originator equivalence has been confirmed, and spacing seems the preferred method to taper TNFi. Finally, the risk of anterior uveitis seems lowest with monoclonal TNFi compared to other bDMARDs in axSpA. This SLR provides important new insights into the management of patients with bDMARDs, across the entire spectrum of axSpA.

Author affiliations
[1]Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Centre+, Maastricht, The Netherlands

[2]Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands
[3]Rheumatology Unit, Department of Medicine DIMED, University of Padua, Padua, Italy
[4]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[5]NOVA Medical School, Universidade Nova de Lisboa, Lisboa, Portugal
[6]Health Economics and Decision Science, School of Health and Related Research, The University of Sheffield, Sheffield, UK
[7]Rheumazentrum Ruhrgebiet, Ruhr University Bochum, Herne, Germany
[8]Department of Clinical Immunology and Rheumatology, Amsterdam University Medical Centre, Amsterdam, The Netherlands
[9]Department of Rheumatology, Zuyderland Medical Centre Heerlen, Heerlen, The Netherlands
[10]Department of Rheumatology, King's College Hospital, London, UK
[11]Centre for Rheumatic Diseases, King's College London, London, UK

Twitter Alexandre Sepriano @AlexSepriano and Elena Nikiphorou @ElenaNikiUK

Acknowledgements The authors would like to thank Dr Mikhail Protopopov for his assistance in translating two reports.

Contributors All authors contributed and finally approved the current manuscript.

Funding European Alliance of Associations for Rheumatology and Assessment of SpondyloArthritis international Society.

Competing interests CW, AO and LF have nothing to declare. AS has received speaker/consulting fees from UCB and Novartis. XB received consulting fees and research grants from AbbVie, BMS, Eli-Lilly, Galapagos, Janssen, MSD, Novartis, Pfizer, Roche, Sandoz, Sanofi and UCB, and is an Editorial Board member of Annals of Rheumatic Diseases. RBML has received consulting fees from AbbVie, Bristol Myers Squibb, Celgene, Jansen, Galapagos, GlaxoSmithKline, Novartis, Pfizer and UCB, and is Director of Rheumatology Consultancy BV. SR received research grants from AbbVie, Galapagos, Novartis, Pfizer and UCB, and consulting fees from AbbVie, Eli Lilly, Novartis, MSD, Pfizer, UCB and Sanofi. DvdH received consulting fees from AbbVie, Bayer, BMS, Cyxone, Eisai, Galapagos, Gilead, GlaxoSmithKline, Janssen, Lilly, Novartis, Pfizer and UCB Pharma, and is Director of Imaging Rheumatology BV. EN has received speaker honoraria/participated in advisory boards for Celltrion, Pfizer, Sanofi, Gilead, Galapagos, AbbVie, Lilly and holds research grants from Pfizer and Lilly.

Patient and public involvement statement The Task force on this project involved two patient research partners (Boryana Boteva and Mark Telkman), who participated in the Task force meeting where the results of this SLR were presented and discussed.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to this study are published in the article or in the supplemental files.

ORCID iDs
Casper Webers http://orcid.org/0000-0003-3011-8547
Augusta Ortolan http://orcid.org/0000-0002-3131-0939
Alexandre Sepriano http://orcid.org/0000-0003-1954-0229
Louise Falzon http://orcid.org/0000-0002-9449-6056
Xenofon Baraliakos http://orcid.org/0000-0002-9475-9362
Robert B M Landewé http://orcid.org/0000-0002-0577-6620
Sofia Ramiro http://orcid.org/0000-0002-8899-9087
Désirée van der Heijde http://orcid.org/0000-0002-5781-158X
Elena Nikiphorou http://orcid.org/0000-0001-6847-3726

