Efficacy and safety of non-pharmacological and non-biological interventions

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

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ABSTRACT

Objective To update the evidence of non-biological treatments for axial spondyloarthritis (axSpA), as a basis for the 2022 Assessment of SpondyloArthritis international Society-European Alliance of Associations for Rheumatology (ASAS-EULAR) recommendations for the management of axSpA.

Methods A systematic literature review (2016–2021) on efficacy and safety of non-pharmacological and non-biological pharmacological treatments was performed, up to 1 January 2022. The research question was formulated according to the PICO format: Population: adult patients with r-axSpA and nr-axSpA; Intervention: non-pharmacological and non-biological pharmacological treatments; Comparator: active comparator or placebo; Outcomes: all relevant efficacy and safety outcomes. Type of studies included were: randomised controlled trials (RCTs), observational studies (for efficacy of non-pharmacological treatments, and safety), qualitative studies. Cohen's effect size (ES) was calculated for non-pharmacological and risk ratio (RR) for pharmacological treatments.

Results Of 107 publications included, 63 addressed non-pharmacological interventions, including education (n=8) and exercise (n=20). The ES for education on disease activity, function, mobility was small to moderate (eg. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), ES: 0.06–0.59). Exercise had moderate to high ES on these outcomes (eg. BASDAI, ES: 0.14–1.43). Six RCTs on targeted synthetic disease-modifying antirheumatic drugs (DMARDs) showed efficacy of tofacitinib, upadacitinib and filgotinib (phase 2 only) in r-axSpA (range RR vs placebo for ASAS20: 1.91–3.10), while apremilast and nilotinib were not efficacious. Studies on conventional synthetic DMARDs (n=3), non-steroidal anti-inflammatory drugs (NSAIDs, n=8) and other drugs (n=12) did not provide new evidence on efficacy/safety (efficacy of NSAIDs confirmed; limited efficacy of short-term glucocorticoids in one RCT).

Conclusions Education, exercise and NSAIDs confirmed to be efficacious in axSpA. JAKi were proved efficacious in r-axSpA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ New evidence about the efficacy and safety of non-pharmacological and non-biological interventions has become available since the 2016 update of the recommendations for axial spondylarthritis (axSpA) management. This prompted a new systematic literature review (SLR) to inform the 2022 update of these recommendations.

WHAT THIS STUDY ADDS

⇒ The efficacy of education and exercise in axSpA has been confirmed by new studies.
⇒ Alendronate is not effective in axSpA, while limited efficacy of short-term use of high-dose glucocorticoids has been shown.
⇒ This review includes qualitative research, focusing on the patient perspective.
⇒ Among targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), filgotinib, tofacitinib and upadacitinib have shown efficacy in radiographic axSpA, with an acceptable short-term safety profile.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This SLR informed the 2022 Assessment of SpondyloArthritis international Society-European Alliance of Associations for Rheumatology recommendations for the management of axSpA, adding relevant evidence on non-pharmacological treatments and non-biological drugs, particularly tsDMARDs.

INTRODUCTION

Current treatment of axial spondyloarthritis (axSpA) encompasses both non-pharmacological and pharmacological therapies, with the aim to improve patients' long-term quality of life.[1]

Evidence-based treatment strategies have been proposed by the 2016 recommendations for axSpA management, which resulted from a joint endeavour of the Assessment of SpondyloArthritis international Society (ASAS) and the European Alliance of Associations for Rheumatology (EULAR).[1] These have been the first set of recommendations aimed at the

entire spectrum of axSpA, including both radiographic and non-radiographic axSpA (r-axSpA, nr-axSpA). In fact, former recommendations were targeted to r-axSpA (also previously known as ankylosing spondylitis).[2] However, since then it became clearer that axSpA represents a spectrum of disease, with nr-axSpA presenting less structurally advanced form of axSpA, and that similar therapeutic strategies are successful for nr-axSpA and r-axSpA.[3] Since the publication of 2016 ASAS/EULAR recommendations, though, many important advances have been made in the field of axSpA treatment: more cytokine-targeted therapies have become available, for example, new interleukin 17 inhibitors,[4 5] treat-to-target and tapering strategies were tested,[6] and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs) have been evaluated in axSpA.[7–9]

This systematic literature review (SLR) updates the evidence on the efficacy and safety of non-pharmacological and non-biological pharmacological treatments in axSpA, to inform the 2022 ASAS/EULAR recommendations.[10] A second SLR has been conducted focusing on biological DMARDs (bDMARDs) and is presented separately.[11]

METHODS

The protocol for the present SLR has been registered in PROSPERO with number CRD42021261959.

