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REVIEW

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

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ABSTRACT

Objectives: To update the evidence for the efficacy and safety of (b)biological and (ts)targeted-synthetic disease-modifying anti-rheumatic drugs (DMARDs) in patients with axial spondyloarthritis (axSpA) to inform the 2016 update of the Assessment of SpondyloArthritis international Society/European League Against Rheumatism (ASAS/EULAR) recommendations for the management of axSpA.

Methods: Systematic literature review (2009–2016) for randomised controlled trials (RCT), including long-term extensions, strategy trials and observational studies (the latter was only for safety assessment and a comparator was required). Interventions were any bDMARD or tsDMARD. All relevant efficacy and safety outcomes were included.

Results: 76 papers and 24 abstracts fulfilled the inclusion criteria. Large treatment effects were found both in radiographic axSpA (r-axSpA) and non-radiographic axSpA (nr-axSpA) for all tumour necrosis factor inhibitors (TNFi) (NNT to achieve ASAS40 response ranged between 2.6–5.2 for r-axSpA and 2.3–5.4 for nr-axSpA). For nr-axSpA, efficacy was superior for those who had objective signs of inflammation (positive C reactive protein or inflammation on MRI-SI). Secukinumab 150 mg has shown efficacy in two phase 3 RCTs (NNT to achieve ASAS40 response: 3.4 and 4.0). Ustekinumab and tofacitinib have shown positive results in phase 2/proof-of-concept trials; trials with apremilast, rituximab, interleukin (IL)-6 antagonists and abatacept have failed their primary end points. New (unknown) safety signals were not found in the trials but long-term observational safety data for TNFi are still scarce.

Conclusions: New evidence supports the efficacy and safety of TNFi both in r-axSpA and nr-axSpA. Secukinumab is the first drug targeting the IL-17 pathway in r-axSpA that has shown efficacy.

INTRODUCTION

In 2003, the Assessment of SpondyloArthritis international Society (ASAS) published the first consensus statement on the use of tumour necrosis factor inhibitors (TNFi) for treating patients with radiographic axial spondyloarthritis (r-axSpA; formerly-labelled ankylosing spondylitis (AS)) as defined by the modified New York criteria—mNY).[1 2] The rapidly evolving field demanded regular updates; the first was published in 2006 and the second in 2010.[3 4]

A better recognition of early forms of the disease (not captured by the mNY) has motivated the development and validation of the ASAS axial spondyloarthritis (axSpA) classification criteria, which aggregate both patients with non-radiographic (nr-axSpA) and radiographic axial SpA (r-axSpA), as a continuous disease spectrum with similar clinical features and a common genetic background.[5] Thereafter, compelling evidence has shown a similar disease burden of patients with r-axSpA and nr-axSpA and the first trials in nr-axSpA have also shown good treatment effects.[6 7] This has finally led to the inclusion of the entire spectrum of axSpA in the 2010 update of the recommendations for the use of TNFi.[4]

Since the last systematic literature review (SLR) informing the 2010 update,[8] a large number of trials have been performed that further expanded the range of available therapeutic options, including both biological disease modifying antirheumatic drugs (bDMARDs) targeting new pathways and, more recently, targeted-synthetic DMARDs (tsDMARDs).[9] Landmark trials of TNFi including only patients with early nr-axSpA were undertaken and the first biosimilar (CT-P13) has been compared to its originator drug. Studies addressing strategies for biological treatment tapering have been performed and data from long-term extensions of the first trials on TNFi have become available. In addition, there are now more observational data on long-term safety of these drugs in clinical practice.

In 2010, two separate sets of recommendations had been released: (1) the international ASAS recommendations for the use of TNFi in patients with axSpA;[4] and (2) the ASAS/European League Against Rheumatism (EULAR) recommendations for the management of AS,[10] which was an update of the first recommendations issued.[11] Since then, many new developments (extending also to non-biological therapies) have prompted a collaborative effort of ASAS and the EULAR to update the recommendations for the management of axSpA, which for the first time incorporate the different aspects of management into one set and also cover the whole spectrum of the disease (2016 update of the ASAS-EULAR management recommendations for axial Spondyloarthritis. van der Heijde D, Ramiro S, Landewé R, *et al. Ann Rheum Dis* 2016, submitted for publication). The overarching aim of this SLR was to inform the ASAS/EULAR task force on the new evidence for the efficacy and safety of treatment with bDMARDs and tsDMARDs. In this manuscript, the results of SLR on bDMARDs and tsDMARDs are described, whereas the results for the SLR on non-pharmacological and non-biological pharmacological treatments are shown separately (Regel A, Sepriano A, Baraliakos X, *et al.* Efficacy and safety of non-pharmacological and non-biological pharmacological treatment: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. *Ann Rheum Dis* 2016, submitted for publication).

METHODS

Literature search

The steering group of the ASAS/EULAR task force for the update of the axSpA management recommendations (all coauthors) outlined the scope of the literature search according to the Population, Intervention, Comparator, Outcomes (PICO) format and defined the criteria for a study being eligible.[12] The population was defined as adult (≥18 years) patients with axSpA, both r-axSpA and nr-axSpA. Studies also including patients with other diagnoses were eligible only if the results for axSpA were presented separately. The intervention was defined as any biological drug, including biosimilars (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol, secukinumab, ustekinumab, tocilizumab, sarilumab, abatacept, rituximab, all formulations and treatment duration) or any tsDMARD (apremilast, tofacitinib). The comparator was the same drug (different dose or regimen), another b/tsDMARD, any non-biological drug, combination therapy (biological and non-biological), placebo or 'none' (if population-based incidence rates were reported).

