ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update

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Abstract

Objectives: To update the ASAS-EULAR recommendations for the management of axial spondyloarthritis (axSpA).

Methods: Following the EULAR Standardised Operating Procedures, two systematic literature reviews were conducted on non-pharmacological and pharmacological treatment of axSpA. In a task force meeting the evidence was presented, discussed, and overarching principles and recommendations were updated, followed by voting.

Results: Five overarching principles and 15 recommendations with a focus on personalised medicine were agreed: eight remained unchanged from the previous recommendations; three with minor edits on nomenclature; two with relevant updates (#9,12); two newly formulated (#10,11). The first 5 recommendations focus on treatment target and monitoring, non-pharmacological management and non-steroidal anti-inflammatory drugs (NSAIDs) as first choice pharmacological treatment. Recommendations 6-8 deal with analgesics and discourage long-term glucocorticoids and conventional synthetic DMARDs for pure axial involvement. Recommendation 9 describes the indication of biological DMARDs (bDMARDs i.e. TNFi, IL-17i) and targeted synthetic DMARDs (tsDMARDs i.e. JAKi) for patients who have ASDAS≥2.1 and failed ≥2 NSAIDs and also have either elevated CRP, MRI inflammation of sacroiliac joints or radiographic sacroiliitis. Current practice is to start a TNFi or IL-17i. Recommendation 10 addresses extra-musculoskeletal manifestations with TNF monoclonal antibodies preferred for recurrent uveitis or inflammatory bowel disease, and IL-17i for significant psoriasis. Treatment failure should prompt re-evaluation of the diagnosis and consideration of the presence of comorbidities (#11). If active axSpA is confirmed, switching to another b/tsDMARD is recommended (#12). Tapering, rather than immediate discontinuation of a bDMARD, can be considered in patients in sustained remission (#13). The last recommendations (#14,15) deal with surgery and spinal fractures.

Conclusions: The 2022 ASAS-EULAR recommendations provide up-to-date guidance on the management of patients with axSpA.

Introduction

Axial Spondyloarthritis (axSpA) is a chronic inflammatory rheumatic musculoskeletal disease with a predilection for the axial skeleton. Peripheral (arthritis, enthesitis and dactylitis) and extra-musculoskeletal manifestations (EMMs), the latter referring to acute anterior uveitis, inflammatory bowel disease (IBD) and psoriasis, are frequently present.[1] AxSpA comprises the whole spectrum of patients with and without radiographic sacroiliitis, i.e. radiographic axSpA (r-axSpA; also known as ankylosing spondylitis) and non-radiographic axSpA (nr-axSpA), respectively.[2-4] Through the years it has been shown that r-axSpA and nr-axSpA are part of the same disease spectrum and that patients with r-axSpA and nr-axSpA are largely similar with regard to clinical presentation, burden of disease, including the presence of comorbidities, treatment received and response.[5-7] Taken together, there is ample evidence to favour the term axSpA, which is why this term has been chosen in these recommendations.[8]

The management of patients with axSpA includes non-pharmacological and pharmacological interventions. The armamentarium of pharmacological options for axSpA has expanded significantly in recent years. For a long time, if a patient failed non-steroidal anti-inflammatory drugs (NSAIDs), the only alternative options were tumour necrosis factor (TNF)-inhibitors (TNFi). Currently, the availability of TNFi, as well as interleukin-17 (IL17)-inhibitors (IL-17i) and Janus kinase (JAK)-inhibitors (JAKi) presents more therapeutic options and hope for people living with this disease. Data on the different treatment options come mainly from placebo-controlled trials, with no relevant head-to-head studies performed to date in axSpA. On the other hand, in routine clinical practice, choices between different drugs need to be made throughout the course of patient management. A personalised approach to care, based on individual needs and supported by scientific evidence where available, is crucial. Existing recommendations have tended to show preference for efficacy data along with safety data from observational studies, since these better reflect real-life populations and clinical practice.

Evidence on the efficacy of the different drugs on the EMMs has been accumulating, with data available in patients with pure axSpA or in other populations such as patients with psoriasis, psoriatic arthritis (PsA) or IBD. The efficacy of drugs on EMMs often guide therapeutic choices, hence their value in the management of patients with axSpA. All these aspects underline the importance of regularly updated clinical recommendations that incorporate new evidence to support clinicians in providing optimal management for their patients in daily clinical practice.

The ASAS-EULAR (Assessment of SpondyloArthritis international Society-European Alliance of Associations for Rheumatology) recommendations for the management of axSpA were first developed in 2006 and updated in 2010, both covering only r-axSpA; then further updated and expanded to the entire axSpA spectrum in 2016.[9-11] The current work represents the 2022 update of the ASAS-EULAR recommendations for the management of axSpA guided by the newly available evidence since the 2016 update.

The target users of these recommendations include various stakeholders: 1) all health care professionals taking care of patients with axSpA, including not only rheumatologists and health professionals in rheumatology (such as rheumatology nurses or physiotherapists), but also general practitioners, other medical specialists

and physicians in training, including medical students; 2) patients with axSpA, to be better informed for optimal shared-decision making; and 3) other stakeholders including patient organizations, regulatory agencies and reimbursement institutions, policy makers, health insurance companies and the pharmaceutical industry.

Methods

The update of the axSpA management recommendations was conducted as a joint project between ASAS and EULAR as per previous years and followed the 2014 EULAR Standardised Operating Procedures.[12] Following approval by the ASAS Executive Committee and the EULAR Council, the convenors (DvdH, SR) set up a steering committee which included methodologists (EN, AS), fellows (AO, CW) who conducted the systematic literature reviews (SLRs) and two SpA-expert rheumatologists (RL, XB). Subsequently the remaining task force members were invited, making a total of 33 participants, from 16 countries across Europe and North America. The current task force consisted of 52% new members compared to the 2016 task force. The 2022 task force membership included rheumatologists, epidemiologists, EULAR representatives from the health professionals committee, People with Arthritis/Rheumatism across Europe (PARE), EMerging EUlar NETwork (EMEUNET) and Young-ASAS (Y-ASAS). Additionally, five members were recruited through an open call to EULAR countries via a competitive application process. As required by the EULAR SOP, all members disclosed their conflicts of interest upfront.[12]

The Steering Committee defined the research questions of the SLRs. Under the guidance of the methodologists, two fellows performed two SLRs: one focused on non-pharmacological and non-biological pharmacological treatment (AO), the second addressed biological disease modifying antirheumatic drugs (bDMARDs) (CW). These SLRs included studies published from the end search date of the previous SLRs (i.e. 2016) up until the 1st January 2022, and are published separately.[13,14] The SLRs and the current recommendations manuscript form an integral and inseparable part and should be read as such. The results of the SLRs were discussed with the Steering Committee, which prepared the first draft of the update of the overarching principles (OAPs) and recommendations. The 2016 recommendations were used as a basis, to facilitate the start of the discussion with the complete task force. The basic rule was that a change would only be made if new evidence mandated it.

