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Regel, A., Sepriano, A., Baraliakos, X. et al. (6 more authors) (2017) 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. RMD Open, 3 (1). e000397. ISSN 2056-5933

https://doi.org/10.1136/rmdopen-2016-000397

RMD Open
Rheumatic & Musculoskeletal Diseases

REVIEW

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

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To cite: 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. *RMD Open* 2017;**3**:e000397. doi:10.1136/rmdopen-2016-000397

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/rmdopen-2016-000397).

Received 4 November 2016
Revised 22 December 2016
Accepted 3 January 2017

Linked

► http://dx.doi.org/10.1136/rmdopen-2016-000396

CrossMark

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ABSTRACT

To assess the efficacy and safety of non-biological therapies in patients with axial spondyloarthritis (axSpA) to inform the update of the Assessment of SpondyloArthritis international Society (ASAS)/European League Against Rheumatism (EULAR) recommendations for the management of axSpA. A systematic literature review (2009–2016) of all non-pharmacological treatments, non-biological drugs (except targeted synthetic disease-modifying antirheumatic drugs (DMARDs)) and surgical therapies was performed. Randomised controlled trials (RCTs) and clinical controlled trials were assessed for efficacy and safety, while observational studies with a comparator were assessed for safety. All relevant efficacy and safety outcomes were included. Study heterogeneity precluded data pooling. If possible, Cohen's effect size was calculated for non-pharmacological treatments. In total, 45 papers and 2 abstracts were included. Studies on non-pharmacological treatments were very heterogeneous but overall confirmed a benefit for regular exercises, with small improvements in disease activity, function and spinal mobility. New studies on non-steroidal anti-inflammatory drugs (NSAIDs) confirmed their efficacy and new safety signals were not found. NSAIDs used continuously compared with on-demand did not reduce the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) mean change over 2 years in patients with ankylosing spondylitis with normal C reactive protein (CRP; ≤5 mg/L) (1 'negative' RCT (0.9 vs 0.8; p=0.62)), while for patients with high CRP, conflicting results were found (1 'positive' RCT (0.2 vs 1.7; p=0.003), 1 'negative' RCT (1.68 vs 0.96; p=0.28)). No new trials were found for conventional synthetic DMARDs (csDMARDs). Short-term high-dose systemic glucocorticoids showed limited efficacy. Regular exercises may improve several outcomes. Efficacy and safety of NSAIDs in axSpA are confirmed. Glucocorticoids are not proven to be effective in axSpA and new data on csDMARDs are lacking.

Key messages

- Regular exercises may improve several outcomes.
- Efficacy and safety of NSAIDs in axSpA are confirmed.
- Glucocorticoids are not proven to be effective in axSpA.
- No new data on csDMARDs in axSpA was found.

INTRODUCTION

Treatment of axial spondyloarthritis (axSpA) can be a challenge due to a limited number of therapeutic alternatives.[1] In the past decade, a plethora of non-pharmacological and pharmacological therapies have been applied, aiming to improve the patient's quality of life, to reduce pain and physical impairment and to avoid work disability. Treatment with tumour necrosis factor α inhibitors (TNFi) is especially efficacious but because of drug cost treatment has been reserved for patients failing the so-called conventional compounds such as non-steroidal anti-inflammatory drugs (NSAIDs).[2] Overall, a multidisciplinary approach with a combination of non-pharmacological and pharmaco-

logical treatment and, if needed, a surgical intervention comprises the full spectrum of the treatment of axSpA.[2]

A collaboration between the Assessment of SpondyloArthritis international Society (ASAS) and the European League Against Rheumatism (EULAR) has led to the first publication of the ASAS/EULAR recommendations for the management of ankylosing spondylitis (AS) in 2006,[1] while an update had been published in 2010,[2] based on evidence from systematic literature reviews (SLRs).[3 4] In these recommendations, treatment was constrained to patients in later stages of axSpA (radiographic axSpA—r-axSpA—or AS). Another ASAS initiative issued recommendations for the use of TNFi in patients with axSpA, also taking the earlier, non-radiographic stages (nr-axSpA) into account.[5] Still, no recommendations had yet covered the whole management spectrum (including non-pharmacological and pharmacological management) and the full spectrum of axSpA (including both nr-axSpA and r-axSpA). During the past years, accumulating evidence has shown that the disease is one continuum, including nr-axSpA and r-axSpA.[6] This, together with the progress witnessed in the area of management of axSpA in the past years, justified an update of the recommendations for the management of axSpA.

