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APLAR RECOMMENDATION

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2018 APLAR axial spondyloarthritis treatment recommendations

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Abstract

Introduction: Despite the availability of axial spondyloarthritis (SpA) recommendations proposed by various rheumatology societies, we considered that a region-specific guideline was of substantial added value to clinicians of the Asia-Pacific region, given the wide variations in predisposition to infections and other patient factors, local practice patterns, and access to treatment across countries.

Materials and methods: Systematic reviews were undertaken of English-language articles published between 2000 and 2016, identified from MEDLINE using PubMed, EMBASE and Cochrane databases. The strength of available evidence was graded using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. Recommendations were developed through consensus using the Delphi technique.

Results: Fourteen axial SpA treatment recommendations were developed based on evidence summaries and consensus. The first 2 recommendations cover non-pharmacological approaches to management. Recommendations 3 to 5 describe the following: the use of non-steroidal anti-inflammatory drugs as first-line symptomatic treatment; the avoidance of long-term corticosteroid use; and the utility of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) for peripheral or extra-articular manifestations. Recommendation 6 refers to the indications for biological DMARDs (bDMARDs). Recommendation 7 deals specifically with screening for infections endemic to Asia, prior to use of bDMARDs. Recommendations 7 to 13 cover the role of bDMARDs in the treatment of active axial SpA and include related issues such as continuing therapy and use in special populations. Recommendation 14 deals with the utility of surgical intervention in axial SpA.

Conclusion: These recommendations provide up-to-date guidance for treatment of axial SpA to help meet the needs of patients and clinicians in the Asia-Pacific region.

KEYWORDS

ankylosing spondylitis, axial spondyloarthritis, treatment

1 | INTRODUCTION

Axial spondyloarthritis (SpA) is a chronic inflammatory disease that predominantly affects the spine or sacroiliac joints. Persistent inflammation in the axial skeleton results in the predominant symptom of inflammatory back pain and can lead to new bone formation, structural damage and disability.[1,2] Other clinical manifestations may include peripheral arthritis, enthesopathy, and extra-articular features such as uveitis, psoriasis, and inflammatory bowel disease (IBD).[1] Importantly, patients with axial SpA may also suffer from distinct comorbidities, such as osteoporosis, cardiovascular disease,[3] fibromyalgia[4] and depression,[5] which add to the burden of disease and complicate management.

Previously, diagnostic criteria for ankylosing spondylitis (AS) relied on the radiographic detection of sacroiliitis along with symptoms of pain, stiffness, and limited motion of the thoracic and lumbar spine.[6] Recently, it has been recognized that radiographic (plain X-ray) evidence of disease may take many years to develop after symptom onset with early diagnosis demonstrating improved outcomes. For early diagnosis of axial SpA, the Assessment of SpondyloArthritis international Society (ASAS) classification criteria were developed. In particular, magnetic resonance imaging (MRI) evidence of inflammation is increasingly used in symptomatic patients without radiographic sacroiliitis to assist in the earlier diagnosis of axial SpA. Therefore, the classification of axial SpA based on ASAS criteria now includes patients with non-radiographic axial SpA (nr-axial SpA) and patients with AS, the radiographic form of SpA.[7] There is still some controversy as to whether these represent 2 separate disease entities or a disease continuum.

The estimated prevalence of axial SpA in the adult population is 0.9%-1.4% in the USA.[8] In Asia, data extracted from studies showed a mean AS prevalence of 16.7 per 10 000, with an estimated 4.63-4.98 million cases.[9] A survey of rheumatology outpatient clinics estimated that 36.46% of Asian patients with inflammatory back pain met criteria for a classification of nr-axial SpA.[10] In this real-world setting, patients with nr-axial SpA and those with AS had high levels of disease activity, suggesting poor disease control. Both groups of patients had comparable disease burden in terms of functional impairment and limitation. Likewise, surveys from China, which comprises more than 20% of the global population, described early limited mobility and radiographic progression. Peripheral arthritis and hip joint involvement were common and associated with high disease activity.[11] Furthermore, the presence of depressive and anxiety symptoms, as reported in Chinese patients,[12] could further impact quality of life.

As symptoms and physical limitations contribute significantly to the burden of the disease with impairment in quality of life,[13,14] axial SpA is a major health concern. Prompt diagnosis and appropriate treatment are likely to improve outcomes; however, making an appropriate, timely diagnosis may be a challenge, particularly for non-rheumatologists, because of low recognition of SpA features.[15-17] To address this, in recent years, international organizations such as the American College of Rheumatology/Spondyloarthritis Research and Treatment Network/Spondylitis Association of America (ACR/SPARTAN/SAA), and the ASAS/European League Against Rheumatism (EULAR) have provided updated management recommendations;[18,19] these documents set out the goals of axial SpA treatment as improvement of quality of life through control of symptoms and inflammation, prevention of structural damage, and preservation of function and social participation.[19]

However, notably, the Asia-Pacific region is characterized by wide disparities in healthcare systems across countries, driven by varying rates of socioeconomic development, demographic and epidemiological transitions, and political and cultural milieus.[20] Faced with wide variations in

clinical practice, healthcare systems and available resources, Asian clinicians require guidance from experts on how to achieve treatment goals in axial SpA. The Asia-Pacific League of Associations for Rheumatology (APLAR) thus undertook the development of evidence-based recommendations to address concerns specific to the region.