For the efficacy assessment, the following outcomes were considered: ASAS response criteria (ASAS20, ASAS40, ASAS5/6 and ASAS partial remission); Ankylosing Spondylitis Disease Activity Score (ASDAS, based on C reactive protein; CRP) response criteria (clinically important improvement (Δ ≥1.1) and major improvement (Δ ≥2.0)); Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) response (improvement of ≥50% and/or ≥2 units in BASDAI); absolute change in disease activity measures (pain visual analogue scale, BASDAI, ASDAS and patient global assessment); spine mobility as assessed by the Bath Ankylosing Spondylitis Metrology Index (BASMI); physical function as assessed by Bath Ankylosing Spondylitis Functional Index (BASFI); peripheral manifestations (enthesitis, swollen joint count and tender joint count (TJC)); radiographic damage (modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), radiographic sacroiliitis according to the mNY); inflammation on MRI (active sacroiliitis (ASAS/Outcome Measures in Rheumatology (OMERACT) definition), Spondyloarthritis Research Consortium of Canada (SPARCC)-score (sacroiliac joints and spine)); work disability and productivity; cost-efficacy and cost-effectiveness. For the safety assessment, the following outcomes were considered: withdrawals due to adverse events, serious adverse events, infections, malignancies, cardiovascular diseases, infusion/injection-site reactions, demyelinating diseases, renal function impairment, gastrointestinal and hepatic adverse events and haematological abnormalities.

The types of studies considered for inclusion were randomised controlled trials (RCTs), controlled clinical trials (CCTs) and long-term extensions for efficacy and safety assessment. Cohort studies were included only for safety assessment and a minimum of 50 patients per group was required. Moreover, cohort studies had to include a comparator group or otherwise report population-based standardised incidence rates (SIR). SLRs captured by the search were used to obtain references of original studies, which were included if they fulfilled the eligibility criteria, but SLRs (except for Cochrane reviews) were not, in order to avoid duplication of information.

The following bibliographical databases were searched: MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials (CENTRAL), from January 2009 until 26 February 2016, without language restrictions. In order to retrieve additional references, abstracts from the American College of Rheumatology (ACR) and EULAR annual conferences for the years 2014 and 2015 were also searched. References from included studies were screened in order to identify further studies for inclusion. If an included abstract was published in a manuscript before the present paper was submitted in its final format, the data from the manuscript were used. Details on the search strategy are provided in online supplementary text 1.

Study selection, data extraction and assessment of risk of bias

Two reviewers (AS and AR) independently assessed each title and abstract on suitability for inclusion in the review, according to the aforementioned selection criteria, followed by a full-text review if necessary. From the included studies, both reviewers independently extracted data regarding inclusion and exclusion criteria, main study design features, characteristics of the study population, interventions and outcome measures. The same two reviewers independently assessed the risk of bias (RoB) of each included study using The Cochrane Collaboration's tool for RCTs and the 'Hayden-tool' for observational studies.[13 14] For study selection, extraction and RoB assessment, disagreements were discussed until consensus was achieved, and a third reviewer (SR) was involved whenever necessary.

Data analysis

Heterogeneity in study design and target population precluded meta-analyses to be performed. The following measures of treatment effect were calculated to allow, to the extent possible, comparisons between different drugs: (1) dichotomous outcomes: risk ratios (RR) and numbers needed to treat (NNT; number of patients who must be treated in order to obtain the benefit of interest in one additional patient); (2) continuous outcomes: standardised mean differences (SMD; mean difference between the treatment and placebo for a specific outcome divided by the pooled SD).

RESULTS

Of a total of 11 649 references (after de-duplication), 623 were selected for a full-text review. Seventy-six papers and 24 abstracts on bDMARDs and tsDMARDs fulfilled the inclusion criteria (flow chart in online supplementary figure S1). The included publications stem from a total of 42 different trials, and the majority of these (30; 71%) included one of the five TNFi. In addition, we have included one trial for each the new bDMARDs and tsDMARDs (see online supplementary table S1). Patients with r-axSpA according to the mNY were included in most trials (30; 71%). Patients with axSpA according to the ASAS criteria were included in 9 (21%); four of these included only nr-axSpA and one included both patients with r-axSpA and nr-axSpA (see online supplementary table S1.1). In addition, seven observational studies assessing TNFi long-term safety were identified (see online supplementary table S2) as well as one Cochrane review on TNFi efficacy and safety.

TNF inhibitors

A Cochrane meta-analysis of 18 RCTs (up to November 2014) had shown that, compared with placebo, patients with r-axSpA treated with TNFi (certolizumab pegol not included) were significantly more likely to achieve an ASAS40 response at 6 months (NNT range: 3–5).[15] Similarly, good results had been found for improvement in physical function as measured by BASFI (SMD range: 1.1–2.1) and for reduction in spine inflammation as measured by the MRI SPARCC spine score (absolute increased benefit range: −2.5–−6%).