REFERENCES

1 van der Heijde D, Ramiro S, Landewé R, *et al*. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017;76:978–91.
2 Navarro-Compán V, Sepriano A, El-Zorkany B, *et al*. Axial spondyloarthritis. *Ann Rheum Dis* 2021;80:1511–21.
3 Zochling J, van der Heijde D, Dougados M, *et al*. Current evidence for the management of ankylosing spondylitis: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. *Ann Rheum Dis* 2006;65:423–32.
4 Braun J, Pham T, Sieper J, *et al*. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2003;62:817–24.
5 Braun J, Davis J, Dougados M, *et al*. First update of the International ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2006;65:316–20.
6 van der Heijde D, Sieper J, Maksymowych WP, *et al*. 2010 update of the International ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011;70:905–8.
7 Zochling J, van der Heijde D, Burgos-Vargas R, *et al*. ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006;65:442–52.
8 Braun J, van den Berg R, Baraliakos X, *et al*. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2011;70:896–904.
9 Sepriano A, Regel A, van der Heijde D, *et al*. Efficacy and safety of biological and targeted-synthetic DMARDs: a systematic literature review Informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. *RMD Open* 2017;3:e000396.
10 Fragoulis GE, Siebert S. Treatment strategies in axial spondyloarthritis: what, when and how? *Rheumatology* 2020;59:iv79–89.
11 Ortolan A, Webers C, Sepriano A. Efficacy and safety of non-pharmacological and non-biological interventions: a systematic literature review Informing the 2022 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. *Ann Rheum Dis* 2023;82:142–52.
12 Ramiro S, Nikiphorou E, Sepriano A, *et al*. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Accepted for publication* 2022. doi:10.1136/ard-2022-223296
13 Webers C, Ortolan A, Sepriano A, *et al*. Efficacy and safety of biological DMARDs: a systematic review Informing the 2022 update of the ASAS-EULAR recommendations for the management of axial spondyloarthritis. Prospero 2021 CRD42021257588. Available: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021257588
14 Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
15 Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;144:427–37.
16 Hayden JA, van der Windt DA, Cartwright JL, *et al*. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280–6.
17 Deodhar A, Reveille JD, Harrison DD, *et al*. Safety and efficacy of golimumab administered intravenously in adults with ankylosing spondylitis: results through week 28 of the GO-ALIVE study. *J Rheumatol* 2018;45:341–8.
18 Krabbe S, Østergaard M, Eshed I, *et al*. Whole-Body magnetic resonance imaging in axial spondyloarthritis: reduction of Sacroiliac, spinal, and Entheseal inflammation in a placebo-controlled trial of adalimumab. *J Rheumatol* 2018;45:621–9.
19 Deodhar A, Gensler LS, Kay J, *et al*. A Fifty-Two-Week, randomized, placebo-controlled trial of Certolizumab pegol in Nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2019;71:1101–11.
20 Rusman T, van der Weijden MAC, Nurmohamed MT, *et al*. Is treatment in patients with suspected Nonradiographic axial spondyloarthritis effective? six-month results of a placebo-controlled trial. *Arthritis Rheumatol* 2021;73:806–15.
21 Wei JC-C, Tsou H-K, Leong P-Y, *et al*. Head-To-Head comparison of etanercept vs. adalimumab in the treatment of ankylosing spondylitis: an open-label randomized controlled crossover clinical trial. *Front Med* 2020;7:566160.
22 Li Z, Wu J, *et al*. IBI303, a biosimilar to adalimumab, for the treatment of patients with ankylosing spondylitis in China: a randomised, double-blind, phase 3 equivalence trial. *The Lancet Rheumatology* 2019;1:e35–43.
23 Su J, Li M, He L, *et al*. Comparison of the efficacy and safety of adalimumab (Humira) and the adalimumab Biosimilar candidate (HS016) in Chinese patients with active ankylosing spondylitis: a multicenter, randomized, double-blind, parallel, phase III clinical trial. *BioDrugs* 2020;34:381–93.
24 Zhao D, He D, Bi L, *et al*. Safety and efficacy of prefilled liquid Etanercept-Biosimilar Yisaipu for active ankylosing spondylitis: a multi-center phase III trial. *Rheumatol Ther* 2021;8:361–74.
25 Jørgensen KK, Olsen IC, Goll GL, *et al*. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet* 2017;389:2304–16.
26 Pavelka K, Kivitz A, Dokoupilova E, *et al*. Efficacy, safety, and tolerability of secukinumab in patients with active ankylosing spondylitis: a randomized, double-blind phase 3 study, measure 3. *Arthritis Res Ther* 2017;19:285.
27 Kivitz AJ, Wagner U, Dokoupilova E, *et al*. Efficacy and Safety of Secukinumab 150 mg with and Without Loading Regimen in Ankylosing Spondylitis: 104-week Results from MEASURE 4 Study. *Rheumatol Ther* 2018;5:447–62.