This set of recommendations focuses on non-pharmacological and pharmacological treatment of patients diagnosed with axial SpA according to ASAS criteria, including recommendations for dealing with specific clinical scenarios, such as when patients have tuberculosis (TB) or hepatitis B virus (HBV) infection. Its target audience includes all clinicians who manage patients with axial SpA.

2 | MATERIALS AND METHODS

A working group was convened to develop a set of APLAR axial SpA treatment recommendations that were practical and relevant to the needs of patients and clinicians in the Asia-Pacific region. All member national organizations of APLAR were invited to nominate a representative to join the group. The final group was, thus, comprised entirely of representatives from the national member organizations of APLAR. In the first meeting, members of the group developed 24 clinically important questions related to the treatment of axial SpA as the basis for the literature search.

Search strategies were developed for each question using medical subject headings for MEDLINE, and adapted for other databases. MEDLINE was searched through PubMed, EMBASE and the Cochrane Library from January 2000 to December 2016, limited to English language articles. Following completion of the search, the collected articles per question were assigned to a working group member for review.

The evidence was presented in summary-of-findings tables to the working group over the subsequent meetings, over the period of November 2016 to November 2017. At the second meeting, the participants discussed the quality of evidence and started to draft the recommendations. The quality of evidence was determined for all outcomes of interest, based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. The strength of a recommendation was described as "strongly in favor", "conditionally in favor", "conditionally against" and "strongly against" (Table 1).[21] Four categories for the quality of evidence were "very low", "low", "moderate" and "high" (Table 2)[21,22] Some recommendations were not graded because of lack of eligible evidence to support them. Such statements were still included to represent practical guidance for common important clinical situations. Supplementary evidence was presented during the 3rd meeting, with the draft recommendations reworded and refined based on the members' evolving understanding of the implications of the enlarging evidence base. At the conclusion of the 3rd meeting a final set of 14 draft recommendations was agreed upon which covered key aspects of the management of axial SpA.

A voting group was then convened, comprised of members of APLAR's Axial SpA Special Interest Group. The consensus process was a modification of the Delphi technique: members of the voting group were asked to rate their agreement with each recommendation on a 5-point Likert scale (ie: 5, strongly agree; 4, agree; 3, neither agree nor disagree; 2, disagree; 1 strongly disagree); agreement by 75% of total voting members (ie proportion of members indicating "strongly agree" plus proportion indicating "agree" equals 75%) was previously defined as achieving consensus on a statement.

Consensus was achieved on all statements in the first voting round. If consensus had not been reached, members of the original working group would have convened to discuss suggested modifications based on feedback from the 1st voting round; statements for which consensus was not achieved would have been modified accordingly, and another vote conducted.

Draft recommendations developed by the group were sent to Professor Iain McInnes, Professor Denis Poddubnyy and Professor Syed Atiqul Haq for review and comments. The draft recommendations were also presented in an open forum during the 2018 APLAR Congress to seek opinions and suggestions from participants. Feedback from the respondents was used to finalize the recommendations and inform supporting text.

3 | RESULTS

The recommendations are presented with their level of agreement and overall grade. Some recommendations are accompanied by supporting statements for additional guidance. Each recommendation is followed by a discussion of the evidence and rationale supporting its inclusion. Table 3 provides a summary of the 14 recommendations.

TABLE 1 Strength of recommendations[21]

Strength	Interpretation	Implications for clinicians	Implications for policymakers
Strongly in favor	Almost all informed patients would choose to receive the intervention	Should be accepted by most patients to whom it is offered	Should be adopted as policy
Conditionally in favor	Most informed patients would choose the intervention, but a sizable minority would not	Large role for education and shared decision-making	Requires stakeholder engagement and discussion
Conditionally against	Most informed patients would not choose the intervention, but a small minority would	Large role for education and shared decision-making	Requires stakeholder engagement and discussion
Strongly against	Most patients should not receive the intervention	Should not be offered to patients	Should be adopted as policy

TABLE 2 Grade for quality of evidence[22]

Quality of evidence	Meaning
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

TABLE 3 APLAR axial spondyloarthritis treatment recommendations

	Recommendation	Grade of evidence
1	We conditionally recommend physical therapy (preferably supervised) and exercise in patients with axial SpA	Very low
2	Smoking cessation is strongly encouraged in patients with axial SpA	Low
3	We strongly recommend treatment with NSAIDs for patients with active axial SpA as first-line treatment for symptom control	Moderate
4	We strongly recommend against the long-term use of corticosteroids to treat axial SpA	Very low
5	We conditionally recommend the use of csDMARDs in axial SpA patients with peripheral or extra-articular manifestations, or in resource-poor settings	Low
6	We strongly recommend the use of bDMARDs in patients with active disease who have failed treatment with 2 different NSAIDs	Moderate
7	We conditionally recommend, prior to starting bDMARD, to screen for TB, HBV, HCV and human HIV (in high-risk populations). Treatment for latent TB (according to local guidelines) and pre-emptive therapy for chronic hepatitis B infection are also conditionally recommended	Very low
8	We strongly recommend using a TNF inhibitor as the initial bDMARD treatment	Very low
9	We conditionally recommend using TNF inhibitor monoclonal antibodies over fusion protein in patients with features beyond arthritis and enthesitis, such as concomitant inflammatory bowel disease, recurrent anterior uveitis, and psoriasis.	Low
10	In adults with persistent active axial SpA despite an adequate trial of the 1st TNF inhibitor for at least 12 weeks, we conditionally recommend treatment with another TNF inhibitor or secukinumab	Very low
11	We conditionally recommend continuing bDMARD therapy in patients who respond well to treatment, but a reduced dose or increased interval may be considered in patients in sustained remission	Low
12	Special situations. (a) For patients with axial SpA in whom disease cannot otherwise be controlled, we conditionally recommend continuing TNF inhibitors throughout pregnancy. (b) While biologics can be used in renal failure, caution is advised and treatment considered on a case-to-case basis.	Very low
13	We strongly recommend reviewing the vaccination status of patients with axial SpA, following local guidelines	Not graded
14	We conditionally recommend 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 may be considered in patients with severe disabling deformity	Very low