In the current SLR, RCTs on the full spectrum of axSpA were included (see online supplementary tables S3–S34).[16–28] Given the time span (2009–2016) of the SLR, the main phase 3 RCTs for etanercept, infliximab, adalimumab and golimumab in r-axSpA were not included, but only their LTE or other (subsequent) trials in different populations. These relevant data, included in previous SLRs,[8 10] are therefore also shown in table 1 together with the new evidence.[29–33] The treatment effect on ASAS40 was large both for r-axSpA (response rate range from 2009 onwards: 44.5% to 47.7% (NNT range: 2.6–5.2); response rate range before 2009: 39.4–54.3% (NNT: 2.6–3.8)) and nr-axSpA (response rate range: 33.3–61.1%; NNT range: 2.3–5.4) (table 1 and table 2). The RAPID-axSpA is the only trial including both patients with r-axSpA and nr-axSpA with either positive CRP or MRI (with stratified randomisation for the presence of radiographic sacroiliitis).[18] In this study, largely overlapping results were observed between the two groups for ASAS20 and ASAS40, but the improvement in disability (BASFI) was greater for patients with nr-axSpA (SMD (95% CI): 1.02 (0.59 to 1.44)) as compared to those with r-axSpA (SMD (95% CI) 0.65 (0.28 to 1.01)).

In three separate trials, the treatment effect of etanercept, adalimumab and golimumab in patients with nr-axSpA was tested according to the MRI/CRP status at treatment start (table 3).[24 26 27] For all drugs, the effect on ASAS20 and ASAS40 responses was far smaller (and not statistically significant) in patients with a normal CRP and MRI at baseline (NNT range: 2.5–33.3). In patients who had a positive MRI or an increased CRP (adalimumab and golimumab) and in patients who had both (etanercept), the effect sizes were far greater and statistically significant (NNT range: 2.5–4.7).

TNFi have also shown good results for other outcomes, including ASDAS, BASDAI, CRP, TJC, spine mobility and axial inflammation on MRI (see online supplementary tables S3–S34). In addition, long-term extension studies of trials in r-axSpA have revealed high retention rates after 2 years (range: 71–81%), 5 years (range: 55–69%) and 8 years (48%) (see online supplementary table S33).

In the aforementioned Cochrane review,[15] a meta-analysis of all the TNFi combined against placebo (16 studies) has shown an increased risk of withdrawal due to adverse events in the TNFi group (Peto's OR

Table 1 Effect of TNFi on ASAS20, ASAS40 and BASFI in patients with r-axSpA (mNY) (RCTs)

Outcome Drug	<2009 (previous SLRs)[8 10] N patients (Study)	Time-point (weeks)	Response treatment (%)	Response placebo (%)	RR (95% CI)	NNT	≥2009 (current SLR) N patients (Study)	Time-point (weeks)	Response treatment (%)	Response placebo (%)	RR (95% CI)	NNT
ASAS20												
Etanercept	40 (Gorman *et al*[29])	16	80	30	2.67 (1.32 to 5.39)	2.0	81 (Dijkmans 2009[16])	12	60.0	23.0	2.61 (1.36 to 4.52)	2.7
	277 (Davis *et al*[30])	24	57	22	2.59 (1.80 to 3.57)	2.9	82 (SPINE[17])	12	68.4	35.9	1.91 (1.21 to 3.21)	3.1
Infliximab	279 (ASSERT[31])	24	61.2	19.2	3.18 (2.00 to 5.08)	2.4	76 (Inman 2010[18])	12	54.0	31.0	1.74 (1.02 to 3.22)	4.3
Adalimumab	315 (ATLAS[32])	12	58.2	20.6	2.83 (1.92 to 4.18)	2.7	261 (Huang 2014[19])	12	67.2	30.4	2.21 (1.78 to 3.29)	2.7
Golimumab	216* (GO-RAISE[33])	14	59.4	21.8	2.73 (1.75 to 4.24)	2.7	213 (Bao 2014[20])	24	50.0	22.9	2.18 (1.55 to 3.45)	3.7
							41 (Tam 2014[21])	24	55.0	14.0	3.93 (1.26 to 11.80)	2.4
Certolizumab	NA	NA	NA	NA	NA	NA	122† (RAPID-axSpA[22])	24	67.7	33.3	2.03 (1.36 to 3.04)	2.9
ASAS40												
Etanercept	–	–	–	–	–	–	82 (SPINE[17])	12	44.7	25.6	1.75 (0.99 to 3.59)	5.2
Infliximab	279 (ASSERT[31])	24	47.0	12.0	3.92 (2.13 to 7.55)	2.9	76 (Inman 2010[18])	12	46.0	8.0	5.75 (1.83 to 17.74)	2.6
Adalimumab	315 (ATLAS[32])	12	39.4	13.1	3.01 (1.82 to 5.11)	3.8	344 (Huang 2014[19])	12	44.5	9.6	4.64 (2.61 to 8.32)	2.9
Golimumab	216* (GO-RAISE[33])	24	54.3	15.4	3.53 (2.05 to 6.08)	2.6	–	–	–	–	–	–
Certolizumab	NA	NA	NA	NA	NA	NA	122† (RAPID-axSpA[22])	24	47.7	15.8	3.02 (1.57 to 5.79)	3.1