At the task force's one-day online meeting in February 2022, the SLRs were first presented, and their findings discussed. The evidence collected in the previous SLRs was also taken into account and summarized to the entire task force.[15-19] In addition to the evidence from the SLRs, expert opinion was considered when formulating OAPs and recommendations. Efficacy and safety, as well as cost-related aspects of interventions were considered. Costs were considered particularly relevant when different therapies presented similar efficacy and safety, as expensive drugs impose an important burden on healthcare budgets. The usual terminology for DMARDs has also been applied here: conventional synthetic (cs)DMARDs for drugs such as sulfasalazine and methotrexate; bDMARDs for drugs such as TNFi and IL-17i and targeted synthetic (ts)DMARDs for JAKi.[20]

Recommendations were edited live according to the comments made, followed by a formal voting using anonymised polls. Consensus was reached if ≥75% of the members voted in favour of the recommendations in the first (or ≥67% and ≥50% in a second and third) round. If multiple rounds of voting were necessary, discussion took place in between voting rounds to refine the drafted statements.

After the meeting, the levels of evidence (LoE) and grades of recommendation (GoR) derived from the SLRs following the standards of the Oxford Center for Evidence Based Medicine were added by the Steering Committee to each of the recommendations.[21] Finally, each task force member anonymously indicated their level of agreement (LoA) through an online survey (numeric rating scale ranging from 0=’do not agree at all’ to 10=’fully agree’). The mean and standard deviation (SD) of the LoA as well as the percentage of agreement ≥8 was presented.

Based on identified gaps in evidence a research agenda was formulated. The draft of the manuscript was sent to all task force members for review. The final manuscript was approved by all authors, the ASAS Executive Committee and the EULAR Council.

Results

Overarching principles

As commonly seen, OAPs precede the recommendations to indicate a set of crucial principles in the treatment of axSpA, reflecting state-of-the-art management (Table 1). Five OAPs were agreed and unchanged compared to the 2016 update.

A. Axial Spondyloarthritis (axSpA) is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary management coordinated by the rheumatologist

This OAP underlines two important aspects. Firstly, that musculoskeletal and extra-musculoskeletal manifestations of axSpA often have an important impact on patient’s life[22]. Secondly, that the rheumatologist, as the expert across the spectrum of the disease, should coordinate the multidisciplinary management. Other medical specialists as well as health professionals may have relevant contributions to the management of patients with axSpA.

B. The primary goal of treating the patient with axSpA is to maximise long term health related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, and preservation/normalisation of function and social participation.

Management should be aimed at obtaining the best possible health-related quality of life (HRQoL). One way to achieve this is to intervene on disease domains that ultimately impact on HRQoL, namely disease activity, structural damage and function as demonstrated in a stratified model for health outcomes in axSpA.[23,24] As axSpA is an inflammatory disease, with most available treatments aimed at reducing inflammatory burden, the control of inflammation has a prominent place in its management, given the impact of disease activity on structural damage and function.[25-27]

C. The optimal management of patients with axSpA requires a combination of non-pharmacological and pharmacological treatment modalities.

This OAP applies to several, and likely all, rheumatic and musculoskeletal diseases. Nevertheless, the combination of both treatment modalities is particularly relevant in axSpA and none should be neglected.[14,19] Non-pharmacological treatment is integral to optimal axSpA management.

D. Treatment of axSpA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.

Each individual patient should get the best possible care, preferably tailored to their situation. The decision on the best care for an individual patient has to be taken after careful and informative dialogue between the patient and the health care provider (‘shared decision’). As such, this OAP is generic, and can be found in several EULAR management recommendations.[28] Shared decision making is formally defined as a collaborative process between patients and healthcare providers, whereby care decisions are agreed and based on the best scientific evidence available, the health professional's experience, as well as the patient's values and preferences.[29] Shared decision making is strongly supported by organisations such as ASAS and EULAR as an essential component of the patient’s care plan.

E. AxSpA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.

It is crucial to keep the high costs associated with axSpA in mind, in the broader sense, while trying to achieve the best possible balance in the management of the patient. For the individual patient, the disease represents suffering and burden of disease, with adverse effects on work productivity and consequently economic burden, to the person living with the disease but also family members. Societal costs are mainly driven by healthcare costs and by impaired work productivity with presenteeism, sick leave and work disability, all of them contributing to the economic burden.[30] Expensive modern drugs substantially contribute to healthcare costs. Rheumatologists have thus additional societal, as well as individual responsibility for considering costs when making treatment decisions, particularly since more efficient allocation of limited resources will allow the treatment of more patients.[31] Notwithstanding, this OAP must not contradict the previous one, which implies that cost considerations cannot overrule the best care for the individual patient.

Combining both principles, deliberately presented in this order, means that when a choice needs to be made between two drugs with comparable efficacy and safety, then the one with the lowest cost is preferable. This principle was also taken into account when formulating the recommendations.

Recommendations

Fifteen recommendations were agreed: eight remained unchanged from the previous recommendations (#2,3,6,7,8,13,14,15), three received minor edits, mostly on nomenclature (#1,4,5), two were significantly updated (#9,12), while two were newly formulated (#10,11). Table 1 displays all recommendations, with their corresponding LoE, GoR and LoA. LoA was very high, around or above 9. Figure 1 depicts the algorithm summarizing the recommendations, which requires the explanatory text below.

Recommendation 1
The treatment of patients with axSpA should be individualised according to the current signs and symptoms of the disease (axial, peripheral, extra-musculoskeletal manifestations) and the patient characteristics including comorbidities and psychosocial factors.

AxSpA has a heterogeneous presentation, and individual disease characteristics and patient needs necessitate a personalised approach to care with shared decision making at its core. Particularly when making treatment decisions, the rheumatologist needs to be informed on the presence as well as the extent of the different SpA manifestations, namely axial, peripheral and EMMs. Compared to the previous recommendations, only a minor edit was made to reflect the update of the nomenclature, as EMMs is the currently used term to refer to uveitis, psoriasis and IBD.[32] The recommendation intentionally mentions comorbidities due to their impact on disease assessment, outcomes and treatment.[33]

The task force considered important to emphasize, first and foremost, that a diagnosis of axSpA should be made or confirmed by a rheumatologist (Figure 1). A clinical diagnosis of axSpA, based on the clinical presentation, in combination with laboratory and imaging tests, and excluding other potentially more likely diagnoses, is the starting point and should not be based on classification criteria (e.g. ASAS axSpA classification criteria). Fulfilment of classification criteria is used for research purposes, to include a homogeneous patient population in a study, but falls short for diagnosis.

Recommendation 2
Disease monitoring of patients with axSpA should include patient reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and treatment.