Search strategy and inclusion criteria

An online literature search was conducted by an expert librarian (LF) via Medline (Ovid), Cochrane Database of Systematic Reviews CENTRAL, Embase (Ovid) and Epistemonikos, including records from 1 January 2016 up to 1 January 2022, without language restrictions. The detailed search strategy is presented in the online supplemental file 1. The research question was formulated according to the PICO format (Population, Intervention, Comparator, Outcome).[12] The population of interest were adult (≥18 years) patients with axSpA. Studies with mixed populations were included only if data on axSpA were presented separately. Any non-pharmacological treatment, including—but not limited to—education, exercise, physiotherapy, surgery, as well as any non-biological pharmacological therapy, were taken into consideration. The following pharmacological treatments were considered: (1) csDMARDs: methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine, cyclophosphamide, auranofin, penicillamine or thalidomide; (2) non-disease modifying drugs: non-steroidal anti-inflammatory drugs (NSAIDs), local and systemic glucocorticoids, bisphosphonates, analgesics, opioids, opioid-like drug, neuromodulators (antidepressants, anticonvulsants, and muscle relaxants), or others; (3) tsDMARDs: apremilast, tofacitinib, upadacitinib, filgotinib, nilotinib. All doses, formulations, regimens (eg, on-demand, continuous) and duration of these therapies, as well as any combination of those were assessed. Comparators were defined as other non-pharmacological treatments, same treatments in different dose or regimens, other non-biological drug treatments (comparators to bDMARDs are included in the SLR about bDMARDs), any combination therapy, or placebo. The absence of a comparator was only accepted for the safety outcome, when incidence rates were described in long-term extensions of randomised controlled trials (RCTs). The outcomes of interest were all relevant efficacy and safety outcomes. Efficacy outcomes included: (1) ASAS response criteria: ASAS 20, ASAS 40, ASAS 5/6, ASAS partial remission and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 50 ; (2) Ankylosing Spondylitis Disease Activity Score (ASDAS) response criteria: clinically important improvement (ASDAS-CII), major improvement (ASDAS-MI), low disease activity (ASDAS-LDA), inactive disease (ASDAS-ID) (3) disease activity: BASDAI, ASDAS ; (4) visual analogical scale (VAS) of patient's global assessment; (5) VAS of diurnal, nocturnal and global pain; (6) physical function: Bath Ankylosing Spondylitis Functional Index (BASFI); (7) spinal mobility: Bath Ankylosing Spondylitis Metrology Index (BASMI) or the individual spinal mobility measures; (8) enthesitis, swollen joint count, tender joint count (66/68); (9) global functioning and health: ASAS health Index; (10) radiographic damage: modified Stoke Ankylosing Spondylitis Spine Score, radiographic sacroiliitis according to modified New York criteria (mNY); (11) inflammation on MRI: presence of active sacroiliitis according to the ASAS/Outcome Measures in Rheumatology (OMERACT) definition, Spondyloarthritis Research Consortium of Canada scoring system both for sacroiliac joints and spine; (12) extra musculoskeletal manifestations that is, inflammatory bowel disease, psoriasis and uveitis; (13) work disability and work productivity (any instrument). Safety outcomes were: number of total and serious adverse events (AE), deaths, withdrawals due to AEs, any infection, serious infections, tuberculosis, opportunistic infections, malignancies, congestive heart failure, cardiovascular disease, infusion/injection-site reactions, lipid levels, renal function, hepatotoxicity, haematological abnormalities, gastrointestinal effects, demyelinating disease. Types of studies included were: RCTs, controlled clinical trials (CCTs), cohort studies with a comparator and at least 50 participants per group (for efficacy of non-pharmacological therapy and for the safety outcomes; full texts of cohort studies with fewer participants were examined and used only if they provided relevant evidence). Qualitative studies were also considered. Published SLRs were only used to identify references from original studies, with the exception of Cochrane reviews, that qualified for inclusion. Publications in the form of abstracts from American College of Rheumatology and EULAR 2020 and 2021 congresses were also included (via Embase).

Selection process and risk of bias assessment

A random selection of 20% of all records was screened independently by two reviewers (AO, CW), to assess agreement. In view of high agreement (kappa>0.90), the remaining screening and full-text reading was completed by a single reviewer (AO). For subsequent data extraction and risk of bias (RoB) assessment, a similar process was adopted: since agreement on a random 20% of records was confirmed (kappa>0.90), a single reviewer completed the process. In the presence of any discrepancies on inclusion/exclusion, data extraction or RoB assessment, this was resolved by consensus involving the two methodologists (EN, AS). Data regarding study design and characteristics, population, type of treatment and comparator, main efficacy and safety outcomes were extracted on a preset Excel sheet. RoB was assessed according to Version 2 of the Cochrane RoB tool (RoB 2) for RCTs and the Quality In Prognosis Studies tool for observational studies.[13–15] The overall RoB was defined, with both tools, as 'low', 'unclear' or 'high'. For conference abstracts, the RoB was indicated as 'unknown'. All studies were included for qualitative synthesis, but main conclusions on efficacy and safety of treatments were largely drawn from low or unclear RoB studies.

Data synthesis

Data on all outcomes were analysed descriptively. For non-pharmacological treatments, Cohen's effect sizes (ES) were

calculated (mean change in score divided by the baseline SD). ES in the range 0–0.49 corresponded to a small improvement in the outcomes, 0.5–0.79 to a moderate effect and ES≥0.8 to a large effect. ES<0 were interpreted as worsening. For pharmacological treatment, if relevant, binary outcomes were also presented as risk ratios (RR) with their relative 95% CI, and number needed to treat, while continuous outcomes as standardised mean differences (SMD: mean difference between intervention and comparator divided by pooled SD) and 95% CI.

Due to the heterogeneity across the included studies, meta-analysis was not performed.

RESULTS

After deduplication, the literature search yielded 17 480 records. The full texts of 283 articles were examined, of which 107 were finally included (online supplemental figure S1). Sixty-three publications, including eight qualitative studies, addressed non-pharmacological interventions, namely education, exercise, diet, surgery and others (online supplemental table S1). Regarding pharmacological therapy (online supplemental table S2), 20 studies were found on non-csDMARDs/non-tsDMARDs: 8 on NSAIDs and 12 on other drugs including glucocorticoids and bisphosphonates. Two new RCTs and one strategy trial focused on csDMARDs. Twelve publications, corresponding to six RCTs, studied tsDMARDs in patients with r-axSpA except one, which was conducted in axSpA. Nine publications, of which seven on pharmacological interventions, focused on safety.