The objective of the current SLR was to update the evidence on efficacy and safety of non-biological interventions (non-pharmacological treatment, non-biological drugs and surgical therapies). This SLR was performed together with another on biological and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs).[7 8] Both SLRs aimed to inform the task force responsible for the update of the ASAS/EULAR recommendations for the management of axSpA.[9]

METHODS

Search methodology and study selection

The systematic literature search was performed by using references from MEDLINE, EMBASE and Cochrane CENTRAL databases and as an update of the previous SLR conducted in 2009.[4] The articles included in the present SLR had to be published between 1 January 2009 and 26 February 2016. In addition, abstracts from the annual conferences of EULAR and the American College of Rheumatology (ACR) 2014 and 2015 were included. The search strategy is presented in online supplementary text 1. Eligible study types for efficacy and safety assessment were randomised controlled trials (RCTs), clinical controlled trials (CCTs) and open-label long-term extension studies. Cohort studies or registries were considered for safety assessment but only if a comparator treatment was available, or if population-based incidence rates were reported and at least 50 participants per group were included. For surgical interventions, cohort studies with a comparator group, as well as case–control studies, were used to assess both efficacy and safety. SLRs were only considered appropriate to identify references from original studies, except for Cochrane reviews, which were included anyway. Research questions were reformulated according to the PICO (Participants, Interventions, Comparisons and Outcomes) method.[10] Studies were selected with adult patients (age ≥18 years) and a diagnosis of axSpA. The interventions in the current SLR were defined as (1) non-pharmacological interventions (physiotherapy, exercise, balneotherapy, spa therapy, diet, education, self-education groups), (2) non-biological drugs, such as NSAIDs, local and systemic glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporine, cyclophosphamide, auranofin, penicillamine or thalidomide), bisphosphonates, analgesics, opioids, opioid-like drugs, neuromodulators (antidepressants, anticonvulsants and muscle relaxants) and probiotics, and (3) surgical therapies. All doses, formulations, regimens (eg, on-demand, continuous) and treatment durations were assessed. Treatment comparators were defined as any non-pharmacological or surgical intervention, same non-biological interventions in different doses or regimens, other non-biological drugs, any combination therapy, placebo or none.

Outcomes considered for the assessment of treatment efficacy were the Bath AS Disease Activity Index (BASDAI[11]), Bath AS Functional Index (BASFI[12]), Bath AS Metrology Index (BASMI[13]), AS Disease Activity Score (ASDAS[14 15]) and ASDAS disease activity status,[16] ASAS partial remission,[17] patient's global assessment of disease activity, pain levels, assessments of enthesitis, swollen and tender joint count. Outcomes considered for patient's response to treatment were the ASAS response criteria[17] (ASAS20, ASAS40 and ASAS5/6),[18] ASDAS clinically important improvement (Δ≥1.1) and ASDAS major improvement (Δ≥2.0)[16] and BASDAI response (improvement of ≥50% and/or ≥2 units). The AS Quality of Life (ASQoL[19]) index was considered to evaluate the Quality of Life. Additionally, work disability, work productivity, cost-efficacy and cost-effectiveness were assessed. Radiographic progression of the spine was assessed by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS[20]). Inflammation on magnetic resonance imaging (MRI) was measured by the ASAS/Outcome Measures in Rheumatology (OMERACT) definition[21] and the Spondyloarthritis Research Consortium of Canada (SPARCC) score (sacroiliac joints[22] and spine[23]).

For safety outcomes, information was collected on withdrawals due to adverse events (AEs), serious AEs, infections, malignancies, cardiovascular disease, infusion/injection-site reactions, renal, gastrointestinal (GI) and hepatic effects, haematological abnormalities and demyelinating disease.

Data extraction and assessment of risk of bias (RoB)

Each article or abstract identified was assessed independently by two reviewers (AR and AS) for suitability according to the predefined inclusion criteria, followed by a

full-text review. For every included study, relevant data were extracted. Additionally, the two reviewers evaluated the RoB of each study according to the 'Cochrane tool' for RCTs,[24] the 'Hayden-tool' for cohort studies[25] and the Newcastle-Ottawa Scale for case–control studies.[26] Disagreements regarding the eligibility of the studies, data extraction and RoB assessment were resolved by discussion and consensus. In case of persistent disagreement, a third reviewer (SR) was involved.

Data analysis

Owing to the large heterogeneity of the studies, data could not be pooled and results are presented descriptively. As in the previous SLR,[4] if possible, Cohen's effect size (ES) (mean change in score divided by the baseline standard deviation (SD)) was calculated for non-pharmacological interventions, with Cohen's ES<0 meaning worsening, 0–0.49 a small positive effect (ie, improvement), 0.5–0.79 a moderate effect and ≥0.8 a large effect. Additionally, if possible, the number needed to treat (NNT, number of patients who must be treated in order to obtain the benefit of interest in one additional patient) was presented.

RESULTS

Overall, the search yielded 11 649 articles (after de-duplication), of which 45 full-text articles and 2 abstracts were included in this SLR (flow chart in online supplementary figure S1 and online supplementary tables S1–S4; the articles on biological DMARDs and tsDMARDs are included in a separate SLR[8]). In total, 29 trials investigated benefits and harms of non-pharmacological therapies (28 papers;[27–54] 1 abstract[55]), 15 publications focused on non-biological drugs (13 papers;[56–68] 1 abstract;[69] 1 Cochrane review[70]), and 3 articles[71–73] assessed the efficacy of surgical interventions.

