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 biological and targeted-synthetic disease-modifying anti-rheumatic drugs (DMARDs) in patients with axial spondyloarthritis (axSpA) to inform the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. RMD Open 2017;3:e000396. doi:10.1136/rmdopen-2016-000396

Methods: Systematic literature review (2009–2016) for randomised controlled trials (RCT), including long-term extensions, strategy trials and observational studies. 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). 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; and (2) the ASAS/European League Against Rheumatism (EULAR) recommendations for the management of AS, which was an update of the first recommendations issued. Since then, many new developments (extend- ing 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. 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 (SPARC)-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...
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.15 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 text 1). 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 of 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 MRI and CRP 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
| Outcome | Drug | N patients (Study) | Time-point (weeks) | Response treatment (%) | Response placebo (%) | RR (95% CI) | NNT | 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 81) | 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 (SPINE17) | 12 | 68.4 | 35.9 | 1.91 (1.21 to 3.21) | 3.1 |
| | | 277 (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 |
| | 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) | 24 | 54.3 | 15.4 | 3.53 (2.05 to 6.08) | 2.6 | 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 | 315 (ATLAS 34) | 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 | 67.7 | 33.3 | 2.03 (1.36 to 3.04) | 2.9 |
| **ASAS40** | Etanercept | – | – | – | – | – | – | 82 (SPINE17) | 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) | 24 | 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 | 315 (ATLAS 34) | 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 |

*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.
(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 S55–S65). 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 (cDMARDs) 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)),39 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).40 Secukinumab 150 mg has proven to be effective in both studies (ASAS40 response rate 42% (NNT: 3.4) and 36% (NNT: 4.0) for MEASURE-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-naive 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-naive and 25.0% (NNT: 4.0) for TNFi-experienced patients).41