Efficacy of non-pharmacological interventions

Eight publications focused on education: six RCTs in r-axSpA,[16–20] one in axSpA,[21] and two observational studies in r-axSpA[22 23] (online supplemental tables S3–S5). Overall, the ES for education on disease activity, function and mobility were small to moderate (ES range in RCTs of education for BASDAI: 0.06–0.59, BASFI: 0.04–0.58, BASMI: 0.07–0.54). One RCT, at unclear RoB, demonstrated efficacy of a behavioural programme in increasing the level of physical activity, measured with an accelerometer (increase in minutes of moderate/vigorous physical activity per week: +58 min (range: −4 to 146) in the behavioural programme versus −65 min (range: −155 to 17) in the control group)[18] (table 1).

Twenty publications focused on exercise, corresponding to 17 main studies (RCTs or CCTs),[24–39] and four post-hoc analysis (table 1 and online supplemental tables S6–S8).[40–43] The type, intensity and duration of exercise were very heterogeneous, ranging from Tai-Chi to high intensity exercise. In addition, some of the programmes were supervised by physiotherapist, while others were not. The ES on disease activity, function and pain were moderate or high (range in RCTs of exercise for ASDAS: 0.29–0.94, BASDAI: 0.14–1.43, BASFI: 0.04–0.92, BASMI: 0.06–1.14). One RCT, at unclear RoB, in axSpA showed that a 3-month high-intensity exercise programme (supervised in two out of three sessions per week) reduced disease activity (primary outcome) (ASDAS 2.6–1.9 in the intervention group vs 2.7–2.6 in controls), and improved function (BASFI 2.9–1.8 vs 3.6–3.2), mobility (BASMI 2.9–2.5 vs 2.6–2.5) and cardiovascular health[38] (table 1). Post-hoc analyses of this trial showed also beneficial effects of this programme on fatigue, sleep, mood and general health.[41 42]

Other types of non-pharmacological interventions (eg, transcutaneous electrical nerve stimulation, ultrasound therapy, moxibustion) were investigated in 14 RCTs/CCTs[44–57] and two observational studies (online supplemental tables S9–S14).[58 59] All these studies were conducted in r-axSpA except one in axSpA in general.[46] The RoB was high for all except two studies at unclear RoB on ultrasound therapy combined with exercise (table 1). A higher decrease in ASDAS, BASFI and BASMI was shown in the ultrasound combined with exercise group compared with the control group (exercise only).[49 50]

Eleven retrospective cohort studies compared patients with r-axSpA undergoing surgery with other populations (online supplemental tables S15–S17).[60–70] For advanced spine kyphosis, nine studies reviewing cases of pedicle subtraction osteotomy and/or vertebral column decancellation (removal of bony structures to create a posterior or anterior wedge that enables spine realignment) showed good results in terms of kyphosis correction and subjective outcomes for both techniques.[60 61 64–70] Furthermore, two studies on hip arthroplasty for advanced hip involvement in r-axSpA showed satisfactory clinical and radiological outcomes.[62 63]

Eight qualitative studies, three of which in r-axSpA,[71–73] and five in axSpA,[74–78] were also included (online supplemental tables S18–S20). These studies found that a combination of face-to-face contact and self-education is preferred by the patients, and that E-tools (eg, a web interface to monitor patients' symptoms, quality of life and physical activity) can be useful for disease monitoring.[73 76] It was found that patients with axSpA can exercise and experience this positively,[72 74] and that supervision can enhance adherence to physical activity.[71 74]

Efficacy of pharmacological interventions: non-tsDMARDs

Two RCTs on csDMARDs, one on sulfasalazine (for axial involvement) and one on iguratimod (a csDMARD that inhibits nuclear factor-kappa B), were retrieved.[79 80] In these two small studies at high RoB, efficacy was shown for some outcomes such as disease activity or function, but not in others (eg, C Reactive Protein-CRP, or quality of life)[79 80] (online supplemental tables S21–S23). An additional strategy RCT has shown that methotrexate in combination with adalimumab reduces the formation of anti-adalimumab antibodies. However, methotrexate did not prolong the survival of adalimumab (online supplemental tables S24–S25, S26).[81]

Eight studies on NSAIDs were included, of which two non-inferiority RCTs in r-axSpA, one at low and one at unclear RoB (table 2).[82–89] The first study demonstrated non-inferiority of two doses of etoricoxib (60 and 90 mg daily) versus naproxen 1000 mg daily on VAS spinal pain (SMD between etoricoxib 60 mg and 90 mg with naproxen: 0.07 (−0.24, 0.10) and 0.03 (−0.19, 0.26).[82] The second RCT demonstrated the non-inferiority of two doses of celecoxib (400 mg and 200 mg) versus diclofenac 150 mg daily in VAS global pain (SMD not possible to calculate). The other studies were at a high RoB, and did not provide new information about efficacy or safety of NSAIDs (online supplemental tables S27-S29).