Disease monitoring should reflect the different manifestations of the disease and the core domains that have been selected by experts and patients as being the most

important. Although these core domains are selected for use in clinical trials, they indicate what patients and rheumatologists consider important.[23,32] As an inflammatory disease, monitoring disease activity is crucial in axSpA. In the last decade the Ankylosing Spondylitis Disease Activity Score (ASDAS) has emerged as the most appropriate instrument for the assessment of disease activity, being recommended when monitoring patients with axSpA.[32,34] ASDAS, preferably calculated using CRP, is a well-balanced index without redundancy across its items, in contrast to the historically more widely used Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).[35] Moreover, ASDAS incorporates the perspective of the patient and includes CRP as an objective measure of inflammation while the BASDAI reflects only the patient perspective.[35,36] ASDAS has also been validated with a quick-quantitative CRP-assay, further improving its feasibility for daily clinical practice.[37,38] ASDAS has been shown to be longitudinally associated with syndesmophyte formation.[25,27,39] BASDAI alone was not associated with damage progression, except when combined with CRP and with a weaker relationship compared to ASDAS.[25] Specific cut-offs have been validated for the ASDAS to define disease activity states and improvement and worsening criteria.[40,41] Furthermore, the ASAS core set for monitoring in clinical practice remains an important guide.[42] This includes questionnaires collecting patient reported outcomes (PROs) for levels of pain, fatigue, morning stiffness, and physical function (Bath Ankylosing Spondylitis Functional Index, BASFI), as well as swollen joint counts, spinal mobility and assessment of EMMs.[42,43] A more recently developed instrument, the ASAS Health Index (ASAS-HI), is disease-specific and measures overall functioning and health.[44] In the context of several PROs used in the monitoring of axSpA, remote monitoring or e-health, with the use of apps or PROs imported into electronic medical records, can contribute to a more comprehensive assessment of the patient to inform further treatment decisions.[45,46] Also in line with the ASAS Quality Standards, the task force recommends comprehensive assessments of the patient, including an initial assessment and a comprehensive annual review.[47] This is meant to ensure a holistic approach to the patient and that all aspects of the disease are under control, aiming at achieving the treatment goal (OAP 2). Following OAP 1, such assessments should be performed by a multidisciplinary team coordinated by the rheumatologist.

Magnetic resonance imaging (MRI) of the sacroiliac joints (SIJ, MRI-SIJ) or of the spine can assess axial inflammation. However, the association between clinical disease activity measures and MRI inflammation is only modest.[48-50] MRI is not routinely recommended for monitoring, as its value for this purpose is still unclear and its frequent use is considered unfeasible due to the high costs. Nevertheless, when in doubt about the origin of complaints or about the presence of inflammatory activity, MRI can assist in determining whether inflammation is present and thereby guide the therapeutic decision.

Structural damage can be assessed with radiographs of the spine and the presence of syndesmophytes has a prognostic value, as it reflects higher risk for the development of more syndesmophytes.[25,27,51,52] However, structural damage progression occurs at a slow rate and therefore subsequent radiographs of the spine, if performed, should have at least 2-year intervals.[51,53]

Recommendation 3
Treatment should be guided according to a predefined treatment target.

Treatment towards a predefined target, agreed upon via shared decision between patient and rheumatologist, has been increasingly used in the area of inflammatory arthritis. In axSpA, evidence has only more recently emerged that a higher ASDAS leads to more syndesmophyte formation, which makes ASDAS an appropriate target.[25,27] Subsequently, one treat-to-target (T2T) trial has been conducted, TICOSPA, showing that T2T with ASDAS<2.1 as the target is not significantly superior to usual care in achieving an improvement in the ASAS-HI ≥30%, the primary endpoint of that trial.[54] While formally a negative trial, T2T showed some efficacy on secondary outcomes. Altogether, the real effectiveness of T2T in axSpA remains undetermined. Therefore, the task force emphasized that a treatment target should be used as a guidance, but should only result in intensifying immunosuppressive treatment if physician and patient are convinced of the presence of residual inflammatory activity and other (contextual) factors do not impede such an intensification. These include aspects that can potentially influence the assessment of disease activity, such as fibromyalgia and other comorbidities.

Recommendation 4
Patients should be educated about axSpA and encouraged to exercise on a regular basis and stop smoking; physiotherapy should be considered.

This recommendation focuses on non-pharmacological treatment, which in axSpA is of prime importance (Figure 1).[55] All patients should receive education about the disease, as the starting point of self-management, to empower and involve them as active partners in their care.[28,56] Patient education in broader terms should include information on the disease, its symptoms and recognition, disease course, treatment options and prognosis.

Exercise is a cornerstone in the management of axSpA, with demonstrated benefits on disease outcomes independent of pharmacological treatment.[14,57] While exercise in general should always be part of the disease management, evidence from qualitative studies shows that adherence is higher if supervised.[14] Physiotherapy, specifically supervised exercise, has also proven to be more efficacious than home exercises.[58] Of note, the heterogeneity and methodological limitations across studies on exercise and physiotherapy hamper a definitive conclusion regarding which exercises are best to perform.[14] On an individual basis, physiotherapy should be considered, especially if a patient does not exercise on their own. The task force underlined that *physiotherapy* should not be an umbrella term also used for interventions that are not widely tested or have proven benefit, like needle knife or alternative medicine derived practices.[14,59,60] After discussion, the task force concluded that ‘physiotherapy’ is a more appropriate term than ‘physical therapy’ as used in the previous version of the recommendations and therefore this small change was incorporated.

Smoking has been shown as a risk factor for spinal inflammation and disease progression in axSpA.[61-65] Though no formal investigation has been conducted on the benefits of smoking cessation on axSpA outcomes, it seemed reasonable to recommend it, on the basis of all well-known health risks associated with smoking.

Recommendation 5
Patients suffering from pain and stiffness should use an NSAID as first line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs, continuous use is preferred if needed to control symptoms.

NSAIDs are the first line of the pharmacological treatment in axSpA (Figure 1). By suppressing inflammation, NSAIDs often suffice in keeping disease activity and symptoms under control.[66] This recommendation only has a minor textual change in its last part, which was considered to convey the message more clearly. The task force supports using continuous NSAIDs above on-demand only if needed to control symptoms. Whenever continuous use is not needed to control symptoms, preference should be given to on-demand NSAIDs treatment, given the risks of long-term use. Historically, this recommendation has also been discussed in light of the contradictory evidence on the effect of NSAIDs on the inhibition of structural damage progression.[67-70] The task force hereby emphasises that, to date, the decision on the continuous use of NSAIDs should be based solely on the control of symptoms and not on any attempt to control structural disease progression.

Recommendation 6
Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated.

This recommendation, driven by expert opinion, remained unchanged, due to the lack of trials on analgesics in axSpA. While short-term use of opioid-(like) drugs may have an acceptable risk-benefit profile, caution is advised for long-term use, which is in general not recommended.[71] The ambivalence about this recommendation with the risk of addiction without proven efficacy in axSpA is also reflected in the lowest LoA among all recommendations (although still high). Given that residual pain is a frequent problem encountered in clinical practice, trials should be conducted to provide the necessary evidence, with the recommendation adapted as appropriate. Approach to pain management can also be guided by specific EULAR recommendations.[72]

Recommendation 7
Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids.

This recommendation, also unchanged, addresses the use of glucocorticoid injections as an option to treat local inflammation (Figure 1). Even though glucocorticoid injections have not been tested on arthritis or enthesitis in patients with axSpA, task force members are of the opinion that they can be efficacious. Local site injections, possibly guided by ultrasound, also refer to injections of the SIJ, which showed improvement in pain, though only tested in very small and old trials.[73,74]

Notwithstanding, a definite answer on the efficacy of SIJ injections based on low risk of bias trials is still needed.

Regarding systemic glucocorticoids for purely axial disease, evidence exists on short-term glucocorticoids only. Two studies suggest that short-term high dose glucocorticoids (50mg/day or 60mg/day tapered over 24 weeks) could have a modest effect on signs and symptoms in patients with purely axial disease.[14,75,76] Data on prolonged use of glucocorticoids in axSpA is lacking and, due to their known adverse events, the task force does not support their chronic use for axial disease.