APLAR, Asia-Pacific League of Associations for Rheumatology; SpA, spondyloarthritis; NSAID, nonsteroidal anti-inflammatory drug; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; bDMARD, biological DMARD; TB, tuberculosis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; TNF, tumor necrosis factor.

Recommendations

1. We conditionally recommend physical therapy (preferably supervised) and exercise in patients with axial SpA (Vote 100% agreement; grade of evidence very low).

The effectiveness of exercise and physical therapy for axial SpA is recognized based on preliminary evidence.[23] Results of a 2016 meta-analysis confirmed that physical therapy improved measures of impairment (Bath Ankylosing Spondylitis Metrology Index [BASMI], Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]) and participation restrictions (Bath Ankylosing Spondylitis Functional Index [BASFI]), and exercise improved specific measures of chest expansion, endurance in walking, and lumbar spine flexibility.[24] Eight randomized controlled trials (RCTs) that compared the effectiveness of specific exercises with physical therapy, conducted over a period of 12 weeks to 6 months, were included in the analysis. In the literature, the terms

"exercise" and "physical therapy" were usually interchangeable. The meta-analysis defined these separately: specific exercises included Pilates, aerobics, aquatic exercise, and the Global Postural Re-education method, while physical therapy involved flexibility, muscular strength, stretching and respiratory strength training under the supervision of a physiotherapist, at home or in the hospital. Additionally, the panel analyzed the use of physical therapy or supervised exercise in 6 RCTs, in which program durations ranged from 8 weeks to 7 months, and from an observational study of a 6-week, home-based exercise program. The trials showed improvements in function, disease activity and pain.[25-31] Cardiovascular risk benefits were also confirmed.[30]

As in other parts of the world, management of axial SpA in the Asia-Pacific region involves a multimodal approach that combines exercise and physical therapy with pharmacological therapy to meet treatment goals. Although the efficacy of exercise and physical therapy in improving axial SpA symptoms and disabilities is well documented, the panel judged the evidence of benefits to be marginal, and the quality of evidence was rated as low based mainly on risk of bias across studies. Also, the cost of supervised therapy and access to exercise programs, and availability of physical therapists, may vary across countries in the Asia-Pacific, which justified the inclusion of a conditional recommendation.

2. Smoking cessation is strongly encouraged in patients with axial SpA (Vote 100% agreement; grade of evidence low).

Quitting smoking is particularly relevant for patients with SpA because smoking is associated with higher levels of disease activity and disability in patients with axial SpA who were smokers, compared with non-smokers.[32] In addition, it has a negative influence on bronchopulmonary and cardiovascular outcomes in SpA[33] and is a major risk factor for cancers of the lung and multiple other sites.[34]

Smoking cessation may be beneficial, based on the review of five cross-sectional studies that linked smoking with poorer treatment outcomes such as disease activity, quality of life and structural progression.[35-39] Although there are no interventional studies to confirm the benefits of quitting smoking on axial SpA signs and symptoms or on cardiovascular endpoints in patients with SpA, the group agreed to issue a strong recommendation against smoking to emphasize the benefits of quitting on general health and the potential benefits in axial SpA. This statement is highly relevant to the Asia-Pacific region, which has seen a rise in tobacco use through the years. This rise in smoking is more in developing countries of the region which lack quality tobacco control programs, and in these countries, a link between smoking and a high risk of death from cardiovascular disease, cancer and respiratory disease has been shown.[34]

3. We strongly recommend treatment with non-steroidal anti-inflammatory drugs (NSAIDs) for patients with active axial SpA as first-line treatment for symptom control (Vote 100% agreement; grade of evidence moderate).

Supporting statements

- For patients at high risk of progressive structural damage (eg smoker, high C-reactive protein [CRP], syndesmophytes present at time of diagnosis, positive MRI, male sex, human leukocyte antigen [HLA] B27+), continuous treatment with an NSAID/cyclooxygenase 2 (COX-2) inhibitor may be considered given their possible benefits on inhibition of new bone formation (Grade of evidence low).
- We strongly recommend that treatment with NSAIDs should be individualized according to the patient's response to treatment and their risk for major cardiovascular events, gastrointestinal (GI) complications or renal disease (Grade of evidence moderate).
- We strongly recommend that the duration of treatment should depend on the balance between the benefits of treatment and the risk of adverse events (Grade of evidence moderate).