One trial examined the efficacy of a short course of oral prednisolone, starting from 60 mg daily, tapered to 10 mg in 6 weeks, then 5 mg for 18 weeks, versus placebo.[90] The primary endpoint (BASDAI 50 at week 24) was met, with 12 (37.5%) patients in the prednisolone arm and 3 (9.1%) in the placebo arm reaching this outcome (RR 4.1, 95% CI 1.3 to 13.3). However, other major endpoints such as ASAS 20 and 40 were not met (ASAS 20: 44% vs 24%, RR 1.80, 95% CI 0.90 to 3.70; ASAS 40: 37% vs 15%, RR 2.5, 95% CI 0.98 to 6.20).

Another RCT testing alendronate failed to meet its primary endpoint (BAS-G change for alendronate: 4.3 to 2.5 vs placebo: 4.2 to 2.7, SMD 0.13 (−0.13, 0.42)), as well as all the other

Table 1 Efficacy of non-pharmacological interventions: Cohen's effect size for the main outcomes

Study ID	Study design	Interventions	Population	Sample size	Duration (weeks)	Frequency of intervention	Primary endpoint	ASDAS	BASDAI	BASFI	BASMI	VASp	Risk of bias
Education													
O'Dwyer 2017 J Physiother (INPACT-AS)	Single-blind RCT	Behavioural programme	r-axSpA	40	12	Individually tailored frequency	Increase in physical activity (+)	NR	0.50	NR	0.54	NR	Unclear
		Standard care				N/A			0.05		0.07		
Molto 2021 Rheumatology (COMEDSPA)	Open RCT	Nurse led-programme SA-SM	axSpA	502	12	Once, at the start of the study	Level of coping (0–10) (–)	0	0.06	0.04	NR	NR	Unclear
		Comorbidity assessment						0	–0.07	0.03			
Exercise													
Sveaas 2017 Scand J Rheumatol*	Pilot study	Cardiorespiratory and strength exercises	axSpA	28	12	3 times a week	Delta-ASDAS (–)	0.83	1.43	0.50	0.20	NR	Unclear
		Standard care				N/A		0.13	0.08	0.00	0.06		
Sveaas 2020 Br J Sports Med	Single-blind RCT	High-intensity exercise	axSpA	100	12	3 times a week	Delta-ASDAS (+)	0.87	1.00	0.61	0.30	NR	Unclear
		Standard care				N/A		0.16	0.30	0.19	0.07		
Physiotherapy													
Şilte Karamanlioglu 2016 Rheumatol Int	Double-blind RCT	US+exercise	r-axSpA	53	2	10 sessions over 2 weeks	NR	1.53	1.18	0.87	1.40	1.76	Unclear
		PBO+exercise						0.71	0.70	0.78	0.58	0.92	
Sun 2018 Altern Ther Health Med	Double-blind RCT	US+exercise	r-axSpA	62	8	15″ sessions 3 times a week	NR	NR	1.75	1.54	1.40	2.38	Unclear
		PBO+exercise							1.10	0.95	0.58	1.10	

Cohen's d (effect size): <0.0 worsening; 0.0–0.49 small effect; 0.50–0.79 moderate effect; >0.80 large effect.
(+): Positive trial; (–): negative trial. Studies with high risk of bias are not presented.
*This paper reports post-hoc analyses of an RCT already included in the 2016 SLR (Sveaas SH, et al. PLoS One 2014); outcomes were also retrieved from the original paper.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; N/A, not applicable; NR, not reported; PBO, placebo; RCT, randomised controlled trial; SA-SM, self-assessment and self-management; US, ultrasound; VASp, Visual Analogue Scale of pain.

Table 2 Efficacy of pharmacological non-biological interventions

Study ID	Study design	Interventions (study arms)	Population	Sample size	Primary end point	Timepoint of primary endpoint	Primary endpoint in each group	ASAS 20	ASAS 40	Delta ASDAS	Delta BASDAI	Delta BASFI	Risk of bias
NSAIDs													
Balazcs 2016 BMC Musculoskelet Disord	Non-inferiority RCT	etoricoxib 60 mg QD etoricoxib 90 mg QD naproxen 1000 mg QD	r-axSpA	1015	**VAS spinal pain (0–10) (+)**	6	−2.9 −3.2 −3.1	NR	NR	NR	−1.9 −2.1 −1.9	NR	Low
Walker 2016 Research (Wash DC)	Non-inferiority RCT	celecoxib 200 mg QD celecoxib 400 mg QD diclofenac 50 mg TID	r-axSpA	330	**VAS global pain (0–10) (+)**	12	−2.6 −3.1 −2.8	51% 60% 57%	NR	NR	−1.7 −2.1 −1.9	−1.5 −1.8 −1.8	Unclear
Other drugs													
Coates 2019 Clin Experim Rheum	Double-blind RCT	Alendronate 70 mg/ week PBO	r-axSpA	180	**BAS-G (0–10) (−)**	104	−0.2 −0.4	30% 21%	9% 12%	NR	−0.36 −0.32	−0.13 0.12	Low
Mishra 2020 Rheumatology (**COBRA_AS**)	Proof-of-concept RCT	Step down oral prednisolone regimen* PBO	axSpA (ASAS 2009)	64	**BASDAI 50 (+)**	24	**37%** 9%	43% 24%	37% 15%	**−1.1** −0.3	**−1.9** −0.5	−1.3 −0.5	Unclear

(+): Positive trial; (−): negative trial. Studies with high risk of bias are not presented. Significant results compared with placebo highlighted in bold.
*Step down oral prednisolone regimen: starting from 60 mg and tapered to 10 mg in 6 weeks; then 5 mg for 18 weeks.
ASAS20, 20% improvement according to the ASAS response criteria; ASAS40, 40% improvement according to the ASAS response criteria; ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; NR, not reported; QD, once a day; RCT, randomised controlled trial; TID, three times a day; VAS, Visual Analogue Scale.