No studies were found on csDMARDs, neuromodulators, diet or self-education groups.

Non-pharmacological interventions

Twenty-nine trials were identified assessing different non-pharmacological interventions in patients with axSpA (for details, see online supplementary tables S5–S9 (Exercises), S10–S14 (Education), and S15–S19 (Other non-pharmacological interventions)).[27–55]

Overall, the studies were heterogeneous (figure 1), differing mainly in the type and duration of intervention, group size and outcome parameters. The group size was often small: only four studies[44–46 50] included more than 90 patients. One study[51] enrolled patients with active axSpA defined according to the ASAS classification criteria and with a BASDAI≥3.5.[6] All the remaining studies focused on patients with established r-axSpA according to the modified New York (mNY) criteria.

Nine studies[28 29 34 42 44 45 49 51 53] had a low or unclear RoB and we have therefore focused on these,

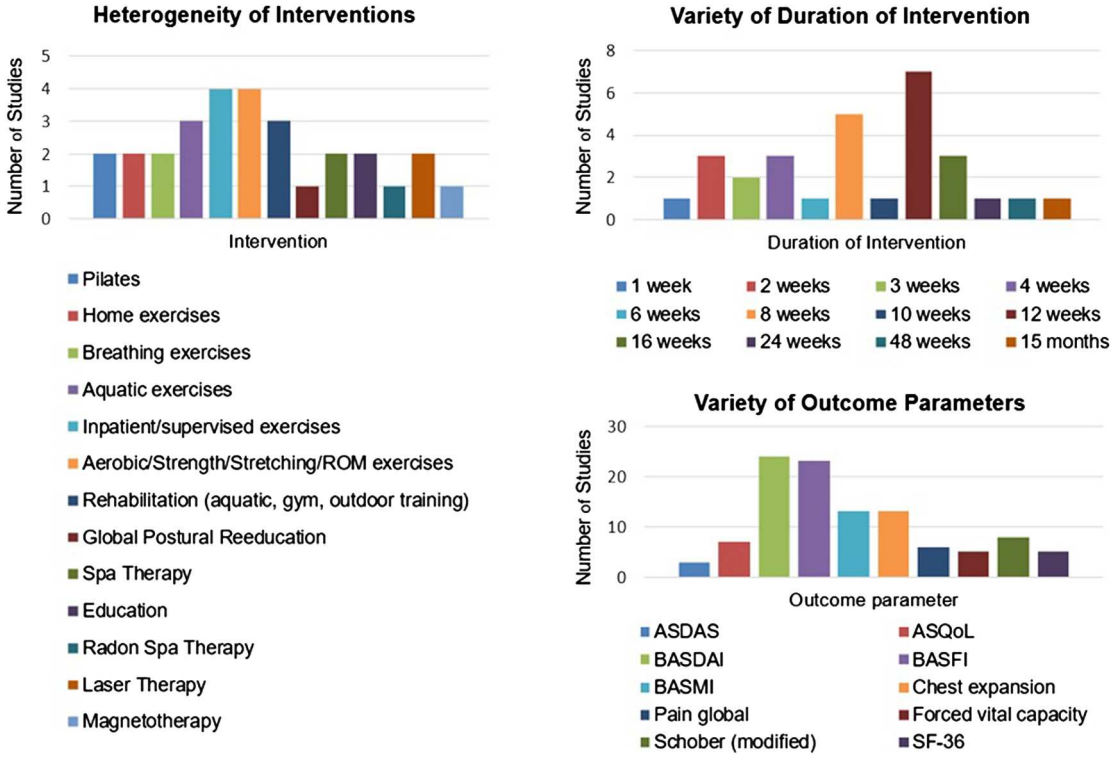

Figure 1 Characteristics of the included trials on non-pharmacological treatment. ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; ROM, range-of-motion exercises; SF-36, short-form health survey 36.

Table 1 Cohen's effect size for several outcomes of non-pharmacological interventions