	N patients (Study)	Time point (weeks)	Impr. treatment mean (SD)	Impr. placebo mean (SD)	SMD (95% CI)	N patients (Study)	Time point (weeks)	Impr. treatment mean (SD)	Impr. placebo mean (SD)	SMD (95% CI)
BASFI (Δ‡)										
Etanercept	40 (Gorman *et al*[29])	16	2.3 (–)	0.1 (–)	n/e	40 (Barkham 2010[23])	12	1.35 (–)	−0.21 (–)	n/e
	277 (Davis *et al*[30])	24	1.6 (–)	0.2 (–)	n/e	82 (SPINE[17])	12	2.20 (1.8)	1.00 (1.8)	0.19 (−1.31 to 1.68)
Infliximab	279 (ASSERT[31])	24	1.7 (–)	0.0 (–)	n/e	–	–	–	–	–
Adalimumab	315 (ATLAS[32])	–	–	–	–	261 (Huang 2014[19])	12	1.8 (2.0)	0.47 (1.6)	0.69 (0.46 to 0.92)
						315 (ATLAS[24])	24	2.00 (–)	0.50 (–)	n/e
Golimumab	216† (GO-RAISE[33])	24	1.6 (–)	−0.4 (–)	n/e	213 (Bao 2014[20])	24	1.26 (2.6)	−0.11 (2.1)	0.58 (0.30 to 0.85)
						41 (Tam 2014[21])	24	1.27 (2.5)	−1.73 (7.2)	0.55 (−0.08 to 1.16)
Certolizumab	NA	NA	NA	NA	NA	122† (RAPID-axSpA[22])	24	2.30 (2.4)	0.90 (1.8)	0.65 (0.28 to 1.01)

*Golimumab 50 mg versus placebo.
†Certolizumab pegol 200 mg versus placebo.
‡Mean improvement compared to baseline value (range: 0–10).
r-axSpA, radiographic axial spondyloarthritis; mNY, modified New York criteria; NNT, number needed to treat; RR, risk ratio; SMD, standardised mean difference; n/e, not possible to estimate; Impr, improvement; ASAS, Assessment of SpondyloArthritis international Society; BASFI, Bath Ankylosing Spondylitis Functional Index NA, not applicable.

Table 2 Effect of TNFi on ASAS20, ASAS40 and BASFI in patients with nr-axSpA (ASAS criteria) (RCTs)

Outcome Drug	N patients (Study)	Time point (weeks)	Response treatment (%)	Response placebo (%)	RR (95% CI)	NNT
ASAS20						
Etanercept	215 (EMBARK[25])	12	52.4	36.1	1.45 (1.06 to 1.90)	6.1
Infliximab*	–	–	–	–	–	–
Adalimumab	185 (ABILITY-1[27])	12	51.6	30.9	1.67 (1.17 to 2.40)	4.8
Golimumab	198 (GO-AHEAD[28])	16	71.1	40.0	1.78 (1.43 to 2.43)	3.2
Certolizumab	96† (RAPID-axSpA[22])	24	65.2	24.0	2.72 (1.59 to 4.65)	2.4
ASAS40						
Etanercept	215 (EMBARK[25])	12	33.3	14.8	2.25 (1.33 to 3.81)	5.4
Infliximab*	40 (Barkham 2009[26])	16	61.1	17.6	3.47 (1.16 to 10.31)	2.3
Adalimumab	185 (ABILITY-1[27])	12	36.3	14.9	2.44 (1.40 to 4.25)	4.7
Golimumab	198 (GO-AHEAD[28])	16	56.7	23.0	2.47 (1.67 to 3.70)	3.0
Certolizumab	96† (RAPID-axSpA[22])	24	56.5	14.0	4.04 (1.94 to 8.40)	2.7
			Impr. mean (SD)	Impr. mean (SD)	SMD (95% CI)	
BASFI (Δ‡)						
Etanercept	215 (EMBARK[25])	12	1.40 (0.2)	0.80 (0.2)	3.00 (2.61 to 3.39)	
Infliximab*	40 (Barkham 2009[26])	16	2.70 (2.36)	0.47 (2.25)	0.97 (0.31 to 1.62)	
Adalimumab	185 (ABILITY-1[27])	12	1.10 (–)	0.60 (–)	n/e	
Golimumab	–	–	–	–	–	
Certolizumab	96† (RAPID-axSpA[22])	24	2.50 (2.4)	0.10 (2.3)	1.02 (0.59 to 1.44)	

*nr-axSpA defined by: inflammatory back pain (Calin definition) within 3 months to 3 years AND sacroiliitis on MRI AND HLA-B27 positivity.
†Certolizumab pegol 200 mg versus placebo.
‡Mean improvement compared to baseline value (range: 0–10).
ASAS, Assessment in SpondyloArthritis international Society; BASFI, Bath Ankylosing Spondylitis Functional Index; HLA, human leucocyte antigen; Impr, improvement; NA, not applicable; n/e, not possible to estimate; nr-axSpA, non-radiographic axial spondyloarthritis; NNT, number needed to treat; RR, risk ratio; SMD, standardised mean difference.

(pOR): 2.44 (1.26 to 4.72)) but not for serious adverse events (pOR: 1.45 (0.85 to 2.48). Data from RCTs included in the current review do not indicate new and unknown safety signals for TNFi (see online supplementary tables S35–S44).

We identified seven observational cohort studies assessing TNFi long-term safety (table 4; and online supplementary tables S45–S56). Three studies (at moderate RoB) revealed no increased risk of malignancies as compared to the general population.[34–36] Two studies (at low RoB) showed no increased risk of infections in TNFi users versus non-users (adjusted OR (95% CI) 1.25 (0.90 to 1.73);[37] adjusted HR (95% CI) 1.05 (0.45 to 2.45)).[38] In both studies, the estimates were adjusted for concomitant use of glucocorticoids, conventional synthetic DMARDs (csDMARDs) and comorbidities. Finally, we found conflicting data concerning the risk of tuberculosis in two studies at moderate RoB. One study has shown an increased risk in TNFi-treated patients compared to non-treated patients (unadjusted HR: 4.9 (1.5 to 15.4)),[40] while another study did not (unadjusted HR: 0.53 (0.14 to 1.91)).[39]