important secondary endpoints.[91] Studies on the other pharmacological interventions were all at a high RoB (online supplemental tables S30–S32).

online supplemental tables S30–S32

Efficacy of pharmacological interventions: tsDMARDs

Efficacy of four tsDMARDs (apremilast, filgotinib, tofacitinib, upadacitinib) was assessed in r-axSpA in 5 RCTs, all at low RoB (table 3, online supplemental tables S33–S37).[7 9 92–94] The efficacy of filgotinib was demonstrated in a phase-2 RCT, in which filgotinib was superior to placebo in meeting the primary endpoint (delta-ASDAS at week 12: SMD −0.96, 95% CI −1.34 to −0.57).[9] Since the 2016 SLR, complete results for the phase-2 tofacitinib RCT became available, and together with the results of the phase-3 RCT, consolidated the evidence for tofacitinib efficacy. Both studies proved superiority of tofacitinib 5 mg two times a day compared with placebo in reaching ASAS 20 (phase 2: RR 2.35, 95% CI 1.25 to 4.41; phase 3: 3.10, 95% CI 1.90 to 5.07).[7 93] Upadacitinib was efficacious in r-axSpA versus placebo, with higher percentages of patients reaching the primary endpoint ASAS 40 (RR 2.02, 95% CI 1.36 to 3.01). Secondary endpoints were also largely met in all these studies (table 3 and online supplemental tables S34–S35). Importantly, the large majority of the included patients were bDMARD-naïve, with the exception of the TORTUGA RCT of filgotinib, which included 9.5% of bDMARDs-experienced patients, and of the phase-3 RCT of tofacitinib, in which 23% of patients had previously used bDMARDs. More patients reached ASAS 20 and 40 in the tumor necrosis factor inhibitor (TNFi)-experienced group with tofacitinib compared with placebo (39% vs 16% and 25% vs 6%); while these figures were somewhat higher in the TNFi-naïve group (ASAS 20: 62% vs 33% ; ASAS40: 45% vs 14%).[7]

Apremilast was not effective in a phase-3 RCT (online supplemental tables S33–S35).[92] Negative results were found in a proof-of-concept RCT, evaluating nilotinib, a tyrosine kinase inhibitor (table 3, online supplemental table S36). This RCT, at unclear RoB, was conducted in both axSpA and pSpA, and data were available only for 17 patients with axSpA. In this study, disease activity even worsened in the treatment arm compared with placebo.[95]

Safety: observational studies

Observational studies focused on NSAIDs, glucocorticoids and csDMARDs (table 4) and surgery (online supplemental table S38). Most studies used claims databases and were at high RoB. One observational study showed a 16% increase in mortality with NSAIDs and a 69% increase with csDMARDs in patients with r-axSpA compared with the general population.[96] Another study evaluated the risk of preventable hospitalisation over 9 years and found that the risk was 5% higher for glucocorticoid users than for non-users.[97] The risk for hospitalisation was, on the contrary, not different whether patients were treated or not with csDMARDs (eg. HR 0.94; 95% CI 0.43 to 2.06).[98] In another study, patients on csDMARDs had a threefold increase in the risk of infection by herpes zoster compared with non-users.[99] Therapy with NSAIDs compared with no use of NSAIDs was associated with a lower risk of cardiovascular disease in patients with r-axSpA.[100 101] The same was observed for sulfasalazine, especially for doses>1 g daily.[101] Recent NSAIDs use in r-axSpA was associated with a higher risk of myocardial infarction than remote use.[102]