Study ID	Intervention	n	Classification criteria	Duration of intervention (weeks)	Primary end point	BASDAI	BASFI	BASMI	Pain global	ASDAS	Risk of bias
Exercises/rehabilitation											
Dundar 2014[34]	Aquatic exercises	35	mNY	4	NR	0.68	0.34	0.48	0.96	–	Unclear
	Land-based exercises	34				0.52	0.39	0.42	0.57	–	
Kjeken 2013*[42]	Rehabilitation programme	29	mNY	3	BASDAI (+) BASFI (–)	–	–	–	–	–	Unclear
	'treatment as usual'	34				–	–	–	–	–	
Niedermann 2013[44]	Nordic walking+flexibility	53	mNY	12	Physical work capacity	0.24	–0.07	0.18	–	–0.29	Unclear
	Attention control+flexibility	53			on bicycle (+)	0.21	0.00	0.07	–	0.07	
Sveaas 2014[51]	Endurance+strength training	10	ASAS 2009†	12	ASDAS (–)	1.43	0.50	0.20	–	0.83	Unclear
	No exercises	24				0.08	0.00	0.06	–	0.13	
Education											
Rodriguez-Lozano 2013[45]	Education+exercises	381	mNY	24	BASDAI (+)	0.28	0.22	–	0.27	–	Unclear
	Standard care‡	375			BASFI (+)	0.16	0.08	–	0.15	–	
Other non-pharmacological interventions											
Annegret 2013[28]	Radon Spa therapy	20	mNY	4	Pain (VAS 0–10) (+)	–	0.12	–	–	–	Low
	Tap water baths	19				–	0.05	–	–	–	
Aydin 2013*[29]	Low-level laser therapy	19	mNY	2	NR	–	–	–	–	–	Unclear
	Placebo laser	18				–	–	–	–	–	
Stasinopoulos 2016[49]	Laser therapy+stretching	24	mNY	8	NR	–	0.84	–	2.48	–	Unclear
	Placebo laser+stretching	24				–	–0.11	–	0.12	–	
Turan 2014*[53]	Magnetotherapy+exercises	35	mNY	2	Harris hip assessment	–	–	–	–	–	Low
	Placebo magnetotherapy	31			index (–)	–	–	–	–	–	

(+): Positive trial; (–): negative trial.
Only studies with a low or an unclear risk of bias are presented.

Cohen´s effect size	< 0.0 worsening	0-0.49 small effect	0.5-0.79 moderate effect	≥ 0.8 large effect

*Cohen's effect size could not be calculated for 3 studies as the results are not shown as mean (SD).
†Active axSpA (BASDAI≥3.5).
‡Pharmacological and non-pharmacological interventions.
ASAS, Assessment of SpondyloArthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; mNY, modified New York criteria; NR, not reported; SD, standard deviation; VAS, visual analogue scale.

that is, we excluded the high RoB studies from in-depth analysis. An overview of these low/unclear RoB studies, together with Cohen's ES for BASDAI, BASFI, pain global and ASDAS, can be found in table 1. In summary, regular exercises can improve disease activity, pain, function and spinal mobility. However, the effects were usually small. Endurance combined with strength training, compared with 'no exercises', provided the largest effect on disease activity, both measured with the ASDAS (mean 2.3 vs 2.7 at start and 1.8 vs 2.6 at the end of observation, respectively) and BASDAI (mean 5.3/10 vs 5.3/10 units at start and 3.3 vs 5.2 at the end of observation, respectively).[51] Laser therapy compared with placebo resulted in the largest effect on function as measured by the BASFI (mean 51.5/100 vs 48.6/100 at start and 37.4/100 vs 50.6/100 at the end of observation, respectively) and pain (mean 70.0/100 vs 67.5/100 at start and 33.1/100 vs 65.6/100 at the end of observation, respectively) (Cohen's ES of 0.84 for BASFI and 2.48 for pain, both for Laser therapy, respectively).[49] Aquatic exercises compared with land-based exercises led to the best improvements in pain (mean 5.1/10 vs 4.9/10 at start and 2.6/10 vs 3.3/10 at the end of observation, respectively) (Cohen's ES of 0.96 for aquatic exercises), also with moderate improvements in BASDAI (at start mean 3.9/10 vs 4.0/10 and 2.6/10 vs 2.8/10 at the end of observation, respectively; Cohen's ES 0.68).[34]

Five studies[31 32 43 48 54] focused on a combination therapy of exercises and TNFi compared with treatment of TNFi only. However, none of these studies showed any additional effect on the function and spinal mobility of patients with axSpA by exercises added to TNFi therapy.

Non-biological drugs

The main characteristics and efficacy data of the included studies on non-biological drugs are presented in tables 2 and 3; safety data from observational studies are shown in table 4. Additional data as well as the RoB assessment are presented in online supplementary tables S20–S24 for efficacy and S25–S27 for safety.

Non-steroidal anti-inflammatory drugs

A Cochrane review,[70] comparing NSAIDs (traditional and cyclooxygenase (COX)-II inhibitors) to placebo as well as between them, included 39 studies (35 RCTs, 2 quasi-RCTs, 2 cohorts) up to June 2014. From the studies included in the Cochrane review, only two studies were published in or after 2009 (Poddubnyy *et al*,[74] Kroon *et al*[59]), thus overlapping with the current SLR. Both focused on the effect of NSAIDs on radiographic progression. This Cochrane review showed that after 6 weeks of treatment, traditional NSAIDs and COX-II inhibitors were more efficacious than placebo (pain visual analogue scale (VAS) 0–100: −16.5 (95% confidence interval (CI) −20.8 to −12.2) with traditional NSAIDs (mean 44/100) versus placebo (mean 60.5), NNT 4 (range 3–6); −21.7 (95% CI −35.9 to −7.4), with COX-II inhibitors (mean 42.3) versus placebo (mean 64), NNT 3 (range 2–24)). Moreover, no measurable differences were seen between the different NSAIDs. No significant increase in AEs at 12 weeks were reported for NSAIDs.