We found moderate- to high-quality evidence for the efficacy of NSAIDs for improvement of SpA disease outcomes, including pain relief, disease activity, and physical function. Four RCTs of traditional and COX-2 NSAIDs showed benefit over placebo in treating axial SpA at 2-6 weeks in terms of pain relief.[40-45] The NSAID group had a lower mean pain score of 18.06 points (95% confidence interval [CI] 13.00-23.11) on a 0-100 visual analog scale (VAS).[44] In 2 studies reviewed, the NSAID group had a lower mean BASDAI score of 17.45 (95% CI 11.80-23.10) to 22.0 (95% CI 16.55-27.44) points from 0-100, after a treatment period of 6-12 weeks.[43,45] The computed difference in functional activity score (BASFI), also after 6-12 weeks, was 9.1 (95% CI 5.1-13.0) to 13.4 (95% CI 9.5-17.4) points from 0-100, favoring the NSAID group. Patient Global Assessment (PGA) score was lower for the NSAID group than the placebo group, with mean PGA score of 17.44 (95% CI 14.16-20.72) to 20.82 (95% CI 11.75-29.88). NSAID use was also effective in improving range of motion of the spine, duration of stiffness, chest expansion and results of the Schober test, as well as reducing levels of acute-phase response proteins.[44] Specific COX-2 inhibitors (COX-2i) were not found to be more beneficial than traditional NSAIDs in improving disease activity, function, and spinal range of motion.[42,43,46]

The question of whether NSAIDs can prevent structural damage in axial SpA or AS was also discussed. No study was found that compared NSAID/COX-2i use versus placebo or another NSAID/COX-2i. While an early controlled trial showed that continuous versus on-demand use of NSAID/COX-2i reduced radiographic progression in active AS, the results, when analyzed with another trial, suggested that on-demand NSAID/COX-2i use (diclofenac, ketoprofen, or celecoxib) may not be inferior to continuous use.[47,48] The combined evidence was judged to have high risk of bias and inconsistency. However, the panel included a conditional recommendation for continuous use to highlight the potential benefit for patients at high risk of structural damage.

In its 2015 guidelines, the ACR/SPARTAN/SAA strongly recommends treatment with NSAIDs over no treatment for adults with active AS. Continuous treatment with NSAIDs was conditionally recommended over on-demand treatment with NSAIDs. There was no

recommendation about the specific duration of NSAID treatment.[18] In the 2016 ASAS/EULAR update of the guidelines for the management of axial SpA, the use of NSAIDs as first-line drug treatment up to the maximum dose is strongly recommended for patients suffering from pain and stiffness. For people who respond well, continuous use of NSAIDs is recommended. There was also no mention of the specific duration for which NSAIDs should be given.[19]

The panel analyzed the evidence for duration of NSAID treatment as well as NSAID safety. Based on moderate- to high-quality evidence, treatment with NSAIDs (traditional NSAIDs and COX-2i) for up to 52 weeks was effective in reducing pain, controlling disease activity, and improving function among patients with axial SpA.[41-43] Trial duration ranged from 2 weeks to 52 weeks. One RCT had a double-blind extension after the original 6-week trial for up to 52 weeks, in which patients remained in the original treatment arm, and showed comparable results as after the 6-week period.[41] Two RCTs showed that the mean BASFI score was 12.72 points lower (95% CI 9.83-15.61) in the intervention group after 6 weeks of treatment with NSAIDs.[18]

Regarding safety, moderate- to high-quality evidence from a meta-analysis showed that the use of NSAIDs increased the risk of major vascular events (myocardial infarction [MI], stroke, or death), and GI complications (bleeding, perforation or obstruction).[50] The meta-analysis of individual participant data from a total of 297 trials compared COX-2i with placebo in terms of major vascular events (fatal and non-fatal MI; fatal or non-fatal stroke; mortality) and GI complications. Annual event rates for all the outcomes among patients randomized to COX-2i were very low: major vascular events 1.15% per year; MI or coronary heart disease death 0.63% per year; upper GI complications 0.38% per year; and GI bleed 0.33% per year.[50]

While the risks for major vascular events and GI complications were increased, the magnitude of risk can be estimated per NSAID and used to guide treatment decisions. Given these findings, the group formed consensus around the principle that treatment with NSAIDs should be individualized, and that the duration of treatment should depend on the balance between treatment benefits and the risk for adverse events. Of note, detailed guidance on choosing an appropriate NSAID is available from Scarpignato et al[51] and Ho et al,[52] but these groups offer very limited guidance on appropriate treatment duration; clinical studies evaluating the optimum duration of NSAID treatment are warranted.

The current trend in Asia and in other regions of the world is for clinicians to prescribe NSAIDs before considering another class of drugs.[53] The evidence for NSAID efficacy in symptom control, together with their relative safety over prolonged administration was highlighted by the group's review of the literature; together with their wide availability and affordability, NSAIDs will continue to be the preferred first-line therapeutic option in the Asia-Pacific region for patients with active axial SpA.

4. We strongly recommend against the long-term use of corticosteroids to treat axial SpA (Vote 93% agreement; grade of evidence very low).