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
RCT 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) 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 (see online 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 (60–79%) 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...
| 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 | Treated (3 TNFi‡) | 761 | 2288 | – | – | 0.92 (0.44 to 1.70) | Moderate |
| | General population | NA | NA | NA | NA | – | – | – |
| Dreyer et al | Treated (3 TNFi‡) | 861 | – | 8 | – | 0.82 (0.41 to 1.64) | Moderate |
| | General population | NA | NA | NA | – | – | – | – |
| Westhovens et al | 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 | 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 | TNFi§ (±csDMARDs) | 714 | – | 57 | 2.44/100py | 1.05 (0.45 to 2.45)** | Low |
| | Only csDMARDs (overall) | 54 | – | 4.12/100py | 1.77 (0.78 to 4.02)** | – | – | – |
| | None | 113 | – | 2.25/100py | REF | – | – | – |
| **Tuberculosis** | | | | | | | | |
| Kim et al | 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 | 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.
| 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       | Baeten et al.†        | Phase 3 RCT           | r-axSpA* TNFi-naive and TFN-failure (≤1 TNFi)                                   | 150 mg Q4W SC                  | 125        | 16                | 61         | <0.01  | 3.1        | 42         | <0.01  | 3.4        | Low          |
|                   | (MEASURE-1†)          | double-blind          |                                                                                  | Placebo                        | 122        | 16                | 29         | REF     | REF        | REF        | REF     | REF        |
| Secukinumab       | Baeten et al.†        | Phase 3 RCT           | r-axSpA* TNFi-naive and TFN-failure (≤1 TNFi)                                   | 75 mg Q4W SC                   | 124        | 16                | 60         | <0.01  | 3.2        | 33         | <0.01  | 5.0        | Low          |
|                   | (MEASURE-2†)          | double-blind          |                                                                                  | Placebo                        | 122        | 16                | 41         | NS      | 7.7         | 26         | NS      | 6.7        | Low          |
| Ustekinumab       | Poddubnyy et al.       | POC                   | r-axSpA* TNFi-naive only                                                         | 90 mg SC                       | 20         | 20                | 75         | NA      | NA         | NA         | NA      | NA         | High         |
|                   | (TOPAS)               | non-controlled open-label trial |                                                                            | Placebo                        | 20         | 24                | 75         | NA      | NA         | NA         | NA      | NA         | Low          |
| Tofacitinib       | van der Heijde et al. | Phase 2 RCT           | r-axSpA* TNFi-naive only                                                         | 2 mg twice a day oral          | 52         | 12                | 51.9       | NS      | 9.3        | 42.3       | <0.05  | 4.4        | Low          |
|                   |                      | double-blind          |                                                                                  | 5 mg twice a day oral          | 52         | 12                | 80.8       | <0.001 | 2.5        | 46.2       | <0.01  | 3.8        | Low          |
|                   |                       |                       |                                                                                  | 10 mg twice a day oral         | 52         | 12                | 55.8       | NS      | 6.8        | 38.5       | <0.05  | 5.3        | Low          |
|                   |                       |                       |                                                                                  | Placebo                        | 51         | 12                | 41.2       | REF     | REF        | REF        | REF     | REF        | Low          |
| Apemilast         | Pathan et al.         | Phase 2 RCT           | r-axSpA* TNFi-naive only                                                         | 30 mg two times a day oral     | 17         | 12                | 35.3       | 0.25    | 5.1        | 23.5       | 0.17    | 5.5        | Low          |
|                   |                      | double-blind          |                                                                                  | Placebo                        | 19         | 12                | 15.8       | REF     | REF        | REF        | REF     | REF        | Low          |
| Rituximab         | Song et al.           | POC                   | r-axSpA* TNFi-naive and TFN-failure (≥1 TNFi)                                   | 1000 mg IV                     | 20         | 24                | 40         | –       | NA         | 25         | –       | NA         | High         |
|                   |                      | non-controlled open-label trial |                                      | TNFi-naive                     | 10         | 24                | 50         | –       | NA         | 40         | –       | NA         | High         |
|                   |                      |                       |                                                                                  | TNFi-failure                   | 10         | 24                | 30         | –       | NA         | 10         | –       | NA         | High         |
| Tocilizumab       | Sieper et al.         | Phase 2 RCT           | r-axSpA* TNFi-naive only                                                         | TCZ 8 mg/Kg Q4W IV             | 51         | 12                | 37.3       | NS      | 10.2       | 11.8       | NS      | 12.8       | Low          |
|                   | (BUILDER-1)           | double-blind          |                                                                                  | Placebo                        | 51         | 12                | 27.5       | REF     | REF        | REF        | REF     | REF        | Low          |
| Sarilumab         | Sieper et al.         | Phase 2 RCT           | r-axSpA* TNFi-naive only                                                         | SAR 100 mg Q2W SC              | 49         | 12                | 24.5       | NS      | 200        | 14.3       | NS      | 15.9       | Low          |
|                   | ARD†                  | double-blind          |                                                                                  | SAR 150 mg Q2W SC              | 50         | 12                | 30.0       | NS      | 16.7       | 16.0       | NS      | 12.5       | Low          |
|                   | (ALIGN)               |                       |                                                                                  | SAR 100 mg QW SC               | 52         | 12                | 19.2       | NS      | 20.8       | 5.8        | NS      | 45.5       | Low          |
|                   |                       |                       |                                                                                  | SAR 200 mg Q2W SC              | 50         | 12                | 30.0       | NS      | 16.7       | 18.0       | NS      | 10.0       | Low          |
|                   |                       |                       |                                                                                  | SAR 150 mg QW SC               | 50         | 12                | 38.0       | NS      | 7.1        | 20.0       | NS      | 8.3        | Low          |
|                   |                       |                       |                                                                                  | Placebo                        | 50         | 12                | 24.0       | REF     | REF        | REF        | REF     | REF        | Low          |
| Abatacept         | Song et al.           | POC                   | r-axSpA* TNFi-naive and TFN-failure                                             | ABA10 mg/Kg Q28D IV (TNFi-naive) | 15         | 24                | 26.7       | –       | NA         | 13.3       | –       | NA         | Low          |
|                   |                      | non-controlled open-label trial |                                      | ABA 10 mg/Kg Q28D IV (TFN-failure) | 15         | 24                | 20         | NA      | 0          | NA         | NA      | NA         | Low          |

*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.
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%).