bDMARDs and tsDMARDs targeting new pathways

A detailed description of each study's main characteristics as well as all efficacy and safety outcomes is shown in online supplementary tables S57–S65. Two large 16-week RCTs (MEASURE-1 and MEASURE-2) assessed the effect of secukinumab (a subcutaneous IL-17 inhibitor) in patients with r-axSpA (both TNFi-naïve and after failure to at least one TNFi).[41] Secukinumab 150 mg has proven to be effective in both studies (ASAS40 response rate 42% (NNT: 3.4) and 36% (NNT: 4.0) for MEAURE-1 and MEASURE-2 respectively). Positive results with a lower dose (75 mg) were only found in MEASURE-1 after an intravenous loading dose (table 5). Large treatment effects were also seen for other disease domains, including axial inflammation and quality of life (see online supplementary tables S61–S65). TNFi-naïve patients have shown better response rates than TNFi-experienced patients, but beneficial effects were also seen in these latter patients (ASAS 40 response rate for secukinumab 150 mg: 43.2% (NNT: 3.9) for TNFi-naïve and 25.0% (NNT: 4.0) for TNFi-experienced patients).[49]

New cases and reactivations of Crohn's disease were observed (5 cases in both studies; pooled incidence rate: 0.7/100 patient-years) irrespective of the dose (see online supplementary table S64), but other relevant safety signals were not found.

In a 24-week uncontrolled and open label (high risk of bias) proof of concept (POC) trial, ustekinumab (IL-12/IL-23 inhibitor) has shown preliminary good results (ASAS20 at week 24: 75%) in TNFi-naive patients with long-standing r-axSpA.[42] Tofacitinib (Janus kinase inhibitor) has been tested in a phase 2 double-blind

Table 3 Effect of TNFi on ASAS20 and ASAS40 responses according to the CRP/MRI status at baseline in patients with nr-axSpA.

Outcome Drug (study)	Time point (weeks)	MRI−AND CRP− N patients	MRI−AND CRP− RR (95% CI)	MRI−AND CRP− NNT	MRI+AND/OR CRP+ N patients	MRI+AND/OR CRP+ RR (95% CI)	MRI+AND/OR CRP+ NNT	MRI+AND CRP+ N patients	MRI+AND CRP+ RR (95% CI)	MRI+AND CRP+ NNT
ASAS 20										
Etanercept (EMBARK[25])	12	26	3.82 (0.95 to 15.36)	2.5	–	–	–	77	1.48 (0.97 to 2.27)	4.7
Adalimumab (ABILITY-1[27])	–	–	–	–	–	–	–	–	–	–
Golimumab (GO-AHEAD[28])	16	39	0.95 (0.50 to 1.81)	n/e	53	2.08 (1.22 to 3.55)	2.5	–	–	–
Certolizumab (RAPID-axSpA[22])	24	NA	NA	NA	96	2.72 (1.59 to 4.65)	2.3	–	–	–
ASAS40										
Etanercept (EMBARK[25])	12	25	6.25 (0.33 to 118.2)	5.5	–	–	–	76	2.09 (1.04 to 4.18)	4.1
Adalimumab (ABILITY-1[27])	12	42	1.14 (0.35 to 3.65)	33.3	142	2.96 (1.56 to 5.63)	3.7	–	–	–
Golimumab (GO-AHEAD[28])	–	–	–	–	–	–	–	–	–	–
Certolizumab (RAPID-axSpA[22])	24	NA	NA	NA	96	4.09 (1.94 to 8.40)	2.7	–	–	–

ASAS, Assessment in SpondyloArthritis international Society; CRP, C reactive protein; NA, not applicable; n/e, not possible to estimate; NNT, number needed to treat; nr-axSpA, non-radiographic axial spondyloarthritis; RR, risk ratio.

RCT[43] and has suggested beneficial effects in various outcome measures, which were statistically significant for both the 5 mg and 10 mg twice a day doses, and with a clear dose–response in the objective outcome measures.

As shown in table 5, phase 2 and POC trials with drugs aiming at other treatment targets did not suggest benefits. These drugs included a phosphodiesterase-4 inhibitor (apremilast),[44] a CD20 (B-cell) inhibitor (rituximab),[45] two IL-6 inhibitors (tocilizumab and sarilumab)[46 47] and a T-cell costimulation inhibitor (abatacept).[48]

Trials with an active comparator

One small (n=50) and underpowered head-to-head, open-label (high RoB) trial has compared two TNFi and did not show statistically significant differences in the main efficacy outcomes between infliximab and etanercept at week 12 (ASAS20: 75% vs 60%; ASAS40: 55 vs 43%; p>0.05 for both).[50]

Two randomised trials have compared etanercept to sulfasalazine (both without a placebo group): the ASCEND (double-blind) trial and the ESTHER (open-label) trial, in established (>5 years) and early axSpA, respectively.[51 52] Etanercept was superior to sulfasalazine and similarly safe, both in r-axSpA and nr-axSpA,[53] and in patients with (ASAS20: 69% vs 50%; p=0.02) and without (ASAS20: 79% vs 55%; p<0.001) peripheral arthritis.[54]

The INFAST trial (n=156) has shown that combination therapy with infliximab and naproxen is superior to naproxen alone in TNFi-naïve early patients with axSpA (not refractory to NSAIDs).[55]

Two small (n=30 and n=60) open-label POC studies have compared TNFi and bisphosphonates and have suggested a larger reduction in disability and objective signs of inflammation for the TNFi.[56 57]

Finally, a non-inferiority RCT (PLANETAS) has shown comparable efficacy and safety profiles between an infliximab biosimilar (CT-P13) and an infliximab originator sustained up to 54 weeks of treatment.[58 59] Details can be found in table 6 and online supplementary tables S66–S73.