Table 3 Efficacy of targeted synthetic disease-modifying antirheumatic drugs

Outcome drug	Study design	Sample size	Population	Time point (weeks)	Dose	Response treatment (%)	Response placebo (%)	RR (95% CI)	NNT	Risk of bias
ASAS20										
Apremilast	RCT phase 3	460	r-axSpA	16	20 mg 30 mg	35 33	37	0.95 (0.75 to 1.27) 0.89 (0.66 to 1.20)	N/A N/A	Low
Filgotinib (TORTUGA)	RCT phase 2	116	r-axSpA	12	200 mg	76	40	**1.91 (1.35 to 2.71)**	2.8	Low
Tofacitinib	RCT phase 2	207	r-axSpA	12	2 mg 5 mg 10 mg	56 63 67	40	**2.16 (1.14 to 4.09)** **2.35 (1.25 to 4.41)** **1.96 (1.02 to 3.77)**	6.3 4.4 3.7	Low
Tofacitinib	RCT phase 3	269	r-axSpA	16	5 mg	56	29	**3.10 (1.90 to 5.07)**	3.7	Low
Upadacitinib (SELECT AXIS 1)	RCT phase 2/3	187	r-axSpA	14	15 mg	65	40	**2.02 (1.36 to 3.01)**	4.0	Low
Nilotinib	Proof of concept	17	axSpA	12	400 mg	NR	NR	NR	N/A	Unclear
ASAS40										
Apremilast	RCT phase 3	460	r-axSpA	16	20 mg 30 mg	36 34	32	1.14 (0.84 to 1.55) 1.06 (0.78 to 1.45)	N/A N/A	Low
Filgotinib (TORTUGA)	RCT phase 2	116	r-axSpA	12	200 mg	38	19	**2.00 (1.07 to 3.74)**	5.3	Low
Tofacitinib	RCT phase 2	207	r-axSpA	12	2 mg 5 mg 10 mg	42 46 38	19	**2.16 (1.14 to 4.09)** **2.35 (1.25 to 4.41)** **1.96 (1.02 to 3.77)**	4.4 3.8 5.3	Low
Tofacitinib	RCT phase 3	269	r-axSpA	16	5 mg	41	12	**3.10 (1.90 to 5.07)**	3.6	Low
Upadacitinib (SELECT AXIS 1)	RCT phase 2/3	187	r-axSpA	14	15 mg	52	26	**2.02 (1.36 to 3.01)**	3.8	Low
Nilotinib	Proof of concept	17	axSpA	12	400 mg	NR	NR	NR	N/A	Unclear
Outcome drug	Study design	Sample size	Population	Time point (weeks)	Dose	Impr. Mean (SD)	Impr. Mean (SD)	SMD (95% CI)		
ASDAS										
Apremilast	RCT phase 3	460	r-axSpA	16	20 mg 30 mg	−0.5 (0.8) −0.4 (0.8)	−0.4 (0.8)	−0.10 (−0.32 to 0.11) −0.03 (−0,24 to 0.19)		Low
Filgotinib (TORTUGA)	RCT phase 2	116	r-axSpA	12	200 mg	−1.5 (1.0)	−0.6 (0.8)	**−0.96 (−1.34 to 0.57)**		Low
Tofacitinib	RCT phase 2	207	r-axSpA	12	2 mg 5 mg 10 mg	−1.2 (0.7) −1.4 (0.7) −1.4 (0.7)	−0.7 (0.7)	**−0.70 (−1.09 to 0.30)** **−0.98 (−1.38 to 0.56)** **−0.98 (−1.38 to 0.56)**		Low
Tofacitinib	RCT phase 3	269	r-axSpA	16	5 mg	−1.4 (0.7)	−0.4 (0.7)	**−1.20 (−1.46, to 0.94)**		Low
Upadacitinib (SELECT AXIS 1)	RCT phase 2/3	187	r-axSpA	14	15 mg	−1.4 (0.8)	−0.5 (0.8)	**−1.08 (−0.77 to 1.38)**		Low
Nilotinib	Proof of concept	17	axSpA	12	400 mg	0.7	−0.8	n/e		Unclear
BASFI										
Apremilast	RCT phase 3	460	r-axSpA	16	20 mg 30 mg	−1.11 −0.99	−0.9	−0.10 (−0.31 to 0.12) −0.03 (−0.24 to 0.19)		Low
Filgotinib (TORTUGA)	RCT phase 2	116	r-axSpA	12	200 mg	−2.4 (1.9)	−1.3 (1.9)	**−0 to 65 (−1.01 to 0.27)**		Low
Tofacitini	RCT phase 2	207	r-axSpA	12	2 mg 5 mg 10 mg	−1.9 (2.2) −2.4 (2.2) −2.2 (2.2)	−1.4 (2.2)	**−0.23 (−0.62 to 0.16)** **−0.46 (−0.85 to 0.07)** **−0.37 (−0.76 to 0.02)**		Low
Tofacitinib	RCT phase 3	269	r-axSpA	16	5 mg	−2.0 (2.0)	−0.8 (2.0)	**−0.63 (−0.87 to 0.38)**		Low
Upadacitinib (SELECT AXIS 1)	RCT phase 2/3	187	r-axSpA	14	15 mg	−2.3 (2.2)	−1.3 (2.2)	**−0.46 (−0.75 to 0.17)**		Low
Nilotinib	Proof of concept	17	axSpA	12	400 mg	NR	NR	n/e		Unclear

Significant results compared with placebo highlighted in bold.
ASAS20, 20% improvement according to the ASAS response criteria; ASAS40, 40% improvement according to the ASAS response criteria; ASAS, Assessment of SpondyloArthritis international Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASFI, Bath Ankylosing Spondylitis Functional Index; N/A, not applicable (number needed to treat not calculated for negative trials); n/e, not possible to estimate; NNT, number needed to treat; NR, not reported; RCT, randomised controlled trial; RR, relative risk; VAS, Visual Analogue Scale.

Safety: RCTs

For non-pharmacological interventions, safety was scantly described, but overall, exercise was considered as safe. Even high intensity exercise (eg, Sveaas 2020 *et al*, where cardiorespiratory and strength exercises were performed) caused, very rarely, only transient pain.[38] For NSAIDs, RCTs did not report safety events different from those well-known in the literature (online supplemental table S39). In the study on oral prednisolone, no serious AEs occurred over a period of 24 weeks. Usual side-effects of glucocorticoids were observed in a minority of patients (eg. dyspepsia, n=4 vs n=2 patients, or facial puffiness n=9 vs n=2 patients in drug vs placebo arm).[90] tsDMARDs were associated with a higher risk of infections than placebo, mostly non-severe infections, in particular herpes zoster, even though not in the first months of treatment (ie. in the placebo-controlled phase of RCTs) (online supplemental tables S40–S41). No major cardiovascular event (MACE) or venous thromboembolism, and only one malignancy (in the upadacitinib RCT, considered to be unrelated with treatment), occurred up to 1 year of observation in phase 3 RCTs of upadacitinib and tofacitinib (online supplemental tables S42–S43). Liver enzyme elevation and CPK elevation occurred, but were infrequent (online supplemental tables S37–S42).