In addition, five RCTs addressing NSAIDs were included in this SLR (tables 2 and 3), two of them focusing on the effect of NSAIDs on radiographic progression.[58 59] Two studies comparing two NSAIDs (table 2, see online supplementary tables S20–S24) were included in the current SLR. Both studies[56 69] confirmed the results of the aforementioned Cochrane review.[70] The first study,[69] at unclear RoB, showed that two different doses of etoricoxib (ETX) were as effective as naproxen (NPX) in improving the spinal pain intensity (SPI) score on a VAS (0–100) in patients with r-axSpA (SPI least square mean change from baseline at week 6: −29.0 for ETX 60 mg, −31.2 for ETX 90 mg, −30.6 for NPX 1000 mg). The second study,[56] also at unclear RoB, demonstrated non-inferiority of celecoxib compared with diclofenac in decreasing the patient's global assessment of pain intensity on a 0–100 scale (mean change at week 6: −23.7 celecoxib 200 mg, −26.7 diclofenac 75 mg).

The third trial (at high RoB) showed a small benefit favouring 'palisade sacroiliac joint radiofrequency neurotomy' in improving the global pain intensity compared with celecoxib (table 2).[57]

The other two RCTs[58 59] focused on radiographic progression. Sieper *et al*[58] 2016, at low RoB, evaluated the effect of diclofenac on spinal radiographic progression in patients with r-axSpA when taken continuously versus on-demand (table 3). No significant differences in the mSASSS mean change over 2 years were found, either in the whole group (1.28 vs 0.79; p=0.39, respectively) or in the subgroup with elevated C reactive protein (CRP) at baseline (1.68 vs 0.96; p=0.28). In contrast, Kroon *et al*[59] (at low RoB) found a significant difference between continuous use of celecoxib versus on-demand in patients with r-axSpA with elevated CRP at baseline (0.2 vs 1.6; p=0.003; favouring continuous use). Study characteristics on both studies are provided in online supplementary table S20.

Two observational studies[60 61] were identified assessing the safety of NSAIDs in axSpA (table 4 and online supplementary tables S25–S27). Only one study, Kristensen *et al*,[60] at moderate RoB, focused on GI AEs. No differences in their incidence were found when comparing COX-II inhibitors with traditional NSAIDs. However, a significantly reduced risk of GI-AEs was identified in patients not using NSAIDs compared with patients on traditional NSAIDs.

Essers *et al*,[61] at moderate RoB, reported a larger risk of ischaemic heart disease in patients with r-axSpA using NSAIDs (adjusted hazard ratio (aHR) (95% CI) 1.36 (1.00 to 1.85)) or COX-II inhibitors (aHR (95% CI) 3.03 (1.61 to 5.69)) compared with the general population. Kristensen *et al*[60] also looked at atherosclerotic events and found no significant differences between traditional NSAIDs and COX-II inhibitors (at moderate RoB).

Table 2 Efficacy of non-biological drugs (RCTs and CCTs)

Study ID	Intervention	n	Classification criteria	Study design	Primary end point	Primary end point in each group	p Value	Time point of primary end point	Primary end point met?	Risk of bias
NSAIDs										
Balazcs ACR 2015[69]	Naproxen 1000 mg/day Etoricoxib 60 mg/day Etoricoxib 90 mg/day	143 660 144	mNY	Non-inferiority trial, RCT	Δ Spinal pain intensity (VAS 0–100)	−30.6 −29.0 −31.2	NR NR NR	6 weeks	(+)	Unclear
Huang 2014[56]	Celecoxib 200 mg/day Diclofenac 75 mg/day	117 115	mNY	Non-inferiority trial, RCT	Δ PatGA of pain intensity (VAS 0–100)	−23.7 (20.6) −26.7 (22.9)	NR NR	6 weeks	(+)	Unclear
Zheng 2014[57]	Palisade sacroiliac joint radiofrequency neurotomy Celecoxib 400 mg/day	82 73	mNY	RCT	Global pain intensity (VAS 0–10)	2.5 (2.2; 3.0) 4.4 (4.0; 4.9)	NR NR	12 weeks	(+)	High
Sieper 2015[58]	Diclofenac continuous 150 mg/day† Diclofenac on-demand	62 60	mNY	RCT	Δ mSASSS	1.28 (0.7; 1.9) 0.79 (0.2; 1.4)	0.39	2 years	(−)	Low
Kroon 2012[59]	Celecoxib continuous 200 mg/day Celecoxib on-demand	52 45	mNY +CRP>5 mg/L*	Post hoc analysis of Wanders 2005[82] (RCT)	Δ mSASSS	0.2 (1.6) 1.7 (2.8)	0.003	2 years	(+)	Low
Glucocorticoids										
Haibel 2014[62]	Placebo Prednisolone 20 mg/day Prednisolone 50 mg/day	13 11 12	mNY	Placebo-controlled RCT	BASDAI 50	8.0% 27.0% 33.0%	Ref 0.30 0.16	2 weeks	(−)	Low
Other non-biological drugs										
Chang 2013[64]	Tramadol 37.5 mg/acetaminophen 325 mg +aceclofenac 100 mg (2 times/day) Placebo+aceclofenac 100 mg (2 times/day)	30 30	mNY	Placebo-controlled RCT	ASAS20	53.3% 31.0%	0.047	12 weeks	(+)	High
Sarkar 2012[65]	Pamidronate 60 mg intravenously monthly Placebo	66 21	Amor	Placebo-controlled CCT	ASAS20	63.6% NR	NR NR	6 months	NR	High
Jenks 2010[66]	Probiotics (about 0.8 g 2 times/day) Placebo	32 31	ESSG	Placebo-controlled RCT	BASFI	2.9 (1.9) 3.1 (2.2)	0.839	12 weeks	(−)	Low
Liu 2014[67]	Xinfeng capsule (1.5 g 3 times/day) Sulfasalazine (1 g 2 times/day)	60 60	ASAS axSpA	RCT	NS	NR NR	NR NR	NR	NR	High
Wang 2013[68]	Jitongning capsule (0.5 g 3 times/day) Sulfasalazine (1 g 2 times/day)	58 53	mNY	RCT	ASAS20	72.4% 67.9%	NS	NR‡	(−)	High