Strategy trials

A high level of heterogeneity in terms of study design and definitions of remission, response and flare was found in the included strategy trials (seeonline supplementary tables S74–S80). Studies assessing stopping treatment have shown that flare or loss of previous response status occurred fast (within 14–40 weeks) in the majority of patients (69–79%) and that restart of treatment failed to restore previous status in a substantial proportion of patients (33–73%).[60 61] In one study, a flare was unlikely after stopping treatment (2.5% vs 7.5%; p=0.62), but more than 50% lost their previous state of remission after follow-up.[62]

Two dose-tapering strategies were tested in two open-label RCTs and have suggested that dose reduction decreases the proportion of patients still responding to the drug (52.2% vs 91.7%),[63] but that carefully increasing

Table 4 Safety outcomes for TNFi on observational studies

Study	Treatment group	N patients	Exposition patient-years	N events	IR /100,000py	Effect size Ratio* (95% CI)	SIR† (95% CI)	Risk of bias
Malignancies								
Carmona *et al*[34]	Treated (3 TNFi‡)	761	2288	–	–	–	0.92 (0.44 to 1.70)	Moderate
	General population	NA	NA	NA	NA			
Dreyer *et al*[35]	Treated (3 TNFi‡)	861	–	8	–	–	0.82 (0.41 to 1.64)	Moderate
	General population	NA	NA	NA	–			
Westhovens *et al*[36]	Treated (females) (4 TNFi‡)	74	1194	–	770.1	–	1.54	Moderate
	General population (females)	NA	(overall)	–	499.1		REF	
	Treated (males) (4 TNFi‡)	157		–	370.2		1.31	
	General population (males)	NA		–	283.4		REF	
Infections								
Wallis[37]	Any TNFi§	264	684	127	19/100py	1.25 (0.90 to 1.73)¶	–	Low
	no-TNFi	186	651	91	14/100py	REF		
Moura *et al*[38]	TNFi§ (±csDMARDs)	714	–	57	2.44/100py	1.05 (0.45 to 2,45)**	–	Low
	Only csDMARDs	(overall)		(overall)	4.12/100py	1.77 (0.78 to 4,02)**		
	None				2.25/100py	REF		
Tuberculosis								
Kim *et al*[39]	Any TNFi	354	1784	3	561	0.53 (0.14: 1.91)††	–	Moderate
	Infliximab	78	366	2	540	1.57 (0.34 to 7.18) ††		
	Adalimumab	66	204	1	308	1.33 (0.17 to 10.44)††		
	Etanercept	210	1214	0	0	NA		
	Controls	909	3247	10	308	REF		
Kim *et al*[40]	Treated (5 TNFi‡)	336	1166	7	600.2	4.9 (1.5 to 15.4)††	–	Moderate
	Controls	986	–	–	123.1	REF		

*Different effect sizes/ratios are provided in the different studies.
†SIR, Standardised Incidence Ratio (the ratio between observed and expected cases during follow-up).
‡3 TNFi (etanercept, infliximab, adalimumab), 4 TNFi (etanercept, infliximab, adalimumab, golimumab), 5 TNFi (etanercept, infliximab, adalimumab, golimumab, certolizumab);.
§Not specified;.
¶aOR: adjusted OR (adjusted for: age, disease duration, smoking, csDMARDs, oral steroids, BASDAI, BASFI, comorbidity score, hospitalisation);.
**aHR, adjusted HR (adjusted for baseline patient sociodemographics, comorbidities, prior health service use, time dependent use of NSAIDs, and corticosteroids);.
††Unadjusted HR;.
IR, incidence rate; NA, not applicable; py, patient-years; REF, reference group; TNFi, tumour necrosis factor inhibitors.

Table 5 Effect of new biological and targeted-synthetic DMARDs on ASAS20 and ASAS40 responses in patients with axSpA