Recommendation 8
Patients with purely axial disease should normally not be treated with csDMARDs; Sulfasalazine may be considered in patients with peripheral arthritis.

The SLR retrieved no relevant new data on csDMARDs, and therefore this recommendation remained the same.[14] csDMARDs are not recommended for purely axial disease due to their lack of efficacy, which has been shown for sulfasalazine, methotrexate and leflunomide.[77-79] However, methodological shortcomings hamper the interpretation of trials with csDMARDs and, most importantly, there is a dearth of such trials and of relevant outcomes tested. Other treatment options for purely axial disease after failing NSAIDs are bDMARDs or tsDMARDs, which are costly and consequently not always available. Therefore, the task force agreed on emphasizing that csDMARDs are normally not used, giving room for their exceptional use, as long as this is aligned with the OAPs, i.e. ensuring the ‘best care’ and in shared decision with the patient. In patients with peripheral arthritis, however, csDMARDs are indicated with sulfasalazine being the preferred option due to its demonstrated efficacy in the subgroup of patients with peripheral arthritis, unlike methotrexate which has not demonstrated efficacy.[77,78]

Recommendation 9
TNFi, IL-17ior JAKi should be considered in patients with persistently high disease activity despite conventional treatments (Figure 2); current practice is to start a TNFi or IL-17i.

After failure of conventional therapy, treatment intensification should be considered for patients with persistently high disease activity. Figure 2 summarizes the important eligibility criteria of patients to the next step in the treatment algorithm. It has previously been shown that adhering to the ASAS-EULAR recommendations for the initiation and continuation of TNFi leads to better functional outcomes and fewer days of sick leave.[80]

As indicated earlier, the task force considered it important to repeat that the first aspect is a clinical diagnosis of axSpA. The second aspect of the eligibility assessment deals with the presence of criteria that have been either associated with

a higher likelihood of response or have been mandated by regulatory authorities. They are listed in decreasing order of the strength of predicting treatment response, namely elevated CRP, followed by presence of inflammation on MRI-SIJ, followed by the presence of radiographic sacroiliitis (according to the modified New York grading: grade ≥2 bilaterally or ≥3 unilaterally). Both elevated CRP and presence of MRI-SIJ inflammation should be related to axSpA, meaning that other plausible causes for such abnormalities should be carefully excluded. Elevated CRP has been identified as the strongest predictor of good response to TNFi therapy, both in patients with r-axSpA and nr-axSpA.[81-84] In addition, inflammation on MRI-SIJ appeared to be the second-best predictor of response to TNFi therapy, again irrespective of the presence of radiographic sacroiliitis.[84-86] Lastly comes the presence of radiographic sacroiliitis, although not being predictive of response,[7,87] but in order to comply with regulatory approval. When TNFi were historically approved for r-axSpA, no other conditions beyond active disease were mandated. It was only much later, when dealing with the approval of TNFi for nr-axSpA, that these drugs were restricted to patients with either elevated CRP or positive MRI-SIJ, given the higher response in patients with these objective signs of inflammation.[84] However, with increasing knowledge of the predictive response of these factors in r-axSpA, the task force now recommends that CRP and (when available) MRI-SIJ are taken into account when deciding to start a b/tsDMARD, irrespective of the presence of radiographic sacroiliitis.[83-86] Of note, at the time of the formulation of the recommendations, radiographic sacroiliitis was mandatory for infliximab and JAKi, which were only approved for r-axSpA. In the meanwhile, upadacitinib has been approved for nr-axSpA by the European Medicines Agency.[88]

Step 3 in the eligibility assessment refers to the failure of conventional treatment. This means non-pharmacological treatment and the use of at least two NSAIDs, in the maximum dose used in axSpA, over a total period of four weeks.[89] In patients with predominantly peripheral manifestations, following recommendations 7 and 8, failure to treatment includes one glucocorticoid injection, if appropriate, and the use of sulfasalazine.

The following step focuses on the level of disease activity. Given the clear advantages of the ASDAS as described in relation to recommendation 2, the task force considers it to be the appropriate disease activity instrument, an observation that has been consolidated over the last decade. The task force therefore decided that high disease activity should be based on the ASDAS≥2.1 criterion alone. If it is impossible to follow this recommendation, the BASDAI criterion (≥4) can be used as an alternative. There is a high agreement between both criteria but, in case of discordance, the ASDAS selects patients with a higher likelihood of response to treatment.[90-92] In any case, the judgment of high disease activity should not be solely based on a score but complemented by the rheumatologist's opinion, which should favour the start of a b/tsDMARD. Like any therapeutic decision, this should also follow OAP D and be part of shared decision making with the patient.

In patients with persistently high disease activity despite conventional treatment, as defined above, TNFi, IL-17i or JAKi should be considered (Figure 1). All these drug classes have demonstrated efficacy in axSpA-trials.[13,14] In the absence of head-to-head trials it is difficult to prioritize any of them in terms of efficacy on axial disease. In the second part of the recommendation, the focus is placed on current practice, which is to start a TNFi or an IL-17i. This recommendation reflects the

longer experience with the use of these drugs, with a larger evidence base, use in patients with multimorbidity (frequently excluded from RCTs) and more knowledge about drug safety.[13,14,18] This decision is analogous to the previous recommendations, in which 'current practice' at that time was to start with a TNFi, for the exact same reasons, while IL-17i were already available. In addition, as only IL-17A inhibitors have so far been approved, reference to IL-17i is limited to IL-17Ai. Dual inhibition of IL-17A and IL-17F with bimekizumab has been tested in a Phase 2 trial[93], but more information is needed about its efficacy and safety profile before it can be taken into consideration. For JAKi, at the moment, we only have RCT data, and only in r-axSpA. Data on nr-axSpA are currently underway, but not publicly available at the time of the formulation of the recommendations. Importantly, observational data and experience from daily clinical practice with JAKi in axSpA are missing, thus precluding the consideration of JAKi in 'current practice' part of the recommendation. In the future, observational data and experience with JAKi should help in addressing concerns with regard to safety, such as those identified with tofacitinib in patients with rheumatoid arthritis (RA). Tofacitinib has been associated with a higher risk of major adverse cardiovascular events (Number needed to harm - NNH- for 5mg twice daily tofacitinib of 113 over 5 years) as well as malignancies (NNH 55 over 5 years), when compared to TNFi. The trial was performed in patients with RA who were at least 50 years old and had at least one cardiovascular risk factor, and the risk was higher in patients over 65 years.[94] During drug development, increases in serum lipid levels and the incidence of cancers, including lymphoma, were observed, prompting further investigation.[95,96] In axSpA, such signals have not been described to date.[14,97-99] Possible explanations for this include the younger age of patients with axSpA and their likely lower risk factor profile (including less comorbidities and less use of glucocorticoids), shorter follow-up and efficacy trials not enriched for a high risk population.[98,100] It is therefore unclear whether the increased risk of cardiovascular events and malignancies is specific to RA, and whether it will apply to axSpA, as well as whether they are specific to tofacitinib or reflect a JAKi class effect. Until more data become available, the task force recommends being restrictive with starting JAKi in patients above the age of 50 with one or more additional cardiovascular risk factors and to those above the age of 65.