ASAS 2009 classification criteria.[6]
Risk of bias according to the Cochrane tool.[24]
Amor classification criteria.[79]
(+): Positive trial; (−): negative trial; Δ: change between baseline and follow-up.
*The results are just shown for this subgroup.
†At least 75 mg/day diclofenac has been taken by every patient; switching to another NSAID was allowed.
‡At both time points (6 and 12 months) no significant differences between both groups in the ASAS20.
ACR, American College of Rheumatology; ASAS, Assessment of SpondyloArthritis international Society; ASAS20, 20% improvement according to the ASAS response criteria; axSpA, axial spondyloarthritis; BASDAI 50, 50% improvement of the initial Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CCT, clinical controlled trial; CRP, C reactive protein; ESSG, European Spondyloarthropathy Study Group;[80] mNY, modified New York criteria;[81] mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; NR, not reported; NS, not significant; NSAID, non-steroidal anti-inflammatory drug; PatGA, patient's global assessment; RCT, randomised controlled trial; VAS, visual analogue scale.

Table 3 Effect of NSAIDs on spinal radiographic progression in patients with r-axSpA

Sieper 2015[58] All	n	mSASSS Baseline mean (SD)	p Value	2 years mean (SD)	p Value	2-years mean change (95% CI)	p Value	Risk of bias
Continuous	62	10.9 (15.5)	0.10	12.2 (16.7)	0.13	1.28 (0.7; 1.9)	0.39	Low
On-demand	60	16.4 (18.2)		17.2 (18.6)		0.79 (0.2; 1.4)		
CRP>5 mg/L at baseline								
Continuous	34	13.9 (17.9)	0.20	15.6 (19.6)	0.22	1.68 (0.7; 2.6)	0.28	
On-demand	35	19.3 (19.0)		20.6 (19.3)		0.96 (0.0; 1.9)		
Kroon 2012[59]	**n**	**mSASSS Baseline mean (SD)**	**p Value**	**2 years mean (SD)**	**p Value**	**2-years mean change (SD)**	**p Value**	**Risk of bias**
CRP>5 mg/L								
Continuous	52	7.9 (14.7)	NR	NR	NR	0.2 (1.6)	**0.003**	Low
On-demand	45	9.3 (15.2)		NR		1.7 (2.8)		

Bold=significant (p<0.05).
Sieper 2015: Diclofenac continuous (150 mg/day, at least 75 mg/day) versus on-demand (negative trial).
Kroon 2012: Celecoxib continuous (200 mg/day, increase to 400 mg/day was allowed) versus on-demand (positive trial).
CI, confidence interval; CRP, C reactive protein; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; NR, not reported; NSAIDs, non-steroidal anti-inflammatory drugs; r-axSpA, radiographic axial spondyloarthritis; SD, standard deviation.

Glucocorticoids

Two studies examined the efficacy and safety of glucocorticoids in r-axSpA (tables 2 and 4 and online supplementary tables S20–S24 and S25–S27).

One RCT[62] (at low RoB), Haibel *et al* (table 2) performed in patients with r-axSpA with active disease (BASDAI≥4) has shown no short-term differences between two different doses of prednisolone and placebo in the primary end point (BASDAI 50 week 2: 8% under placebo; 27% under prednisolone 20 mg, p value versus placebo=0.30; 33% under prednisolone 50 mg, p value versus placebo=0.16). However, there were significant effects observed on ASDAS-CRP (week 2 change scores: −0.34 for placebo; −1.16 for prednisolone 20 mg, p value versus placebo=0.004; −1.56 for prednisolone 50 mg, p value versus placebo=0.010) and CRP (week 2 change scores: −3.19 for placebo; −19.94 for prednisolone 20 mg, p value versus placebo=0.0016; −15.58 for prednisolone 50 mg, p value versus placebo=0.036). The number of AEs at 2 weeks was similar in the three-arm study (n=6 placebo; n=4 under prednisolone 20 mg; n=5 under prednisolone 50 mg).