DISCUSSION

This SLR collected the available evidence on efficacy and safety of non-pharmacological and non-biological pharmacological interventions after 2016. The efficacy of education and exercise, the pillars of non-pharmacological treatment, were confirmed. New studies on NSAIDs in axSpA demonstrated the non-inferiority of cox-inhibitors compared with traditional NSAIDs, adding to the already vast scientific knowledge that support their use as first-line intervention in axSpA. Within the new class of tsDMARDs, tofacitinib, upadacitinib and filgotinib (phase 2 only) were those which, thus far, have been proved to be efficacious in r-axSpA.

Table 4 Safety of pharmacological non-biological and non-tsDMARDs interventions

Study	Population	N*	Registry	Intervention	Control	Outcome	Measure	Effect	Risk of bias
Ben-Shabat 2021 Arthritis Care Res	r-axSpA	34.948	Health maintenance organisation database	NSAIDs csDMARDs	General population	Death	aHR†	1.16 (1.05–1.28) 1.69 (1.36–2.09)	High
Wallace 2019 J Clin Med	r-axSpA	40.747	Health insurance	Glucocorticoids# Methotrexate Sulfasalazine	Non-users	Preventable hospitalisation‡	aOR§	1.05 (1.04–1.07) 1.01 (0.96–1.07) 0.95 (0.87–1.04)	High
Moura 2018 Scand J Rheumatol	r-axSpA	378	Hospital discharge (MED-ÉCHO) databases	csDMARDs	Non-users	Hospitalisation	EAIR aOR¶	4.4/100 PY 0.94 (0.43–2.06)	Unclear
Lim 2018 Mod Rheumatol	r-axSpA	909	Health insurance	csDMARDs	Non-users	Herpes Zoster infection	EAIR Crude OR aOR**	16.7/1000 PY 3.11 (1.47–6.58) 3.70 (9.1–28.0)	High
Wu 2016 Medicine (Baltimore)	r-axSpA	4.112	Health insurance	Diclofenac Naproxen Etoricoxib Celecoxib Celecoxib>300 mg/day Sulfasalazine Sulfasalazine>1 g/day	Non-users	Coronary artery disease	aOR††	1.38 (0.87–2.20) 1.39 (0.94–2.06) 0.27 (0.12–0.61) 0.77 (0.50–1.17) 0.34 (0.13–0.89) 0.66 (0.44–0.99) 0.63 (0.40–0.99)	High
Dubreuil 2018 Ann Rheum Dis	r-axSpA	170	Medical record databases from GPs	Diclofenac Naproxen Other NSAIDs (current use)	Remote users	Myocardial infarction	Crude OR	2.83 (0.92–8.68) 1.14 (0.26–4.94) 1.60 (0.62–4.14)	Unclear
Tam 2017 Int J Rheum Dis	r-axSpA	1.208	Health insurance	Celecoxib Etoricoxib Naproxen Diclofenac Sulfasalazine	Non-users	Cardiovascular disease#	aHR‡‡	0.76 (0.66–0.86) 0.36 (0.25–0.52) 0.82 (0.74–0.91) 0.53 (0.49–0.57) 0.78 (0.58–1.06)	High

*The total number of patients only reflects patients with axial spondyloarthritis treated with non-biological interventions (except for studies where the comparator was another population, in which case the total number of patients includes the comparator too).
†Estimate adjusted for sex, age, comorbidity.
‡Hospitalisation due to care-sensitive conditions likely to be exacerbated by glucocorticoid use.
§Estimate adjusted for demographic factors, baseline health and healthcare utilisation, and disease-associated healthcare utilisation.
¶Estimate adjusted for gender, age at cohort entry, previous hospitalised infection at any point before cohort entry, and socioeconomic status.
**Estimate adjusted for sex, age, comorbidity and use of steroids.
††Estimate adjusted for sex, age, Charlson Comorbidity Index, AS disease duration, hypertension, hyperlipidaemia, and other drugs used such as etoricoxib, naproxen and diclofenac.
‡‡Estimate adjusted for sex, age, Charlson Comorbidity Index, hypertension, hyperlipidaemia and drugs.
aHR, adjusted HR; aOR, adjusted OR; csDMARDs, conventional synthetic DMARDs; EAIR, events adjusted incidence rate; NSAID, non-steroidal anti-inflammatory drugs; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drugs.

Non-pharmacological interventions are important for any rheumatic disease, but especially for axSpA, in which they represent the cornerstone of treatment.[2] The recently formulated ASAS quality standards, that aim to improve the quality of healthcare in patients with axSpA, even suggest two specific quality indicators for non-pharmacological treatment (one aimed at exercise, and one at education and self-management), highlighting the relevance of these therapies.[103] In this context, patient education is a crucial first step. However, assessing the efficacy of education/educational interventions per se can be a challenging task, mostly because of the difficulties in disentangling their effects from co-interventions, but also owing to the variety in content and way of delivery of educational material. Nonetheless, relevant evidence has emerged since the 2016 SLR, suggesting that educational programmes could help achieving specific aims, such as increasing the patients' physical activity.[18] In addition, education can even improve disease activity as measured by PROs,[21] which underlines the importance of education as a necessary complement to pharmacological therapy, and as a means to reach therapeutic objectives for patients.