In this entire document, we refer to both original and biosimilar bDMARDs. Currently, biosimilars are available for TNFi. Taking OAPs into account, costs should be considered when choosing a particular drug. Given the similar expected efficacy and safety, cost is potentially an important consideration in choosing between an original and biosimilar bDMARD. This choice is increasingly determined by payers, and based on cost considerations, rather than by rheumatologists or patients. Cost may also drive the choice between an IL-17i and a (biosimilar) TNFi.

Aside from the importance on deciding when a patient is eligible for treatment with b/tsDMARDs, it is important to also decide on whether treatment is efficacious, and therefore appropriate to continue. Figure 3 summarizes the criteria for continuation, namely that after at least 12 weeks of treatment, the disease activity has substantially decreased, as assessed by the ASDAS clinical important improvement, i.e. improvement in ASDAS≥1.1, together with the positive opinion from the rheumatologist to continue.[40] As always, the final decision on whether to continue the treatment or not is made as a shared decision with the patient. As for the start of treatment, ASDAS is recommend for the assessment of response to treatment. If not

possible to follow this recommendation, BASDAI response (≥2.0) can be used if BASDAI has been used to guide treatment initiation.

Recommendation 10
If there is a history of recurrent uveitis or active IBD, preference should be given to a monoclonal antibody against TNF. In patients with significant psoriasis, an IL-17i may be preferred.

An important element of differentiation across the treatment options is their effect on EMMs[13] leading to this new recommendation. In patients with previous uveitis, monoclonal antibodies against TNF (infliximab, adalimumab, certolizumab pegol, golimumab) have been shown to be efficacious in preventing the recurrence of uveitis, whereas etanercept showed contradictory results.[101-107] In comparative analyses from registry data, monoclonal antibodies have been shown to be more efficacious in preventing a uveitis flare than etanercept or secukinumab.[108,109] Additionally, secukinumab has been tried, unsuccessfully, in patients with non-infectious uveitis.[110] These data led the task force to recommend monoclonal antibodies in patients with a history of recurrent uveitis (Figure 1). Of note, this recommendation is meant to support treatment choice in those patients who have frequent and recent episodes of uveitis. In patients with IBD, existing data point in a similar direction, namely the efficacy of monoclonal antibodies against TNF and the lack of efficacy of etanercept and secukinumab.[111-116] Thus, monoclonal antibodies are also preferred in patients with IBD. IL-17i are contra-indicated in patients with active IBD. Although there are no specific comparative data on psoriasis in patients with axSpA, there is clear data in PsA. Two head-to-head trials have been conducted comparing IL-17i (secukinumab and ixekizumab) to TNFi (adalimumab in both trials), showing superiority of IL-17i in the achievement of robust skin outcomes.[117,118] Therefore, an IL-17i may be preferred in patients with significant psoriasis.

Recommendation 11
Absence of response to treatment should prompt re-evaluation of the diagnosis and consideration of the presence of comorbidities.

Making an appropriate diagnosis of axSpA is not always straightforward. A good response to a bDMARD or JAKi in retrospect may suggest that the diagnosis of axSpA is correct. The task force here reiterates that the absence of clinical response should alert the physician to re-evaluate the patient: instead of a straight switch to a different immunosuppressive treatment, it seems wise to question whether the former diagnosis was indeed correct (Figure 1). Striving for earlier diagnoses, as we nowadays do, may have advantages but also implies that more patients with relatively milder disease, less clear and classic symptoms and a better prognosis will be recognized, and misdiagnosis is increasing. In the past years many efforts have been made in order to increase the awareness of the disease to try to reduce the diagnosis delay (that still exists) but nowadays rheumatologists should also be aware of the risk of misdiagnosis, overdiagnosis and overtreatment.[119]

Additionally, the presence of comorbidities, such as (but not restricted to) fibromyalgia, depression or osteoarthritis, is known to be associated with higher perceived disease activity, particularly if assessed exclusively by patient reported outcome measures, and also associated with poorer treatment outcomes.[120-126] The task force therefore stipulated that the presence of comorbidities should be taken into consideration in the case of absence of response to treatment. A positive rheumatologist's opinion to start treatment with a b/tsDMARD (Figure 2) that complements an assessment of high disease activity, as described in recommendation 9, should therefore take possible comorbidities and their impact on disease activity assessment into account. This recommendation is also in line with a EULAR initiative on difficult-to-treat RA.[127]

Recommendation 12
Following a first b/tsDMARD failure, switching to another bDMARD (TNFi or IL-17i) or a JAKi should be considered.
The expansion of the treatment armamentarium for axSpA, now with three efficacious b/tsDMARD drug classes, each class with several options, opens more possibilities in the treatment of patients. When one treatment fails and the patient still fulfils the criteria to start a new treatment, a switch should be considered (Figure 1). However, the evidence in terms of the efficacy of a given drug (class) after failure of a previous one is very limited. No RCT has been conducted with TNFi in patients failing a first TNFi, i.e. TNFi-insufficient responders (TNFi-IR).[13] Observational data suggest that a second TNFi can still be efficacious in TNFi-IR patients, although the level of efficacy may be lower than with the first TNFi.[128] IL-17i have shown to be efficacious in TNFi-IR patients, also with a lower efficacy than in TNFi-naïve patients (direct comparisons only available for secukinumab).[13,129-134] Data on JAKi separately in bDMARD-IR were not available at the time of the formulation of the recommendations. There are no data on the efficacy of TNFi after IL-17i or JAKi failure, neither on IL-17i in the case of JAKi failure nor JAKi in the case of TNFi or IL-17i failure. All these treatment sequences should be formally investigated and are therefore part of the research agenda (Table 2). In the absence of data showing superiority of switching between different modes of action rather than within the same one, the task force agreed to recommend any switch, keeping all options open, but again taking the precautions for the use of JAKi as described for recommendation 9 (Figure 1).

Recommendation 13
If a patient is in sustained remission, tapering of a bDMARD can be considered.

An accumulating body of evidence shows that abrupt bDMARD withdrawal may lead to a high proportion of flares, while tapering was shown to be successful in maintaining treatment response.[13,18,135-138] One double-blind trial with certolizumab in axSpA compared all three possible actions (continuing vs. tapering vs. stopping) directly and showed a significantly lower risk of flare for those that continued or tapered, compared to those who stopped.[139] Tapering has been mostly studied through spacing drug administration.[13] Although sustained remission has not been formally defined, in line with the advantages of the ASDAS previously mentioned, ASDAS inactive disease or low disease activity could be used

here. ‘Sustained’ has not been defined either, but the task force considered it appropriate to emphasize that before starting to taper treatment a patient should be in remission for a minimum period and that period should be (arbitrarily) at least 6 months. Existing data on tapering were restricted to TNFi.[13] For IL-17i there was only one study with withdrawal of ixekizumab leading to a high proportion of flares and no data on withdrawal or tapering of JAKi.[13,14,140] The task force therefore decided to leave this recommendation unchanged and restricted to bDMARD tapering (Figure 1). Importantly, tapering should be done steadily, with new assessments of the patient before moving further with a next step in the tapering approach. Tapering may ultimately result in discontinuation. During the whole process OAPs should be followed, with ‘best care’ and ‘shared decision’ being key here.