28 Huang F, Sun F, Wan W-G, *et al*. Secukinumab provided significant and sustained improvement in the signs and symptoms of ankylosing spondylitis: results from the 52-week, phase III China-centric study, measure 5. *Chin Med J* 2020;133:2521–31.
29 Behrens F, Sewerin P, de Miguel E, *et al*. Efficacy and safety of secukinumab in patients with spondyloarthritis and enthesitis at the Achilles tendon: results from a phase 3B trial. *Rheumatology* 2022;61:2856–66.
30 Deodhar A, Blanco R, Dokoupilová E, *et al*. Improvement of signs and symptoms of Nonradiographic axial spondyloarthritis in patients treated with Secukinumab: primary results of a randomized, placebo-controlled phase III study. *Arthritis Rheumatol* 2021;73:110–20.
31 Kiltz U, Baraliakos X, Brandt-Juergens J, *et al*. POS0910 EVALUATION OF THE NONSTEROIDAL ANTI-INFLAMMATORY DRUG-SPARING EFFECT OF SECUKINUMAB IN PATIENTS WITH ANKYLOSING SPONDYLITIS: RESULTS OF THE MULTICENTER, RANDOMISED, DOUBLE-BLIND, PHASE IV ASTRUM-TRIAL. *Ann Rheum Dis* 2021;80:714.1–5.
32 Poddubnyy D, Pournara E, Zielińska A, *et al*. Rapid improvement in spinal pain in patients with axial spondyloarthritis treated with secukinumab: primary results from a randomized controlled phase-IIIb trial. *Ther Adv Musculoskelet Dis* 2021;13:1759720X211051471.
33 van der Heijde D, Cheng-Chung Wei J, Dougados M, *et al*. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. *Lancet* 2018;392:2441–51.
34 Deodhar A, Poddubnyy D, Pacheco-Tena C, *et al*. Efficacy and Safety of Ixekizumab in the Treatment of Radiographic Axial Spondyloarthritis: Sixteen-Week Results From a Phase III Randomized, Double-Blind, Placebo-Controlled Trial in Patients With Prior Inadequate Response to or Intolerance of Tumor Necrosis Factor Inhibitors. *Arthritis Rheumatol* 2019;71:599–611.
35 Deodhar A, van der Heijde D, Gensler LS, *et al*. Ixekizumab for patients with non-radiographic axial spondyloarthritis (COAST-X): a randomised, placebo-controlled trial. *Lancet* 2020;395:53–64.
36 Erdes S, Nasonov E, Kunder E, *et al*. Primary efficacy of netakimab, a novel interleukin-17 inhibitor, in the treatment of active ankylosing spondylitis in adults. *Clin Exp Rheumatol* 2020;38:27–34.
37 Mazurov VI, Gaydukova IZ, Erdes S, *et al*. Efficacy and safety of netakimab, anti-IL-17A monoclonal antibody, in patients with ankylosing spondylitis. Results of phase III international, multicenter, randomized double-blind clinical trial BCD-085-5/ASTERA. *Rheumatology Science and Practice* 2020;58:376–86.
38 van der Heijde D, Gensler LS, Deodhar A, *et al*. Dual neutralisation of interleukin-17A and interleukin-17F with bimekizumab in patients with active ankylosing spondylitis: results from a 48-week phase IIb, randomised, double-blind, placebo-controlled, dose-ranging study. *Ann Rheum Dis* 2020;79:595–604.
39 Wei JC-C, Kim T-H, Kishimoto M, *et al*. Efficacy and safety of brodalumab, an anti-IL17RA monoclonal antibody, in patients with axial spondyloarthritis: 16-week results from a randomised, placebo-controlled, phase 3 trial. *Ann Rheum Dis* 2021;80:1014–21.
40 Baeten D, Østergaard M, Wei JC-C, *et al*. Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study. *Ann Rheum Dis* 2018;77:1295–302.
41 Deodhar A, Gensler LS, Sieper J, *et al*. Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. *Arthritis Rheumatol* 2019;71:258–70.