**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 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. 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 long-standing 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.

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. 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, 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.

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). 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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REFERENCES
1. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.
2. Braun J, Pham T, Sieper J, et al. International ASAS consensus statement for the use of anti-TNF agents in patients with ankylosing spondylitis. Ann Rheum Dis 2006;65:316–20.
3. 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.
4. van der Heijde D, Sieper J, Maksymowycz WP, et al. Updated classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2011;70:905–8.
5. Rudwaleit M, van der Heijde D, Landewe R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777–83.
6. Rudwaleit M, Haibel H, Baraliakos X, et al. The early disease stage in axial spondyloarthritis: results from the German SpondyloArthritis Inception Cohort. Arthritis Rheum 2009;60:717–27.
7. Haibel H, Rudwaleit M, Listing J, et al. Efficacy of adalimumab in the treatment of axial spondyloarthritis without radiographically defined
sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis Rheum* 2008;58:1981–91.

8. Baraliakos X, van den Berg R, Braun J, et al. Update of the literature review on treatments with biologics in a basis for the first update of the ASAS/EULAR management recommendations of ankylosing spondylitis. *Rheumatology (Oxford)* 2012;51:1378–87.

9. Smolen JS, van der Heijde D, Machold KP, et al. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2014;73:3–5.

10. 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.

11. 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.

12. Sackett D, WS R, Rosenberg W, et al. Evidence-based medicine: how to practice and teach EBM. London: Churchill Livingstone, 1997.

13. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

14. Hayden JA, Souter P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;144:427–37.

15. Maxwell LJ, Zochling J, Boonen A, et al. TNF-alpha inhibitors for ankylosing spondylitis. *Cochrane Database Syst Rev* 2015;4:CD005468.

16. Dijkmans B, Emery P, Hakala M, et al. Etanercept in the long-term treatment of patients with ankylosing spondylitis. *J Rheumatol* 2009;36:1256–64.

17. Dougados M, Braun J, Szanto S, et al. Efficacy of etanercept on rheumatic signs and pulmonary function tests in advanced ankylosing spondylitis: results of a randomised double-blind placebo-controlled study (SPINE). *Ann Rheum Dis* 2011;70:799–804.

18. Inman RD, Dysmywych WP; CANDLE Study Group. A double-blind, placebo-controlled trial of low dose infliximab in ankylosing spondylitis. *J Rheumatol* 2010;37:1203–10.

19. Huang F, Gu J, Zhu P, et al. Efficacy and safety of adalimumab in Chinese adults with active ankylosing spondylitis: results of a randomised, controlled trial. *Ann Rheum Dis* 2014;73:877–94.

20. Bao C, Huang F, Khan MA, et al. Safety and efficacy of golimumab in Chinese patients with active ankylosing spondylitis: 1-year results of a multicentre, randomized, double-blind, placebo-controlled phase III trial. *Rheumatology (Oxford)* 2014;53:1654–63.

21. Tam LS, Anderson P, Run EW, et al. The effects of golimumab on subclinical atherosclerosis and arterial stiffness in ankylosing spondylitis—a randomized, placebo-controlled pilot trial. *Rheumatology (Oxford)* 2014;53:1065–74.

22. Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis, including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. *Ann Rheum Dis* 2014;73:39–47.

23. Barkham N, Coates LC, Keen H, et al. Double-blind placebo-controlled trial of etanercept in the prevention of work disability in ankylosing spondylitis. *Ann Rheum Dis* 2010;69:1926–8.

24. van der Heijde DM, Revicki DA, Gooch KL, et al. Physical function, disease activity, and health-related quality-of-life outcomes after 3 years of adalimumab treatment in patients with ankylosing spondylitis. *Arthritis Res Ther* 2009;11:R124.

25. Dougados M, van der Heijde D, Sieper J, et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Res Ther* 2014;16:209–10.

26. Barkham N, Keen HI, Coates LC, et al. Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. *Arthritis Rheum* 2009;60:946–54.

27. Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2013;72:815–22.

28. Streib J, van der Heijde D, Dougados M, et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. *Ann Rheum Dis* 2015;74:2702–12.
50. Giardina AR, Ferrante A, Ciccia F, et al. A 2-year comparative open label randomized study of efficacy and safety of etanercept and infliximab in patients with ankylosing spondylitis. *Rheumatol Int* 2010;30:1437–40.

51. Braun J, van der Horst-Bruinsma IE, Huang F, et al. Clinical efficacy and safety of etanercept versus sulfasalazine in patients with ankylosing spondylitis: a randomized, double-blind trial. *Arthritis Rheum* 2011;63:1543–51.

52. Song IH, Hermann K, Haibel H, et al. Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. *Ann Rheum Dis* 2011;70:590–6.

53. Song IH, Weiß A, Hermann KG, et al. Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial. *Ann Rheum Dis* 2013;72:823–5.

54. Braun J, Pavelka K, Ramos-Remus C, et al. Clinical efficacy of etanercept versus sulfasalazine in ankylosing spondylitis subjects with peripheral joint involvement. *J Rheumatol* 2012;39:836–40.

55. Sieper J, Lenaerts J, Wollenhaupt J, et al. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1. *Ann Rheum Dis* 2014;73:101–7.

56. Mok CC, Li OC, Chan KL, et al. Effect of golimumab and pamidronate on clinical efficacy and MRI inflammation in axial spondyloarthritis: a 48-week open randomized trial. *Scand J Rheumatol* 2015;44:480–8.

57. Viapiana O, Gatti D, Idolazzi L, et al. Bisphosphonates vs infliximab in ankylosing spondylitis treatment. *Rheumatology (Oxford)* 2014;53:90–4.

58. 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.

59. Park W, Yoo DH, Jaworski J, et al. Comparable long-term efficacy, as assessed by patient-reported outcomes, safety and pharmacokinetics, of CT-P13 and reference infliximab in patients with ankylosing spondylitis: 54-week results from the randomized, parallel-group PLANETAS study. *Arthritis Res Ther* 2016;18:25.

60. Song IH, Althoff CE, Haibel H, et al. Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial. *Ann Rheum Dis* 2012;71:1212–5.

61. Haibel H, Heldmann F, Braun J, et al. Long-term efficacy of adalimumab after drug withdrawal and retreatment in patients with active non-radiographically evident axial spondyloarthritis who experience a flare. *Arthritis Rheum* 2013;65:2211–3.

62. Sieper J, Lenaerts J, Wollenhaupt J, et al. Maintenance of biologic-free remission with naproxen or no treatment in patients with early, active axial spondyloarthritis: results from a 6-month, randomised, open-label follow-up study, INFAST Part 2. *Ann Rheum Dis* 2014;73:108–13.

63. 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.

64. Cantini F, Niccoli L, Cassaré 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.

65. Cipriani A, Furukawa TA, Churchill R, et al. Validity of indirect comparisons in meta-analysis. *Lancet* 2007;369:270–1. author reply 271.

66. Deodhar A, Reveille JD, van den Bosch F, et al. The concept of axial spondyloarthritis: joint statement of the spondyloarthritis research and treatment network and the Assessment of SpondyloArthritis international Society in response to the US Food and Drug Administration’s comments and concerns. *Arthritis Rheumatol* 2014;66:2649–56.

67. Agency EM. Concept paper on clinical investigation of medicinal products for the treatment of Axial Spondyloarthritis. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/04/WC500185187.pdf

68. Langley RG, Elewski BE, Lebwoh M, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. *N Engl J Med* 2014;371:326–38.

69. Thaci D, Blauvelt A, Reich K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. *J Am Acad Dermatol* 2015;73:100–9.

70. 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.

71. Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn’s disease. *N Engl J Med* 2012;367:1519–28.

72. Leonard CI, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interferon-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008;371:1665–74.

73. https://clinicaltrials.gov/ct2/show/results/NCT01583374?term=apremilast&rank=17&sect=X01256%22