Recommendation 14
Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age; spinal corrective osteotomy in specialised centres may be considered in patients with severe disabling deformity.

This recommendation, unchanged from before, aims at raising awareness into potential surgical indications for problems associated with severe axSpA. Hip involvement is a frequent problem in patients with axSpA and symptomatic destruction should lead to the consideration of a total hip arthroplasty, regardless of the patient’s age.[141] Especially in young patients, cementless prostheses are preferred.[14,142] Patients with severe and disabling spinal deformity may be referred to a specialised surgeon so that corrective osteotomy can be considered.[143,144]

Recommendation 15
If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed.

The final recommendation was kept unchanged and focuses on a (sudden) significant change in the course of the disease, which should trigger a comprehensive assessment of causes other than inflammation. In such a situation, a spinal fracture should be suspected, particularly in patients with ankylosis of the spine, as a fracture is then more likely to occur even with a minor trauma and usually leads to a worse outcome compared to a spinal fracture in the general population.[145] When suspected, appropriate imaging such as MRI and/or computed tomography (CT) scanning should be performed, and an experienced spinal surgeon may need to be consulted.[146]

Research agenda

The SLRs conducted to inform these recommendations highlighted existing gaps in the literature, which together with key discussion points raised during the task force meeting, resulted in our proposed research agenda (Table 2).

Discussion

The ASAS-EULAR recommendations for the management of axSpA have been updated into a set of 5 OAPs and 15 recommendations covering both nr-axSpA and r-axSpA and including non-pharmacological and pharmacological treatment.

Since the last update in 2016, more data have become available on existing treatment options, and particularly on IL-17i. More data on secukinumab as well as on ixekizumab can now be considered, while the latter was not approved for axSpA at the time of the previous recommendations. For both IL-17i efficacy has been shown not only in r-axSpA but also in nr-axSpA.[13] In addition, JAKi represent a completely new drug class in these recommendations, with efficacy demonstrated for tofacitinib and upadacitinib in r-axSpA.[14] The increasing availability of more drugs and with different modes of action raises questions around their positioning in the treatment pathway. With the lack of relevant head-to-head trials to date in axSpA, and with efficacy on axial disease seeming similar across existing drugs, there are no reasons for prioritizing one or the other in terms of efficacy. In this context, given the importance of EMMs in the treatment of axSpA and the distinctive effect of the different drugs on EMMs, a new recommendation has been formulated based on existing evidence: In patients with a history of recurrent uveitis or active IBD, monoclonal antibodies against TNF are preferred, while in patients with significant psoriasis, IL-17i are prioritized.[13,14] The latter aligns with the EULAR recommendations for PsA, also giving preference to an IL-17i in case of significant skin involvement.[147]

In addition to efficacy, drug safety is a central aspect in treatment decisions. The more recently approved drugs naturally have less accumulated safety data. Observational studies include more ‘real-life’ patients, for example with multimorbidity, who tend to be excluded from RCTs and are particularly informative for safety analyses, by allowing for more appropriate comparisons between interventions regarding long-term safety. Unlike in RA where there is a long history of robust observational data e.g. from registries,[148,149] in axSpA (long-term) safety data are generally scarce and almost exclusively on TNFi. Safety data from IL-17i and JAKi are only available from RCTs.[13,14] To date, the long-term safety of JAKi is challenged by the recently reported increased risks of major cardiovascular events and malignancies in patients with RA treated with tofacitinib compared to TNFi.[94] Trials with a safety primary endpoint have not been conducted in axSpA and one cannot exclude that lack of statistical power is the reason that such safety signals have not been shown in current axSpA trials. It is therefore crucial to clarify whether these safety issues also apply to patients with axSpA and whether they represent a JAKi-class concern. Until more solid data are available in axSpA, caution is advised. The task force wished to bring this aspect into the recommendations through the prioritization of TNFi and IL-17i as first line b/tsDMARD treatment in line with current practice.

The increasing number of effective, albeit expensive drugs with different modes of action stimulated much discussion by the task force. This is reflected in the OAPs, where the societal responsibility of rheumatologists is highlighted through the consideration of cost, while striving to provide the best level of care. Newer drugs

coming into the market are more expensive than existing ones and this should be balanced against the expected added value, as perceived by patients.[150]

Recently ASAS has issued quality standards to help improve the quality of healthcare provided to patients with axSpA.[47] Expectedly, and also reassuringly, there are several points of connection between these OAPs and recommendations and the quality standards. For instance, non-pharmacological treatment, while addressed in one OAP and recommendation, is also reflected in two quality standards, emphasizing its importance. Disease monitoring and frequent assessments, including a comprehensive annual review, are part of these recommendations and of the quality standards. These recommendations and ASAS quality standards can therefore be complementary and support clinical practice.

The clear selection of ASDAS as the instrument used to decide upon the eligibility of a patient for treatment with b/tsDMARDs (ASDAS ≥2.1), as well as about treatment continuation (improvement ≥1.1), represents an important novelty of these recommendations. With over a decade of extensive experience with ASDAS and the accumulated data evidencing its superiority, its choice was imperative.[25,35,36,40,90-92] When it is not possible to use the ASDAS, it is better to use the BASDAI than no instrument at all, but we advocate that all efforts are made to implement the ASDAS in daily clinical practice.[37,46]

The task force extensively discussed the topic of treatment failure. Instead of the rather ‘simplistic’ approach of immediately starting a new DMARD once the former DMARD has failed, a careful and comprehensive assessment of the patient is recommended in order to avoid overtreatment.[119] Among the possibilities for consideration are the correctness of the diagnosis and the presence of comorbidities that could influence disease assessment, treatment response or both. This is a new recommendation, driven by expert opinion and directly stemming from daily clinical experience. This, together with the high level of agreement within the task force, attests to the importance of this recommendation.

Peripheral manifestations of axSpA are increasingly recognized to be more frequent than initially thought.[151-154] The assessment of treatment effects on peripheral manifestations has been suboptimal in axSpA, restricted to sub-analyses of patients with peripheral involvement at study inclusion. So far, and in the absence of head-to-head comparisons, no differences have been identified in drug efficacy for peripheral manifestations. The task force considers the current recommendations to apply to patients with axSpA eventually presenting with peripheral manifestations. Notwithstanding, more research on tailored management of peripheral manifestations in axSpA is needed to inform future recommendations.

There are many similarities between the ASAS-EULAR and the ACR-SPARTAN (American College of Rheumatology and SpondyloArthritis Research & Treatment Network) recommendations.[155] Indeed, it is the first time that the two sets of recommendations are thus aligned, which is reassuring in terms of the treatment of patients with axSpA worldwide. Differences are mainly in areas where strong evidence is lacking (e.g. preferred choices when switching, tapering, treat-to-target, spinal osteotomy). However, the format of the two sets of recommendations is substantially different: American recommendations are presented in elaborate detail (86 recommendations), with detailed treatment options and comparisons, while at the same time making the overview more challenging to follow as compared to the 5

OAPs and 15 recommendations from ASAS-EULAR. A few of the unique aspects of the ASAS-EULAR recommendations are: treating axSpA as a single disease, the explicit specifications in which a b/tsDMARD should be started and continued, the inclusion of JAKi as a drug class, treatment according to a target, treatment of axSpA in patients with significant psoriasis, non-pharmacological recommendation for treatment failure, tapering bDMARDs and cost-considerations.