42 Molto A, López-Medina C, Van den Bosch FE, *et al*. Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial. *Ann Rheum Dis* 2021;80:1436–44.
43 Landewé R, Sieper J, Mease P, *et al*. Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. *Lancet* 2018;392:134–44.
44 Landewé RB, van der Heijde D, Dougados M, *et al*. Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. *Ann Rheum Dis* 2020;79:920–8.
45 Van den Bosch F, Wei JCC, Nash P, *et al*. OP0107 Etanercept withdrawal and re-treatment in patients with inactive non-radiographic axial spondyloarthritis at 24 weeks: results of re-embark, an open-label, phase IV trial. *Ann Rheum Dis* 2020;79:70.1–70.
46 Lukas C, Tournadre A, Picot MC, *et al*. OP0138 FEASIBILITY OF PROGRESSIVE ANTI-TNF TAPERING IN AXIAL SPONDYLOARTHRITIS PATIENTS IN LOW DISEASE ACTIVITY: RESULTS FROM THE MULTICENTER NON-INFERIORITY PROSPECTIVE RANDOMIZED CONTROLLED TRIAL SPACING. *Ann Rheum Dis* 2021;80:80.1–1.
47 Gratacós J, Pontes C, Juanola X, *et al*. Non-Inferiority of dose reduction versus standard dosing of TNF-inhibitors in axial spondyloarthritis. *Arthritis Res Ther* 2019;21:11.
48 Syversen SW, Goll GL, Jørgensen KK, *et al*. Effect of therapeutic drug monitoring vs standard therapy during infliximab induction on disease remission in patients with chronic immune-mediated inflammatory diseases: a randomized clinical trial. *JAMA* 2021;325:1744–54.
49 Syversen SW, Jørgensen KK, Goll GL, *et al*. Effect of therapeutic drug monitoring vs standard therapy during maintenance infliximab therapy on disease control in patients with immune-mediated inflammatory diseases: a randomized clinical trial. *JAMA* 2021;326:2375–84.
50 Landewé RB, Gensler LS, Poddubnyy D, *et al*. Continuing versus withdrawing ixekizumab treatment in patients with axial spondyloarthritis who achieved remission: efficacy and safety results from a placebo-controlled, randomised withdrawal study (COAST-Y). *Ann Rheum Dis* 2021;80:1022–30.
51 Rudwaleit M, Rosenbaum JT, Landewé R, *et al*. Observed incidence of uveitis following Certolizumab pegol treatment in patients with axial spondyloarthritis. *Arthritis Care Res* 2016;68:838–44.
52 Dougados M, van der Heijde D, Sieper J, *et al*. Effects of long-term etanercept treatment on clinical outcomes and objective signs of inflammation in early Nonradiographic axial spondyloarthritis: 104-Week results from a randomized, placebo-controlled study. *Arthritis Care Res* 2017;69:1590–8.
53 Heldmann F, Baraliakos X, Kiltz U, *et al*. Clinical experience with the European ankylosing spondylitis infliximab cohort (EASIC): long-term extension over 7 years with focus on clinical efficacy and safety. *Clin Exp Rheumatol* 2016;34:184–90.
54 Park W, Yoo DH, Miranda P, *et al*. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. *Ann Rheum Dis* 2017;76:346–54.
55 van der Heijde D, Dougados M, Maksymowych WP, *et al*. Long-Term tolerability and efficacy of golimumab in active non-radiographic axial spondyloarthritis: results from open-label extension. *Rheumatology* 2022;61:617–27.
56 van der Heijde D, Dougados M, Landewé R, *et al*. Sustained efficacy, safety and patient-reported outcomes of certolizumab pegol in axial spondyloarthritis: 4-year outcomes from RAPID-axSpA. *Rheumatology* 2017;56:1498–509.