One cohort study[63] (at high RoB) assessed the safety of low-dose glucocorticoids and NSAIDS compared with NSAIDs alone in patients with r-axSpA (table 4). No significant differences were reported for serious infections and peptic ulcer disease. On the other hand, a higher incidence of dermatological AEs was found in patients receiving glucocorticoids (incidence rate/1000 patient-years 22.2 vs 6.6; p=0.003).

Other non-biological drugs

Five trials (four studies[64 65 67 68] at high RoB and one study[66] at low RoB) were identified assessing the efficacy and safety of other non-biological drugs such as probiotics and pamidronate (table 2 and online supplementary tables S20–S24). In summary, none of the studies provided convincing evidence that these therapeutic alternatives are effective.

Surgical interventions

Overall, three studies[71–73] (all at high RoB) focusing on surgical interventions in patients with advanced r-axSpA were found. These studies suggested benefits for pedicle subtraction osteotomy and total hip replacement in patients with a fixed kyphotic deformity or advanced hip joint deformity, respectively (see online supplementary tables S28–S31).

DISCUSSION

This SLR summarises the current state of evidence for non-pharmacological treatments, non-biological drugs and surgical interventions in the treatment of axSpA, published after 2009.

The evidence favouring the efficacy of non-pharmacological interventions such as exercises, education and physiotherapy confirmed previous findings.[4] Almost all studies that were analysed demonstrated that regular exercises may improve disease activity, function, spinal mobility and pain in patients with axSpA. However, since the trials were so heterogeneous, no data pooling could be performed. The absence of a meta-analysis makes it difficult to decide which type of exercise is preferable, also because improvements were often small, regardless of the type of intervention. Only one study[51] focused on axSpA according to the ASAS criteria,[6] including early and advanced stages of disease, and required a high disease activity (BASDAI≥3.5) for inclusion. All remaining trials included patients with

Table 4 Safety of non-biological drugs (observational studies)

Study ID	Group	n	Atherosclerotic events* aIR/1000py (95% CI)	Atherosclerotic events* aRR (95% CI)	IHD aHR (95% CI)	GI-events aIR/1000py (95% CI)	GI-events aRR (95% CI)	Serious infections IR/1000py	DAE IR/1000py	Risk of bias
NSAIDs										
Kristensen 2015[60]	Etoricoxib	1655	2.9 (1.4; 6.3)	0.8 (0.4; 1.7)	NR	9.0 (4.1; 19.7)	1.3 (0.6; 2.7)	NR	NR	Moderate
	Celecoxib	858	2.8 (1.2; 6.3)	0.8 (0.3; 1.7)	NR	5.4 (1.8; 15.8)	0.8 (0.3; 2.2)	NR	NR	
	Traditional NSAIDs	15 580	3.7 (2.5; 5.4)	Ref	NR	7.1 (4.6; 10.9)	Ref	NR	NR	
	Non-user	4260	3.8 (2.6; 5.4)	1.0 (0.7; 1.5)	NR	3.4 (2.4; 4.9)	**0.5 (0.3; 0.7)**	NR	NR	
Essers 2016[61]	General population	25 299	NR	NR	Ref†	NR	NR	NR	NR	
	Any NSAID	1233	NR	NR	**1.36 (1.00; 1.85)**	NR	NR	NR	NR	
	Naproxen	291	NR	NR	0.26 (0.04; 1.84)	NR	NR	NR	NR	Moderate
	COX-II inhibitors	287	NR	NR	**3.03 (1.61; 5.69)**	NR	NR	NR	NR	
	Traditional NSAID	692	NR	NR	1.32 (0.93; 1.89)	NR	NR	NR	NR	
GC										
Zhang 2015[63]	GC+NSAIDs	555	NR	NR	NR	NR	NR	4.4	**22.6**	High
	NSAIDs	275	NR	NR	NR	NR	NR	4.4	6.6	

Bold=significant (p<0.05).
Kristensen 2015: Register-based cohort—r-axSpA and spondyloarthritis; median age in the cohort—46 years; follow-up—2006-2009 (3 years).
Essers 2016: Claims data set—patients with r-axSpA (n=3640) compared with general population (n=25 299); both groups—83% <60 years; follow-up—1987–2012 (25 years).
Zhang 2015: Data from Rheumatology Outpatient Department of the First Affiliated Hospital of Shantou University Medical College in China—r-axSpA (n=830); low-dose GC—10 mg prednisone/10 mg methylprednisolone; duration mean (SD)—1.7 (1.6) years; NSAIDs—90 mg acemetacin or 50 mg indomethacin or 7.5 mg meloxicam.
*Atherosclerotic events=cardiac and cardiovascular.
†Patients with r-axSpA with or without recent NSAID use were compared with all controls, irrespective of the use of NSAIDs in the control group.
aHR, adjusted HR; aIR, adjusted incidence rate; aRR, adjusted relative risk; CI, confidence interval; COX, cyclooxygenase; DAE, dermatological adverse events; GC, glucocorticoids; GI, gastrointestinal; IHD, ischaemic heart disease; IR, incidence rate; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; py, patient-years; r-axSpA, radiographic axial spondyloarthritis; ref, reference.

advanced r-axSpA. Furthermore, data on the safety of the exercises were indecisive, since the information about possible AEs, such as vertebral fractures, was not available but may be relevant, particularly in advanced stages of the disease.