Implementation is a crucial aspect in the process of recommendations and that is often neglected.[156] A dissemination strategy is currently underway which we hope will enhance the uptake and implementation of these recommendations. In the future ASAS and EULAR could devote more efforts into implementation of recommendations, beyond their dissemination. Barriers and facilitators should be investigated as well as the uptake of the recommendations and quality standards should be measured to inform further strategies, both at a local and international level.

In conclusion, the 2022 update of the ASAS-EULAR recommendations provides health care professionals taking care of patients with axSpA, patients and other relevant stakeholders with the most up-to-date evidence and expert insights in the management of patients with axSpA. The next update is expected to be undertaken when sufficient new evidence has become available on existing or new treatment options. It is our vision that these recommendations standardise and optimise the treatment of people living with axSpA, contributing to both individual well-being as well as wider societal benefit through better management of the disease.

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Table 1: ASAS-EULAR recommendations for the management of axSpA, 2022 Update

	OVERARCHING PRINCIPLES		**LoA (0-10)**	
			Mean (SD)	**%with score ≥8**
A	Axial Spondyloarthritis (axSpA) is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary management coordinated by the rheumatologist.		9.8 (0.4)	100%
B	The primary goal of treating the patient with axSpA is to maximize health related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, and preservation/normalisation of function and social participation.		9.8 (0.5)	100%
C	The optimal management of patients with axSpA requires a combination of non-pharmacological and pharmacological treatment modalities.		9.8 (0.5)	100%
D	Treatment of axSpA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.		9.5 (1.8)	97%
E	axSpA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist.		9.5 (0.9)	94%
	RECOMMENDATIONS	**Level of evidence / Grade of Recommendation ±**		
1	The treatment of patients with axSpA should be individualised according to the current signs and symptoms of the disease (axial, peripheral, extra-musculoskeletal manifestations) and the patient characteristics including comorbidities and psychosocial factors.	5 / D	9.6 (0.8)	97%
2	Disease monitoring of patients with axSpA should include patient reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and treatment.	5 / D	9.5 (1.1)	97%
3	Treatment should be guided according to a predefined treatment target.	5 / D	9.0 (1.2)	85%
4	Patients should be educated about axSpA and encouraged to exercise on a regular basis and stop smoking; physiotherapy should be considered.	2b / B (education, exercise) 5 / D (stop smoking) 1a / A (physiotherapy)	9.8 (0.5)	100%

5	Patients suffering from pain and stiffness should use an NSAID as first line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs, continuous use is preferred if needed to control symptoms.	1a / A	9.5 (0.8)	97%
6	Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated.	5 / D	8.9 (1.4)	79%
7	Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids.	2 / B (injections) 5 / D (long-term systemic GCs)	9.6 (0.8)	100%
8	Patients with purely axial disease should normally not be treated with csDMARDs; Sulfasalazine may be considered in patients with peripheral arthritis.	1a / A (sulfasalazine, methotrexate) 1b / A (leflunomide) 4 / A (other csDMARDs) 1a /A (sulfasalazine peripheral disease)	9.6 (0.9)	94%
9	TNFi, IL-17i* or JAKi^ should be considered in patients with persistently high disease activity despite conventional treatments (Figure 1); current practice is to start a TNFi or IL-17i*.	1a / A	9.2 (1.2)	94%
10	If there is a history of recurrent uveitis or active IBD±, preference should be given to a monoclonal antibody against TNF**. In patients with significant psoriasis, an IL-17i* may be preferred.	2b / B (uveitis, IBD) 1a / B (psoriasis)	9.1 (1.8)	97%
11	Absence of response to treatment should prompt re-evaluation of the diagnosis and consideration of the presence of comorbidities	5 / D	9.5 (0.8)	97%
12	Following a first b/tsDMARD failure, switching to another bDMARD (TNFi or IL-17i*) or a JAKi^ should be considered.	2b / B (TNFi after TNFi failure) 1b / A (IL-17i after TNFi failure) 5 / D (all other switches)	9.3 (1.1)	88%
13	If a patient is in sustained remission, tapering of a bDMARD can be considered.	1a / B (TNFi), 5 / D (IL-17i)	9.1 (1.2)	82%
14	Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age; spinal corrective osteotomy in specialised centres may be considered in patients with severe disabling deformity.	4 / C	9.5 (0.8)	97%
15	If a significant change in the course of the disease occurs, causes other than inflammation, such as a spinal fracture, should be considered and appropriate evaluation, including imaging, should be performed.	5 / D	9.6 (0.9)	97%

*IL-17i: refers only to IL-17A-inhibitors; ^ The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: age over 65 years, history of current or past smoking, other cardiovascular risk factors, other risk factors for malignancy, risk factors for thromboembolic events; ±In patients with active IBD, IL-17i are contraindicated; **This includes a pegylated Fab' fragment

± Level of recommendation: level 1a, systematic review with homogeneity of RCTs; level 1b, individual RCT (with narrow confidence interval); level 1c, all or none; level 2a, systematic review with homogeneity of cohort studies; level 2b, individual cohort study (including low quality RCT); level 2c, 'outcomes' research, ecological studies; level 3a, systematic review (with homogeneity) of case-control studies; level 3b, individual case-control study; level 4, case-series (and poor quality cohort and case-control studies); level 5, expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'. Grade of recommendation: grade A, consistent level 1 studies; grade B, consistent level 2 or 3 studies or extrapolations from level 1 studies, grade C, level 4 studies or extrapolations from level 2 or 3 studies; grade D, level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

axSpA, axial spondyloarthritis; LoA, level of agreement, SD, standard deviation; NSAIDs, non-steroidal anti-inflammatory drugs; GCs, glucocorticoids; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; TNFi, tumor necrosis factor inhibitor; IL-17i, interleukin-17 inhibitor; JAKi, Janus kinase inhibitor; IBD, inflammatory bowel syndrome; b/tsDMARDs, biological / targeted synthetics disease modifying antirheumatic drugs

Table 2: Research agenda

Treatment target in axSpA or for different disease presentations
Combined clinical and imaging target: superiority to clinical target only?
Assessment of disease activity in patients with fibromyalgia or other causes of chronic pain
Management of peripheral manifestations
Effect of physiotherapy on disease outcomes
Head-to-head comparisons between treatment options (TNFi, IL-17i and JAKi)
Efficacy of switches between different drug classes (switch in case of IL-17i failure or JAKi failure)
Impact of comorbidities on treatment response
Effect of the different drugs on EMMs
Effect of the different drugs on peripheral manifestations
Effect of treatment (NSAIDs, TNFi, IL-17i, JAKi) on structural damage progression
Effect of treatment (NSAIDs, TNFi, IL-17i, JAKi) on SIJ structural damage progression in patients with nr-axSpA
Impact of objective inflammatory markers (CRP+/MRI+) on b/tsDMARD response in r-axSpA
Efficacy and safety of b/tsDMARDs vs NSAIDs in patients without symptoms of the disease but with CRP+ and/or MRI+
Effect of therapeutic drug monitoring in treatment with bDMARDs, especially TNFi
Predictors of response to different drugs/drug classes
Efficacy of drugs stratified by gender
Role of exercise in patients with a high mechanical load (e.g. due to job type)
Potential harmful effects of excessive exercise (on structural damage)
Management of residual pain
Further safety data of TNFi (observational studies)
Safety of IL-17i (observational studies)
Safety of JAKi (observational studies)
Safety of IL-17i and JAKi during pregnancy
Efficacy and safety of combinations of bDMARDs and tsDMARDs
Tapering of IL-17i and JAKi
Definition of sustained remission
Benefits and harms of T2T in axSpA
Role of imaging in monitoring of axSpA – additional value of MRI spine/SIJ, ultrasound/MRI imaging of enthesis for treatment decisions
Impact of tapering b/tsDMARDs on structural damage progression
Efficacy of short-term glucocorticoids
Biomarkers of prognosis
Biomarkers of treatment response
Strategy trials
Start of tapering of b(ts-)DMARDs, which criteria?
Efficacy and safety of analgesics for residual pain in axSpA
Difficult to treat axSpA: definition, best approach to management