Supporting statement

- We \ use of short-term systemic corticosteroids, preferably no longer than 2 weeks, in axial SpA patients with severe active disease. (Grade of evidence high)

Low-level evidence from case series and a retrospective observational study showed that use of systemic corticosteroids may improve AS symptoms.[54,55] Evidence from a single, small RCT was considered of high quality—the trial showed that 2 weeks of prednisolone 50 mg versus placebo improved 5 of 10 clinical outcomes in active AS, including the BASDAI, the BASFI, and pain relief.[58] However, following the recommendations from ACR/SPARTAN/SAA and ASAS/EULAR,[18,19] the group gave a strong recommendation against long-term corticosteroid use, but added a condition for short-term use in active AS. Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered, although there is no direct evidence supporting their use in axial SpA.[18,19]

5. We conditionally recommend the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in axial SpA patients with peripheral or extra-articular manifestations, or in resource-poor settings (Vote 86% agreement; grade of evidence low).

csDMARDs (methotrexate, leflunomide, sulfasalazine) were determined not to be efficacious for treating axial SpA, based on low- to high-quality evidence.[59,60] RCTs also revealed high withdrawal rates from adverse events due to sulfasalazine use.[68,69] Only 1 multi-center, longitudinal, observational study showed that sulfasalazine for SpA with peripheral arthritis improved disease outcomes after 3 months.[72]

However, importantly, csDMARDs constitute much of the treatment armamentarium in many resource-poor settings across the Asia-Pacific region. Where clinicians and patients are unable to access more efficacious therapies, a trial of csDMARDs may be attempted, with careful monitoring for possible adverse events, with the knowledge that a beneficial effect on axial symptoms or signs is unlikely.

6. We strongly recommend the use of biological DMARDs (bDMARDs) in patients with active disease who have failed treatment with 2 different NSAIDs (Vote 86% agreement; grade of evidence moderate).

Supporting statements

- The definition of active disease is considered to be BASDAI ≥4 or Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP ≥2.1, especially in those with elevated CRP or active inflammation on MRI (Not graded).
- The evidence shows that bDMARD therapy is effective in achieving good disease control in the long term, with a reduction in complications, for patients with axial SpA (Not graded).

The MAXIMA survey of management practices, which involved rheumatologists from around the globe (including the Asia-Pacific region), reported that clinicians typically prescribed a round of 1-2 NSAIDs before switching drug classes.[53] Additionally, from a survey of rheumatology outpatient clinics, which also included clinics in Asia, elevated indices of disease activity were observed in patients, suggesting suboptimal disease control potentially necessitating a re-assessment of therapy options. The mean BASDAI was 4.44 ± 2.24, and the mean ASDAS-CRP was 2.81 ± 1.19 for patients treated for chronic low back pain and diagnosed as having axial SpA (n = 686).[10]

Following the 2016 ASAS/EULAR recommendation, consensus was formed around a recommendation to use bDMARDS as next-line therapy following failed treatment with at least 2 NSAIDs[19] for at least 4 to 6 weeks. Specifically, their use is recommended for active disease, defined by using the measures of BASDAI and ASDAS-CRP. The latter was cited by ASAS/EULAR as having a good correlation with both patients' and clinicians' assessments of disease activity.[19]

Moderate- to high-quality evidence for effectiveness of bDMARDs was found for five tumor necrosis factor inhibitor (TNFi) therapies (infliximab, etanercept, adalimumab, golimumab, and certolizumab) in major randomized, placebo-controlled trials.[73,74] Across 16 studies with sample sizes of 44 to 566 participants, biologic therapies were significantly more effective than placebo and resulted in improvements in BASDAI, CRP, ASAS, health status, BASMI and BASFI. Significantly more patients achieved ASAS40 responses (66.9% aggregate).[73,74] There were no head-to-head comparisons between different biologic agents. There were no safety concerns, and adverse events were similar in both the treatment and placebo groups.

Cross-over designs meant that RCT data were mostly limited to short-term efficacy and follow-up of up to 6 months. Long-term follow-up was available for seven major studies, in cohorts of 16-255 patients, for all biologics except secukinumab.[85,86] Follow-up periods varied from 96 weeks to 8 years. Overall, in long-term follow-up studies, between ~50% and 70% of patients were able to remain on an anti-TNF therapy for 5-8 years. Infliximab had the longest follow-up and lowest retention.[85] Sustained response to therapy was seen in approximately 2/3 of patients over these long periods of follow up. Serious adverse events were rare, with the most common being infections. Etanercept was associated with more cases of recurrent uveitis.[86]

7. We conditionally recommend, prior to starting bDMARD, to screen for tuberculosis (TB), hepatitis B virus (HBV), HCV and human immunodeficiency virus (HIV) (in high-risk populations). Treatment for latent TB (according to local guidelines) and pre-emptive therapy for chronic HBV infection are also conditionally recommended (Vote 86% agreement; grade of evidence very low).

Supporting statement

- Liver function tests, HB surface antigen (HBsAg), anti-HBc (core), and anti-HBs should be performed prior to starting bDMARD therapy. Patients with occult HBV infection should have HBV viral DNA load monitored regularly every 6-12 months. For patients with chronic active HB infection, consultation with appropriate specialists for antiviral therapy is recommended prior to targeted therapy (Not graded).

Infectious diseases such as TB, HBV and HCV infections, and HIV/acquired immunodeficiency syndrome (AIDS), are endemic to the Asia-Pacific region. Many Asian countries are currently regarded as "high-burden" for TB;[92] HBV and HCV continue to be major contributors to mortality and overall disease burden in these countries,[93] and the region is second only to Africa in terms of number of people living with HIV.[94] Given the high prevalence of these infectious diseases in the region, and the concern for risk of infection with DMARDs, the group considered it imperative to review the evidence on infections in the DMARD-receiving population. Notably, the majority of studies reviewed were focused on non-Asian subjects; clinical studies in Asian patients are warranted.