Another point of concern is the quality of the studies on non-pharmacological interventions. Although several studies were performed during the past years, the overall RoB was most often 'high'. One main reason for this is the lack of blinding of the outcome assessors, which admittedly is challenging to achieve for some interventions such as physiotherapy or exercises. Still, designing blinded studies for such interventions is not without precedent: previous trials, for example, with a sham intervention as a comparator, have shown that interventions broadly considered to be effective may fail to demonstrate superiority when tested against a formal comparator, and when blinding is ensured.[75]

As already shown in the previous SLRs informing ASAS-EULAR recommendations,[4 76] NSAIDs are effective for the treatment of axSpA with no difference in efficacy between different classes. Compared with the last SLR, new evidence regarding the effect of NSAIDs on radiographic progression has been published but the results are not consistent. Until now, there is no evidence that NSAIDs reduce spinal radiographic progression in patients with r-axSpA with normal CRP, while contradicting evidence towards less radiographic progression is available for patients with elevated CRP and continuous NSAIDs intake.[58 59] In addition, one cohort study showed an inhibitory effect of continuous NSAID use on radiographic progression in patients with r-axSpA and elevated CRP.[74] Taken all together, the potential inhibitory effect of NSAIDs on spinal radiographic progression is still an open question and warrants more research to draw definite conclusions.

In comparison to the previous SLR,[4] no new findings on the safety of NSAIDs were obtained. Overall, only four studies with moderate quality could be analysed on this topic, all together confirming the previous data at least for patients with established r-axSpA, while eligible observational studies focusing on safety in patients with nr-axSpA were not available.

In contrast to the previous SLRs, a low RoB RCT[62] has addressed the short-term efficacy of high doses of systemic glucocorticoids. This study failed to formally demonstrate superior efficacy of glucocorticoids for patients with r-axSpA with active disease (BASDAI≥4), since it did not meet its primary end point (BASDAI 50). However, significant differences in secondary outcomes were found, such as in ASDAS-CRP and CRP levels for prednisolone 20 mg and 50 mg and in the BASDAI levels for prednisolone 50 mg as compared with placebo. This proof-of-concept 2-week trial with high doses of glucocorticoids in axSpA has shown only very modest efficacy.

New trials on other DMARDs were not found in this SLR. From earlier trials, we have obtained evidence that DMARDs are not efficacious in axSpA.[77 78]

Finally, similar to the studies identified in the last SLR,[4] the level of evidence for surgical interventions remained low. Only three small studies testing surgical interventions to a comparator were found. The remaining captured (but not included) studies were case series or cohort studies without a comparator, thus hampering the assessment of possible treatment effects. The limited data suggest that patients with advanced r-axSpA may benefit from spinal corrective osteotomy or total hip arthroplasty when indicated.

In summary, in the latest SLR on non-biological treatment in axSpA, the evidence on efficacy and safety of NSAIDs was confirmed, while no new data were found on treatment with csDMARDs. Thus far, oral glucocorticoids did not demonstrate efficacy in axSpA. Regular exercises may improve outcomes, but with modest effect sizes. This SLR has informed the 2016 update of the ASAS-EULAR recommendations for the management of axSpA.

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Correction notice This article has been corrected since it was first published online.

Funding The study was funded by the European League Against Rheumatism (EULAR), and the Assessment of SpondyloArthritis international Society (ASAS).

Competing interests AS: Fundação para a Ciência e Tecnologia (grant number: SFRH/BD/108246/2015). XB: AbbVie, BMS, Boehringer Ingelheim, Celgene, Centocor, Chugai, Janssen Biologics, Novartis, Pfizer, UCB. DvdH: AbbVie, Amgen, Astellas, AstraZeneca, Bristol Myers Squibb, Boeringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Janssen, Merk, Novartis, Pfizer, Roche, Sanofi-Aventis, UCB, Imaging Rheumatology BV. JB: Abbott, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma. RL: Abbott/AbbVie, Ablynx, Amgen, AstraZeneca, BMS, Centocor, Janssen (formerly Centocor), GSK, Merck, Novo-Nordisk, Novartis, Pfizer, Roche, Schering-Plough, TiGenics UCB, Wyeth, Director of Rheumatology Consultancy BV. FdVB: AbbVie, Celgene, Janssen, Merck, Novartis, Pizer and UCB.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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