57 van der Heijde D, Sieper J, Maksymowych WP, *et al*. Clinical and MRI remission in patients with nonradiographic axial spondyloarthritis who received long-term open-label adalimumab treatment: 3-year results of the ABILITY-1 trial. *Arthritis Res Ther* 2018;20:61.
58 Pavelka K, Kivitz AJ, Dokoupilova E, *et al*. Secukinumab 150/300 Mg provides sustained improvements in the signs and symptoms of active ankylosing spondylitis: 3-year results from the phase 3 measure 3 study. *ACR Open Rheumatol* 2020;2:119–27.
59 Dougados M, Wei JC-C, Landewé R, *et al*. Efficacy and safety of ixekizumab through 52 weeks in two phase 3, randomised, controlled clinical trials in patients with active radiographic axial spondyloarthritis (COAST-V and COAST-W). *Ann Rheum Dis* 2020;79:176–85.
60 Baraliakos X, Braun J, Deodhar A, *et al*. Long-Term efficacy and safety of secukinumab 150 Mg in ankylosing spondylitis: 5-year results from the phase III measure 1 extension study. *RMD Open* 2019;5:e001005.
61 Marzo-Ortega H, Sieper J, Kivitz AJ, *et al*. 5-Year efficacy and safety of secukinumab in patients with ankylosing spondylitis: end-of-study results from the phase 3 measure 2 trial. *Lancet Rheumatol* 2020;2:e339–46.
62 Van der Heijde D, Deodhar A, Gensler LS, *et al*. POS0226 BIMEKIZUMAB LONG-TERM SAFETY AND EFFICACY IN PATIENTS WITH ANKYLOSING SPONDYLITIS: 3-YEAR RESULTS FROM A PHASE 2B STUDY. *Ann Rheum Dis* 2021;80:332–3.
63 Lie E, Lindström U, Zverkova-Sandström T, *et al*. Tumour necrosis factor inhibitor treatment and occurrence of anterior uveitis in ankylosing spondylitis: results from the Swedish biologics register. *Ann Rheum Dis* 2017;76:1515–21.
64 Lindström U, Bengtsson K, Olofsson T, *et al*. Anterior uveitis in patients with spondyloarthritis treated with secukinumab or tumour necrosis factor inhibitors in routine care: does the choice of biological therapy matter? *Ann Rheum Dis* 2021;80:1445–52.
65 Bessette L, Haraoui B, Florica B, *et al*. POS0232 CLINICAL EFFECTIVENESS OF ADALIMUMAB VERSUS NON-BIOLOGIC THERAPY IN THE MANAGEMENT OF EXTRA-ARTICULAR MANIFESTATIONS IN ANKYLOSING SPONDYLITIS PATIENTS OVER 24 MONTHS – RESULTS OF THE COMPLETE-AS CANADIAN OBSERVATIONAL STUDY. *Ann Rheum Dis* 2021;80:336–7.
66 Deodhar A, Winthrop K, Bohn R, *et al*. SAT0370 TUMOUR NECROSIS FACTOR INHIBITOR THERAPY DOES NOT REDUCE THE INCIDENCE OF COMORBIDITIES AND EXTRA-ARTICULAR MANIFESTATIONS IN ANKYLOSING SPONDYLITIS: AN ANALYSIS OF THREE US CLAIMS DATABASES. *Ann Rheum Dis* 2020;79:1132.1–3.
67 Üsküdar Cansu D, Üsküdar Teke H, Temel T, *et al*. Do anti-TNF agents increase the risk of inflammatory bowel disease evolution in patients with ankylosing spondylitis? real life data. *J Natl Med Assoc* 2019;111:262–9.
68 Walsh JA, Song X, Kim G, *et al*. Evaluation of the comorbidity burden in patients with ankylosing spondylitis treated with tumour necrosis factor inhibitors using a large administrative claims data set. *J Pharm Health Serv Res* 2018;9:115–21.
69 Goll GL, Jørgensen KK, Sexton J, *et al*. Long-Term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: open-label extension of the NOR-SWITCH trial. *J Intern Med* 2019;285:653–69.
70 Proft F, Weiß A, Torgutalp M, *et al*. Sustained clinical response and safety of etanercept in patients with early axial spondyloarthritis: 10-year results of the ESTHER trial. *Ther Adv Musculoskelet Dis* 2021;13:1759720X20987700.