Drug Study reference	Study design	Types of patients	Treatment groups	N patients	Time point (weeks)	ASAS20 (%)	p Value	NNT ASAS20	ASAS40 (%)	p Value	NNT ASAS40	Risk of bias
Secukinumab	Phase 3 RCT	r-axSpA* TNFi-naïve and	150 mg Q4W SC	125	16	61	<0.01	3.1	42	<0.01	3.4	Low
Baeten *et al*[41]	double-blind	TNFi-failure (≤1 TNFi)	75 mg Q4W SC	124	16	60	<0.01	3.2	33	<0.01	5.0	
(MEASURE-1†)			Placebo	122	16	29	REF	REF	13	REF	REF	
Secukinumab	Phase 3 RCT	r-axSpA* TNFi-naïve and	150 mg Q4W SC	72	16	61	<0.01	3.0	36	<0.01	4.0	Low
Baeten *et al*[41]	double-blind	TNFi-failure (≤1 TNFi)	75 mg Q4W SC	73	16	41	NS	7.7	26	NS	6.7	
(MEASURE-2†)			Placebo	74	16	28	REF	REF	11	REF	REF	
Ustekinumab	POC	r-axSpA* TNFi-naïve only	90 mg SC	20	24	75	NA	NA	65	NA	NA	High
Poddubnyy	non-controlled											
et al[42] (TOPAS)	open-label trial											
Tofacitinib	Phase 2 RCT	r-axSpA* TNFi-naïve only	2 mg two times a day oral	52	12	51.9	NS	9.3	42.3	<0.05	4.4	Low
van der Heijde	double-blind		5 mg two times a day oral	52	12	80.8	<0.001	2.5	46.2	<0.01	3.8	
et al[43]			10 mg two times a day oral	52	12	55.8	NS	6.8	38.5	<0.05	5.3	
			Placebo	51	12	41.2	REF	REF	19.6	REF	REF	
Apremilast	Phase 2 RCT	r-axSpA* TNFi-naïve only	30 mg two times a day oral	17	12	35.3	0.25	5.1	23.5	0.17	5.5	Low
Pathan *et al*[44]	double-blind		Placebo	19	12	15.8	REF	REF	5.3	REF	REF	
Rituximab	POC	r-axSpA* TNFi-naïve and	1000 mg IV	20	24	40	–	NA	25	–	NA	High
Song *et al*[45]	non-controlled	TNFi-failure (≥1 TNFi)	TNFi-naïve	10	24	50	–	NA	40	–	NA	
	open-label trial		TNFi-failure	10	24	30	–	NA	10	–	NA	
Tocilizumab	Phase 2 RCT	r-axSpA* TNFi-naïve only	TCZ 8 mg/Kg Q4W IV	51	12	37.3	NS	10.2	11.8	NS	12.8	Low
Sieper *et al*[46]	double-blind		Placebo	51	12	27.5	REF	REF	19.6	REF	REF	
(BUILDER-1)												
Sarilumab	Phase 2 RCT	r-axSpA* TNFi-naïve only	SAR 100 mg Q2W SC	49	12	24.5	NS	200	14.3	NS	15.9	Low
Sieper *et al*	double-blind		SAR 150 mg Q2W SC	50	12	30.0	NS	16.7	16.0	NS	12.5	
ARD[47]			SAR 100 mg QW SC	52	12	19.2	NS	20.8	5.8	NS	45.5	
(ALIGN)			SAR 200 mg Q2W SC	50	12	30.0	NS	16.7	18.0	NS	10.0	
			SAR 150 mg QW SC	50	12	38.0	NS	7.1	20.0	NS	8.3	
			Placebo	50	12	24.0	REF	REF	8.0	REF	REF	
Abatacept	POC	r-axSpA* TNFi-naïve and	ABA10 mg/Kg Q28D IV	15	24	26.7	–	NA	13.3	–	NA	Low
Song *et al*[48]	non-controlled	TNFi-failure	(TNFi-naive)									
	open-label trial		ABA 10 mg/Kg Q28D IV	15	24	20		NA	0		NA	
			(TNFi-failure)									

*According to the modified New York criteria.
†Loading dose in MEASURE-1: 10 mg/kg IV 0, 2, 4 weeks and MEASURE 2: 150/75 mg SC 0, 1, 2, 3 weeks.
ASAS, Assessment in SpondyloArthritis international Society; two times a day, twice a day; IV, intravenous; NA, not applicable; NNT, number needed to treat; NS, non-significant (p>0.05); POC, proof of concept; Q28D, every 28 days; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, every week; r-axSpA, radiographic axial spondyloarthritis; RCT, randomised clinical trial; REF, reference group; SC, subcutaneous; TNFi, tumour necrosis factor inhibitor.

Table 6 Trials with an active comparator in patients with axSpA

Study	Study design	Types of patients	Treatment groups	N patients	Time point (weeks)	ASAS20 (%)	p Value	ASAS40 (%)	p Value	Risk of bias
Giardina *et al*[60]	RCT open-label	r-axSpA* TNFi-naïve	INF 5 mg/Kg Q6W IV	25	12	75	NS	55	NS	High
			ETA 50 mg QW SC	25	12	60	REF	43	REF	
Braun *et al*[51] (ASCEND)	RCT double-blind	r-axSpA* TNFi-naïve	ETA 50 mg QW SC	379	16	75.9	<0.001	59.8	<0.001	Low
			SSZ 3g/day oral	187	16	52.9	REF	32.6	REF	
Song *et al*[52] (ESTHER)	RCT open-label	axSpA† TNFi-naïve	ETA 25 mg BiW SC	40	48	85	0.001	70	0.001	Unclear
			SSZ 2–3g/day oral	36	48	42	REF	31	REF	
Park *et al*[58] (PLANETAS)	RCT double-blind (non-inferiority trial)	r-axSpA* TNFi-naïve	CT-P13 5 mg/Kg Q6W IV	125	30	70.5	–	51.8	–	Low
			INF 5 mg/Kg Q6W IV	125	30	72.4	–	47.4	–	
Sieper *et al*[55] (INFAST-1)	RCT double-blind	axSpA† TNFi-naïve not refractory to NSAIDs	INF 5 mg/Kg+NPX	105	28	81.0	0.30	75.2	0.03	Low
			PBO+NPX	51	28	72.5	REF	56.9	REF	
Viapiana *et al*[57]	CCT open-label	r-axSpA* TNFi-naïve	INF 5 mg/Kg Q6W IV	30	24	69	NS	45	NS	High
			Neridronate 100 mg Q4W IV	30	24	68	REF	39	REF	
Mok *et al*[56]	RCT open-label	axSpA† TNFi-naïve	GOL 50 mg Q4W SC	20	48	65	NS	35	NS	Unclear
			PAM 60 mg Q4W IV	9	48	56	REF	11	REF	