A recent meta-analysis evaluating the safety profile of TNFi included 19 RCTs involving 8320 patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or AS.[95] The occurrence of TB was reported as 0.6% in the treatment groups (32 events in 5339 patients), while no event was reported in the control groups (2981 patients). Exposure to TNFi was associated with a statistically significant threefold increase in the risk of TB (odds ratio [OR] 3.29, 95% CI 1.48-7.33). Subgroup analysis by the type of TNFi did not reveal any difference among the drug-specific effect estimates, but the study authors acknowledged the low power of this analysis, and suggested that clinically important differences among TNFi may exist. Our group concluded that, because TNFi significantly increases the risk of TB, screening for TB should be implemented before starting anti-TNF therapy.

Another recent meta-analysis reviewed 63 long-term extension studies on RA, AS, PsA, and other immune-mediated diseases. TB incidence ratio (IR) was reported after various treatments (all 5 TNFi, abatacept, ustekinumab, tofacitinib, rituximab and csDMARDs).[96] TB IR was higher in RA patients treated with anti-TNF monoclonal antibodies (307.71; 95% CI 184.79- 454.93) than in those treated with etanercept (67.58; 95% CI 12.1-163.94), and higher in pooled AS, PsA and psoriasis patients (122.4; 95% CI 34.2-264.9) versus etanercept (60.01; 95% CI 3.6-184.79). The TB IR was higher in high-background TB areas. Because observational studies and clinical trials demonstrated the benefit of the treatment of latent TB infection (LTBI),[97,98] the group recommends screening for LTBI in the Asia-Pacific region.

In three studies conducted in Asian rheumatic patients with a prior HBV infection (HBsAg-negative/anti-HBc-positive, undetectable serum HBV DNA), HBV DNA reactivation was reported in 2.2%-5.2% of cases after bDMARDs or csDMARDs.[100,101] In addition, a study conducted in 88 rheumatologic patients with a prior HBV infection treated with TNF-alpha blockers, using evaluation of aminotransferases as a surrogate marker of HBV reactivation, suggested that the therapy can induce HBV reactivation.[103] Because HBV prevalence is higher in Asian populations, and they have higher odds of elevated liver function test results in previously resolved HBV infection than in patients without histories of HBV

infection, HBV screening is recommended. We further recommend regular monitoring of HBV viral DNA load (every 6-12 months) for patients with occult HBV infection. If HBV-DNA is detectable at baseline or at any stage and the use of TNFi is deemed necessary, the group recommends treatment with anti-viral agents.[104,105]

Similar to HB infection, reactivations of HCV have also been reported, although the reactivation rate varies. Two reviews concluded that TNFi (infliximab, etanercept and adalimumab) posed minimal risks for viral reactivation among patients with immune-mediated diseases (RA, PsA).[106,107] In the 174 HCV-positive patients, only seven cases of HCV reactivation (4.02%) were found after initiation of TNFi. However, the possibility of HCV reactivation could not be ruled out. Until more data from long-term studies become available, caution should be exercised and patients should be screened for HCV before commencing bDMARDs.[108,109]

A systematic review identified 17 case series/case reports of HIV-infected individuals receiving bDMARDs for inflammatory diseases. Biologic treatments included rituximab, etanercept, adalimumab, alefacept, infliximab and ustekinumab. Two cases developed advanced HIV infection with CD4+ T-cell counts ≤50 cells/μL, and four cases developed infectious complications. Due to the very small case numbers, a firm conclusion was not possible regarding the efficacy and safety of biologic agents in HIV-infected individuals.[110] A clear long-term association between the use of bDMARDs and HIV infection is lacking. It is currently not feasible to exclude the possibility of HIV reactivation and infectious complication in patients treated with biologics; therefore, screening for HIV is recommended.

8. We strongly recommend using a TNF inhibitor as the initial bDMARD treatment (Vote 100% agreement; grade of evidence very low).

Supporting statements

- The choice of TNF inhibitor may be influenced by availability, cost, mode of delivery and patient preference (Not graded).
- Secukinumab is a suitable alternative if TNF inhibitors are contraindicated or unavailable, except in the setting of concomitant inflammatory bowel disease (Not graded).

The effectiveness of bDMARDs (TNFi and secukinumab) in axial SpA that have failed NSAID treatment has been already discussed. Head-to-head data exists for infliximab versus etanercept for AS from a 2-year, open-label, randomized study, which may help inform clinicians on which bDMARD to use. However, the study found no differences between groups in point estimates of BASDAI or BASFI at 2 years (no CIs reported). The study was judged as having high risk of bias, further suggesting no difference in efficacy.[111]

No head-to-head data comparing other TNFi, or TNFi versus other bDMARDs with different targets, were found. Indirect analyses have not suggested a difference in efficacy within the TNFi class[112,113] or between TNFi and secukinumab in AS.[115] There are no comparative data for interventions with other mechanisms of action, including the Janus-activated kinase inhibitors, despite preliminary evidence for the efficacy of tofacitinib.[116] Existing RCT data do not provide evidence for the efficacy of therapies that target the interleukin (IL)-23 pathway in axial SpA.[117,118]

Efficacy data from RCTs for TNFi versus placebo exist for nr-axial SpA but currently there are no comparative data. An indirect comparison did not find any difference in efficacy between TNFi.[119]

With the current evidence for the effectiveness of TNFi, especially for continued use over several years, the group recommends this class of drugs be used in preference as a first-line bDMARD. The choice of TNFi will depend on factors such as accessibility to the drug – especially in the Asia-Pacific region where reimbursement options vary across countries – and patient preferences.[120] The novel bDMARD secukinumab, an IL-17A inhibitor, may be an alternative in patients with a contraindication to TNFi.[121] Adverse events in Crohn's disease are common with secukinumab,[122] so it is not advised for use in axial SpA with IBD.