71 Reveille JD, Deodhar A, Caldron PH, *et al*. Safety and efficacy of intravenous golimumab in adults with ankylosing spondylitis: results through 1 year of the GO-ALIVE study. *J Rheumatol* 2019;46:1277–83.
72 Erdes S, Mazurov VI, Dubinina TV, *et al*. Efficacy and safety of a new original interleukin 17A inhibitor in the treatment of patients with active ankylosing spondylitis: results of a basic (BCD-085-3/AILAS) and extended (BCD-085-3ext/AILAS-II) phase II clinical trial. *Rheumatology Science and Practice* 2019;57:668–77.
73 Koo BS, Lim Y-C, Lee M-Y, *et al*. The risk factors and incidence of major infectious diseases in patients with ankylosing spondylitis receiving tumor necrosis factor inhibitors. *Mod Rheumatol* 2021;31:1192–201.
74 Chao W-C, Wang C-Y, Hsu B-C, *et al*. Factors associated with sepsis risk in immune-mediated inflammatory diseases receiving tumor necrosis factor inhibitors: a nationwide study. *Ther Adv Musculoskelet Dis* 2020;12:1759720X20929208.
75 Hellgren K, Dreyer L, Arkema EV, *et al*. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. *Ann Rheum Dis* 2017;76:105–11.
76 Merjanah S, Bittar M, Magrey M. Malignancy risk among patients with ankylosing spondylitis in the United States: a population-based national study. *Arthritis and Rheumatology* 2020;72:2665–7.
77 Kopp TI, Delcoigne B, Arkema EV, *et al*. Risk of neuroinflammatory events in arthritis patients treated with tumour necrosis factor alpha inhibitors: a collaborative population-based cohort study from Denmark and Sweden. *Ann Rheum Dis* 2020;79:566–72.
78 Dreyer L, Magyari M, Laursen B, *et al*. Risk of multiple sclerosis during tumour necrosis factor inhibitor treatment for arthritis: a population-based study from DANBIO and the Danish multiple sclerosis registry. *Ann Rheum Dis* 2016;75:785–6.
79 Deodhar A, Van der Heijde D, Gensler LS, *et al*. POS0939 Bimekizumab in patients with active non-radiographic axial spondyloarthritis: 24-week efficacy & safety from be mobile 1, a phase 3, multicentre, randomised, placebo-controlled study. *Ann Rheum Dis* 2022;81:772–3.
80 Van der Heijde D, Baraliakos X, Dougados M, *et al*. OP0019 Bimekizumab in patients with active ankylosing spondylitis: 24-week efficacy & safety from be mobile 2, a phase 3, multicentre, randomised, placebo-controlled study. *Ann Rheum Dis* 2022;81:12–13.
81 Mease P, van den Bosch F. Il-23 and axial disease: do they come together? *Rheumatology* 2021;60:iv28–33.
82 Baeten D, Adamopoulos IE. Il-23 inhibition in ankylosing spondylitis: where did it go wrong? *Front Immunol* 2020;11:623874.
83 Park W, Hrycaj P, Jeka S, *et al*. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis* 2013;72:1605–12.
84 Yates M, Hamilton LE, Elender F, *et al*. Is etanercept 25 Mg once Weekly as effective as 50 Mg at maintaining response in patients with ankylosing spondylitis? A randomized control trial. *J Rheumatol* 2015;42:1177–85.
85 Cantini F, Niccoli L, Cassarà E, *et al*. Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis: a randomized, prospective, long-term, follow-up study. *Biologics* 2013;7:1–6.
86 Krieckaert CL, van Tubergen A, Gehin JE. EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases. *Ann Rheum Dis* 2023;82:57–65.
87 van der Horst-Bruinsma IE, van Bentum RE, Verbraak FD, *et al*. Reduction of anterior uveitis flares in patients with axial spondyloarthritis on certolizumab pegol treatment: final 2-year results from the multicenter phase IV C-VIEW study. *Ther Adv Musculoskelet Dis* 2021;13:1759720X211003803.
88 van Bentum RE, Heslinga SC, Nurmohamed MT, *et al*. Reduced Occurrence Rate of Acute Anterior Uveitis in Ankylosing Spondylitis Treated with Golimumab - The GO-EASY Study. *J Rheumatol* 2019;46:153–9.
89 Sandborn WJ, Hanauer SB, Rutgeerts P, *et al*. Adalimumab for maintenance treatment of Crohn's disease: results of the classic II trial. *Gut* 2007;56:1232–9.
90 Sandborn WJ, Feagan BG, Stoinov S, *et al*. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007;357:228–38.
91 Hueber W, Sands BE, Lewitzky S, *et al*. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut* 2012;61:1693–700.
92 Sandborn WJ, Hanauer SB, Katz S, *et al*. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2001;121:1088–94.
93 Park JW, Yoon YI, Lee JH, *et al*. Low dose etanercept treatment for maintenance of clinical remission in ankylosing spondylitis. *Clin Exp Rheumatol* 2016;34:592–9.
94 Moura CS, Rahme E, Maksymowych WP, *et al*. Use of disease-modifying anti-rheumatic or anti-tumour necrosis factor drugs and risk of hospitalized infection in ankylosing spondylitis. *Scand J Rheumatol* 2019;48:121–7.
95 Krabbe S, Grøn KL, Glintborg B, *et al*. Risk of serious infections in arthritis patients treated with biological drugs: a matched cohort study and development of prediction model. *Rheumatology* 2021;60:3834–44.
96 Liew JW, Jafarzadeh SR, Dubreuil M, *et al*. The association of tumor necrosis factor inhibitor use with incident hypertension in ankylosing spondylitis: data from the psoas cohort. *J Rheumatol* 2022;49:274–80.