Figure 1: Algorithm based on the ASAS-EULAR recommendations for the management of axial spondyloarthritis.

Figure 2: ASAS-EULAR recommendations for the treatment of patients with axSpA with b/tsDMARDs.

* Radiographic sacroiliitis is mandatory for drugs only approved in case of its presence; at the moment of the formulation of the recommendations: infliximab and JAKi

CRP, C-reactive protein; MRI-SIJ, magnetic resonance imaging of the sacroiliac joints; NSAIDs, non-steroidal anti-inflammatory drugs; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; JAKi, Janus kinase inhibitor; bDMARD, biologic disease modifying antirheumatic drug; tsDMARD, targeted synthetic disease modifying antirheumatic drug

Figure 3: ASAS-EULAR recommendations for the continuation of b/tsDMARDs.

ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; bDMARD, biological disease modifying antirheumatic drug; tsDMARD, targeted synthetic disease modifying antirheumatic drug.

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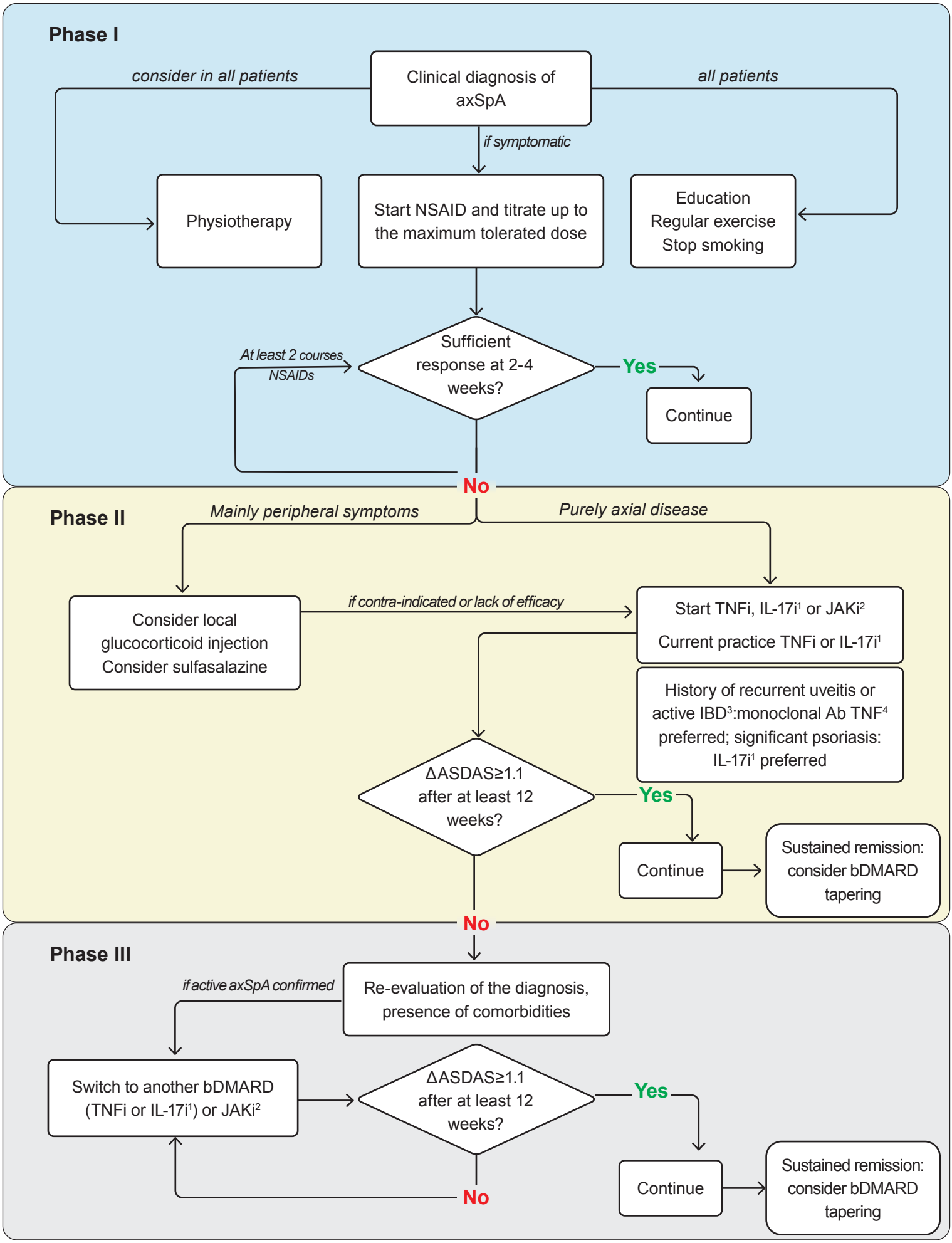

1. *IL-17i refers only to IL-17A-inhibitors*
2. *The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: age over 65 years, history of current or past smoking, other cardiovascular risk factors, other risk factors for malignancy, risk factors for thromboembolic events.*
3. *In patients with active IBD, IL-17i are contraindicated*
4. *Monoclonal antibodies TNF include a pegylated Fab' fragment*

axSpA, axial spondyloarthritis; NSAIDs, non-steroidal anti-inflammatory drugs; ASDAS, ankylosing spondylitis disease activity score; TNFi, tumor necrosis factor inhibitor; IL17-i, interleukin-17 inhibitor, refers only to IL-17A-inhibitors; JAKi, Janus kinase inhibitor; IBD, inflammatory bowel disease; Ab, antibody; bDMARD, biological disease-modifying antirheumatic drug

Rheumatologist's diagnosis of axial SpA

and

Elevated CRP or positive MRI-SIJ or Radiographic sacroiliitis*

and

Failure of standard treatment

All patients

At least 2 NSAIDs over 4 weeks (in total)

Patients with predominant peripheral manifestations

One local steroid injection if appropriate

Normally a therapeutic trial of sulfasalazine

and

High disease activity: ASDAS ≥ 2.1

and

Positive rheumatologist's opinion

* Radiographic sacroiliitis is currently mandatory for infliximab and JAKi

Consider to continue b/tsDMARDs if after at least 12 weeks of treatment

ASDAS improvement ≥ 1.1

and

Positive rheumatologist‘s opinion to continue