9. We conditionally recommend using TNFi monoclonal antibodies over fusion protein in patients with features beyond arthritis and enthesitis, such as concomitant IBD, recurrent anterior uveitis, and psoriasis (Vote 100%; grade of evidence low).

Supporting statements

- For patients with psoriasis, secukinumab may be preferred (Not graded).
- The concomitant use of csDMARD with TNFi in patients with axial SpA does not increase clinical effectiveness and is thus, not recommended (Not graded).
- In patients who do not respond to a TNFi, especially if they have peripheral arthritis, concomitant csDMARD may be considered (Not graded).

Results from mixed-quality evidence (clinical trials and meta-analyses) suggest that lower rates of uveitis flares in AS were associated with adalimumab, infliximab and certolizumab use versus use of etanercept.[78,123,124] For IBD, a pooled analysis of results from seven placebo-controlled trials and two open-label studies showed a lower IR of IBD for infliximab and adalimumab versus etanercept.[129] Infliximab, adalimumab and etanercept were evaluated in 3 RCTs in patients with axial SpA and PsA.[130,131] Infliximab and adalimumab improved skin and joint manifestations compared to placebo over a follow-up of 24-52 weeks. Infliximab showed a rapid and significantly higher level of efficacy until week 24 compared to etanercept, but long-term data showed no significant differences between both groups at week 48.

The group included a conditional recommendation for use of monoclonal antibodies in management of features beyond arthritis and enthesitis in axial SpA, because the overall quality of evidence was graded as low. The choice to use monoclonal antibodies for these features will require a discussion of the individual patient's

condition. Secukinumab has efficacy in psoriasis treatment[133] and may be preferred for axial SpA with psoriasis.

Three RCTs showed that the addition of csDMARDs to infliximab did not increase the clinical effectiveness in patients with axial SpA compared to infliximab alone, as measured by ASAS20, ASAS40, BASDAI, and BASFI.[65,134,135] Other studies also did not show any significant differences in clinical responses between use of csDMARD with TNFi compared to TNFi alone.[136,137] As discussed earlier for recommendation 5, csDMARDs may be considered with TNFi when peripheral arthritis is present.

10. In adults with persistent active axial SpA despite an adequate trial of the first TNFi for at least 12 weeks, we conditionally recommend treatment with another TNFi or secukinumab (Vote 100% agreement; grade of evidence very low).

Based on guidelines from ASAS/EULAR, ACR/SPARTAN/SAA and the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada, switching to another TNFi should be considered after initial TNFi failure.[18,19,138] ASAS/EULAR and this working group considered the evidence from an RCT that showed secukinumab to be superior to placebo in improving ASAS20 in TNFi-intolerant patients.[139,140] Overall very low-quality evidence as cited by the guidelines led to the present conditional recommendation by the panel. Various potential durations for an "adequate trial" were proffered and discussed before consensus was formed for a period of at least 12 weeks, that is, the standard duration of clinical trials assessing TNFi efficacy.

11. We conditionally recommend continuing bDMARD therapy in patients who respond well to treatment, but a reduced dose or increased interval may be considered in patients in sustained remission (Vote 100% agreement; grade of evidence low).

Three observational studies showed that discontinuation of TNFi led to flares in most of the patients with early axial SpA or AS.[69,141,142] When the drug is continued but with a reduced dose, remission can be maintained: a small RCT showed that patients remained in remission even with a reduced dose of etanercept (50 mg every other week or 50 mg weekly).[143] Another study showed that etanercept 25 mg weekly was less effective at maintaining treatment response in the step-down phase, although about half of the patients maintained treatment response with this dose.[144] The panel debated the definition of "sustained remission", after noting marked heterogeneity in trials where some included patients who were in remission for only a few months and others as long as 3 years. Given that there is no clear definition of "sustained remission" in widespread use and the overall quality of evidence is poor, the treating clinician should consider reduction of dose or increase of dosing interval after discussion with the patient.

12. Special situations. (a) For patients with axial SpA in whom disease cannot otherwise be controlled, we conditionally recommend continuing TNFi throughout pregnancy. (b) While biologics can be used in renal failure, caution is advised and treatment considered on a case-to-case basis (Vote 100% agreement; grade of evidence very low).

Supporting statement

- There is no evidence of an increased risk of malignancy in patients receiving long-term biologic therapy, particularly TNFi. However, caution is advised in populations at high risk of skin cancers (Not graded).

There are some concerns on the use of TNFi and biologics for axial SpA with some concomitant conditions. Most of the data on pregnancy and lactation were related to TNFi use (1 for tofaticinib) from observational studies.[145,146] Large monoclonal antibodies do not cross the placenta in the first trimester, as they rely on active transport across placenta via Fc receptors on trophoblasts which only develop by week 14.[145] Certolizumab lacks an Fc receptor and therefore has a theoretical advantage as it does not cross the placenta; therefore it could be safe to use beyond week 14. Although the number of live births was reduced in those patients who had received TNFi, more patients in this group had opted for termination of pregnancy. TNFi was detected in breast milk, but long-term adverse outcomes on the child are unknown.