*According to the modified New York criteria.
†According to the ASAS axSpA criteria.
axSpA, axial spondyloarthritis; CCT, controlled clinical trial; ETA, etanercept; GOL, golimumab; INF, infliximab; IV, intravenous; NA, not applicable; NPX, naproxen; NS, non-significant ($p>0.05$); NSAIDs, Nonsteroidal anti-inflammatory drug; PAM, pamidronate; PBO, placebo; Q4W, every 4 weeks; Q6W, every 6 weeks; QW, every week; r-axSpA, radiographic axial spondyloarthritis; RCT, randomised controlled trial; REF, reference; SC, subcutaneous; SSZ, sulfasalazine; TNFi, tumour necrosis factor inhibitor.

the administration interval ('spacing') may yield similar numbers of patients still in remission after follow-up as compared to the standard strategy (90% vs 86%).[64]

DISCUSSION

This systematic literature review confirms the efficacy and safety of TNFi (including the new data on certolizumab pegol) in patients with r-axSpA. Efficacy was also established in patients with nr-axSpA, especially in those who have objective signs of inflammation (either CRP and/or MRI positivity). bDMARDs and tsDMARDs targeting pathways other than TNFi have so far only been tested in patients with r-axSpA, and secukinumab is the first IL17-inhibiting drug with proven efficacy and safety in phase 3 trials. CT-P13, an infliximab biosimilar, has been shown to be as effective and safe as an infliximab originator in patients with r-axSpA. Preliminary data suggest that TNFi dose tapering may be attainable, but stopping treatment results in unacceptable high rates of disease flares.

Many high-quality placebo-controlled trials have proven the short-term efficacy of TNFi in patients with axSpA. This review suggests that treatment effects across the different TNFi are similar (ASAS40 NNT range: 2.6–5.2), but a valid comparison across drugs cannot be made in the absence of proper head-to-head trials. Differences in study design, patient characteristics and methodological quality may cause differences in treatment effects that cannot be attributed to the tested drugs themselves.[65] Formal head-to-head RCTs including treatments with different modes of action are warranted to draw definite conclusions, since indirect comparisons, albeit fancy, are methodologically flawed and do not allow prioritisation of treatments.

Of note, TNFi are effective in patients with longstanding r-axSpA and in those with nr-axSpA. Only one trial (RAPID-axSpA) included both patients with nr-axSpA and r-axSpA. This study, in which all patients had to have either positive CRP or MRI, yielded similar treatment effects for the two groups on several disease activity outcomes (eg, ASAS40). Congruent with expectations, reduction of disability (as measured by BASFI) was larger in patients with nr-axSpA as compared to those with r-axSpA.

Contrasting with RAPID-axSpA, in three trials performed solely in patients with nr-axSpA, CRP positivity and MRI inflammation were not mandatory for inclusion. Subgroup analyses comparing patients with these objective signs of inflammation to those without revealed significantly better treatment effects in the former. These results were at the basis of the requirement of these objective signs of inflammation in patients with nr-axSpA to be considered for treatment with TNFi.[66 67]

Placebo-controlled safety analyses from RCTs are hampered by a low expected number of events occurring during a short follow-up in patients selected by restrictive inclusion criteria. Observational studies may yield valuable information on drug safety in 'real-world' patients, if well analysed. In axSpA, studies are still very scarce. We could include seven studies which did not reveal new safety signals. Obviously, these positive results should be interpreted in the context of the fact that careful screening and selection of patients by treating rheumatologists was at the basis of these studies.

For long, treatment options in patients with inadequate response to TNFi were limited. Recently, several new drugs have been tested. IL-17 blockade by secukinumab proved to be effective in patients with r-axSpA, both naïve or previously exposed to TNFi therapy. This represents important progress in the management of patients with axSpA, particularly of those who have failed TNFi and now have an alternative option. Of note, for psoriasis, in the light of the results of two head-to-head trials (secukinumab 300 mg compared to etanercept and to ustekinumab), secukinumab is approved as a first-line systemic treatment for adults with moderate-to-severe plaque psoriasis.[68 69] Safety data on secukinumab are still limited, but the overall acceptable safety profile in RCTs is good. However, exacerbations (or new onset) of Crohn's disease with secukinumab deserve attention from clinicians. In fact, IL-17 inhibition is not considered a therapeutic option in Crohn's disease anymore, given the results of one trial,[70] and this should be taken into account when treating patients with axSpA who have concomitant Crohn's disease. The promising (yet preliminary) effects of ustekinumab in r-axSpA in a POC trial included in this SLR suggests that, contrary to rheumatoid arthritis, targeting the IL-23-IL-17 axis may be effective in patients with axSpA. Ustekinumab was also efficacious in patients with psoriasis and Crohn's disease.[71 72]

Tofacitinib (a tsDMARD targeting Janus kinase) has tested positively in a phase 2 RCT. Other treatment targets are less promising: Apremilast has shown rather poor efficacy in a phase 2 trial and preliminary (but still unpublished) reports from one phase 3 RCT suggest a failure of apremilast to meet the primary end point (ASAS 20 at week 16).[73] Definitive conclusions on the role of bisphosphonates on the management of axSpA are hampered by study design shortcomings (eg, absence of a placebo group), and results from these trials are difficult to interpret and not convincing.

Stopping treatment with TNFi early in the disease course was so far tested in three studies which have shown that individual patients may achieve sustained drug-free remission but that, at the group level, the proportion of patients losing their previous good response is large and remission is not easily regained after resuming TNFi treatment. Careful spacing (increasing the interval) may lead to acceptable long-term outcomes. However, reliable information about which patients may apply for tapering is still lacking.

In summary, this SLR has documented that patients with the entire spectrum of axial SpA can be treated effectively and safely with several bDMARDs, that the options rapidly expand and that several tsDMARDs are in development for the treatment of axSpA.

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