One Cochrane review from 2008 provided solid evidence on the benefits of exercise on function, mobility and pain.[103] Specifically, this Cochrane review found that an individual home-based exercise, or a supervised exercise programme (ie. physiotherapy), is more efficacious than no intervention. However, group physiotherapy is superior to home exercises, and combined inpatient exercise followed by group physiotherapy is even superior to group physiotherapy alone.[103] Later studies included in the 2016 SLR, and in the current SLR, were too heterogeneous and mostly at high RoB, precluding further conclusions on the benefit of a particular form of exercise over another.[104] A conclusion that certainly can be drawn from the literature is that exercise, supervised or unsupervised, has an independent positive effect on disease activity and function, thus representing a safe and effective treatment option. Admittedly, the majority of RCTs on exercise retrieved were at high RoB, partly due to an objective difficulty in blinding the control arm. To obtain additional relevant clinical information, future RCTs should aim at a clear definition of a primary endpoint and should include a prespecified statistical analysis plan, and assessment of treatment adherence.[24–37 39] Other non-pharmacological interventions comprise an extremely heterogenous array of treatments, such as moxibustion, cryotherapy and acupuncture, with little evidence supporting their use in axSpA.

Evidence on surgical treatment is limited to retrospective, high RoB studies, that is, review of surgical cases. These studies show the benefits of surgery for advanced spinal kyphosis and for hip involvement in advanced r-axSpA. Different approaches for advanced spinal kyphosis surgery were reviewed, without observing major differences in the outcomes.[66–69] Total hip replacement also seems an effective option for patients with severe structural changes in the hip joint.[63] Interestingly, the mean age of the patients included in these studies was mostly between 30 and 40, confirming that surgery is an option for young patients too.

A unique approach to the present SLR is the inclusion of qualitative research, which was especially aimed at better capturing the patient's perspective and possible non-pharmacological interventions, whose effect might not be easily quantifiable (eg. cognitive–behavioural therapy). These studies confirmed perceived efficacy and highlighted the value of education, exercise and non-pharmacological therapy in general, when used alongside pharmacological interventions.[71–78]

It is already well established that csDMARDs are ineffective in treating axial symptoms in patients with in axSpA,[105 106] a finding once again observed in this SLR. It is also already known that comedication with csDMARDs can reduce immunogenicity against bDMARDs. However, the clinical meaning of this finding remains unclear: in fact, in the study by Ducourau *et al*, efficacy outcomes were not different between adalimumab alone or in combination with methotrexate.[81] Therefore, also in this respect, the role of csDMARD comedication remains doubtful at best.

NSAIDs are the first-line pharmacological treatment of axSpA and their effectiveness is hardly debated. Two new studies confirmed the non-inferiority of cox inhibitors compared with traditional NSAIDs, suggesting comparable efficacy of various compounds.[82 89] However, concerns remain on the possible side effects with long-term use. Evidence from observational studies on safety provide conflicting results. Use of NSAIDs in r-axSpA was associated with a higher risk of death than the general population but, among patients with axSpA, those treated with NSAIDs seemed to have a lower cardiovascular risk compared with non-users. Although confounding cannot be entirely ruled out, this finding could suggest that treating inflammation in r-axSpA is better than leaving it untreated also in terms of cardiovascular health. However, in theory, this should be an effect common to any drug that suppresses inflammation. Of note, compared with the 2016 SLR, no new studies on the effect of NSAIDs on radiographic progression were found.

A particularly interesting RCT of this SLR was a study on prednisolone tapering (starting at 60 mg/day, followed by rapid de-escalation to 5 mg/day and continued up to 24 weeks). This study met the primary endpoint BASDAI50, as well as other important secondary endpoints. However, efficacy was not demonstrated in important domains (eg, inflammation, general health, mobility). Thus, considering the important side effects of long-term use, and the limited efficacy of short-term use, the place of glucorticoids in treating patients with axSpA remains unclear.[90]

Finally, a relevant novelty was the ample evidence of efficacy of some JAKi: in particular, successful phase 3 RCTs were completed for tofacitinib and upadacitinib, while for filgotinib only results of a positive phase 2 RCT were available. The efficacy of these drugs was seen across all disease domains, including disease activity, function, mobility, quality of life and MRI inflammation (bone marrow oedema). At the time of the literature search, only data on r-axSpA were available, and mostly on bDMARD-naïve patients. After our SLR, data have been presented at EULAR 2022 demonstrating the efficacy of upadacitinib in patients with nr-axSpA, as well as in patients with r-axSpA who were inadequate responders to bDMARDs.[107 108] Data on the safety of JAKi were substantially limited to the first year of the RCTs. There was a low but non-negligibly increased incidence of herpes with upadacitinib and tofacitinib versus placebo during the first 12 months. For filgotinib, only data about the placebo-controlled phase were available, highlighting no cases of herpes zoster, like for upadacitinib and tofacitinib in the same phase of the RCTs. Of note, no cases of MACE or venous thromboembolism, and only one case of malignancy (not related to treatment according to the investigators), were observed in the first year of treatment with upadacitinib and tofacitinib. Observational long-term data on JAKi in axSpA are warranted to clarify whether the safety concerns observed in rheumatoid arthritis also apply to the usually younger patients with axSpA.[109 110] Future studies should also inform on tapering, or switch from other modes of action to JAK inhibition. Other tsDMARDs such as apremilast and nilotinib were proved to be inefficacious.

In conclusion, this SLR has consolidated the evidence for non-pharmacological interventions, particularly education and exercise in axSpA, and confirmed the current knowledge about NSAIDs, csDMARDs and other compounds. In addition, it provided new evidence on the use of tsDMARDs, suggesting that treatment options for patients with axSpA are expanding, and highlighting new potential areas of research. The present SLR, together with the SLR on bDMARDs, provided updated information on current treatment options for axSpA.

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