Malignancy rates (all cancers, excluding non-melanoma skin cancers) were evaluated in both randomized controlled trials and observational studies.[73,76,78,79,83,116,121,161,162] Although there was no evidence of increased malignancy in the randomized trials, exclusion criteria were strict, and follow-up was of short duration.[73,76,79,83,116,121,161-163] Two large observational studies of patients with SpA did not suggest increased malignancy risk with patients on TNFi.[164,165]

Data on the use of biologics in renal failure are limited. However, antibodies are not excreted by the kidney. No adverse events were noted in case reports on the use of TNFi in end-stage renal failure patients with SpA.[167,168] In addition, several case reports of chronic inflammatory or rheumatic diseases described use of tofacitinib and ustekinumab in renal failure without any adverse events.[172,173]

The panel judged the overall quality of evidence to be very low. Thus, the members agreed that the use of TNFi in special situations such as pregnancy, lactation, renal failure and in those with a history of previous malignancy, should be cautiously undertaken and individualized for each case.

13. We strongly recommend reviewing the vaccination status of patients with axial SpA, following local guidelines (Vote 93% agreement; not graded).

Supporting statements

- Vaccination should be undertaken prior to initiating bDMARD (Not graded).
- During bDMARD therapy, live attenuated vaccines are contraindicated. Pneumococcal and influenza vaccines are recommended.

Vaccines for HBV, human papilloma virus (HPV) and meningococcal infections are conditionally recommended (Not graded).

There is some concern about the host immune response post-vaccination for patients with an immunosuppressive disease or who will potentially need medication that may compromise the immune response, such as bDMARDs. The question of vaccination in patients with axial SpA was not directly addressed by individual studies. Available evidence came from reviews and guidelines for patients with autoimmune inflammatory rheumatic disease (eg systemic lupus erythematosus and RA).[177,178] After reviewing the guidelines, the working group agreed that generally, inactivated vaccines are safe and do not exacerbate the underlying rheumatic disease. Live vaccination is a contraindication in the immunosuppressed host and should not be undertaken with bDMARD therapy.[179,180] Pneumococcal and influenza vaccination humoral response was not changed in patients on bDMARD therapy;[177] thus these are recommended by the working group for patients with axial SpA. HBV, HPV and meningococcal vaccines should be considered according to the patient's risk of infection and clinical status.[177,180] In concordance with available guidelines, the group recommends that vaccination status should be assessed in the initial work-up of patients with axial SpA, according to each country's national guidelines.

14. We conditionally recommend total hip arthroplasty in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal corrective osteotomy may be considered in patients with severe disabling deformity (Vote 100% agreement; grade of evidence very low).

The evidence for this statement was derived from 1 observational study and 7 case series. The observational study addressed total range of motion (ROM) in metal-on-metal resurfacing (n = 38) compared with total hip arthroplasty (THA); no true placebo or non-surgical control groups were included. The THA group (n = 25 patients, 41 hips) followed for a mean of 2.9 years demonstrated a mean Harris Hip Score (HHS) improvement of 39.4, pain score improvement of 3.12, and 113 degree total ROM improvement compared with baseline.[181] Seven case series (n = 275 patients, 474 hips) followed for a median of 7.4 years demonstrated a median HHS improvement of 55 points (5 studies). ROM improvements were substantial across studies, but reported differently, preventing aggregation of results.[181,182] Only 2 studies reported verifying the diagnosis of AS according to current criteria. Results were described as 65%-85% "good/excellent" in two studies.

ACR/SPARTAN/SAA and ASAS/EULAR have recommended surgery for hip involvement that severely impacts mobility and quality of life. They further recommended surgical consultation in patients with refractory pain or disability and radiographic evidence of structural damage, based on low-quality evidence from observational studies and case series.[18,19] The working group agreed that lack of high-quality evidence was not necessarily evidence of lack of efficacy, and decided to provide a recommendation that echoed current guidelines. The group's discussions emphasized the importance of routine assessment of spinal compression fractures; and that if a patient with axial SpA were to undergo a surgical procedure, optimum preoperative care should include temporary discontinuation of biologic therapy.

4 | DISCUSSION

Representing 15 countries from the Asia-Pacific region, the members of the recommendations working group aimed to provide practical guidance to all clinicians working with patients with axial SpA. Insights and practice points from the individual members enabled the working group to identify the region's clinically important questions in the treatment of patients with axial SpA. The panel decided to focus on general principles of treatment, and elected not to cover diagnosis, treatment of peripheral SpA, and treatment of complications. The final scope of the resulting recommendations included non-pharmacological management (exercise, physical therapy, smoking cessation), pharmacological treatment (NSAIDs, corticosteroids, csDMARDs, bDMARDs), issues that may affect axial SpA treatment (concomitant medical conditions, risk of malignancy, vaccination) and surgical treatment.

4.1 | Use of the GRADE approach

The group used the GRADE approach to make judgements about the quality of evidence found via the literature search and to determine the strength of each final recommendation. The GRADE approach is now the international standard for assessing the quality of evidence and strength of recommendations of clinical practice guidelines (CPGs). GRADE was initially developed by an international panel of methodologists who considered clinical questions on diagnosis, screening, prevention, and therapy, making it applicable for use in a wide range of health-related fields. The GRADE approach provides a systematic process of evaluating evidence, requiring the reviewer to explicitly state his or her judgment on the quality of evidence for each outcome critical to decision-making. The GRADE approach also explicitly incorporates the quality of evidence, the balance between benefit, harm and costs, and values and preferences in the final recommendations.

Through the GRADE method, the panel reviewed the evidence across studies and developed summary-of-evidence tables. These tables proved invaluable to members of the working group, who referred to them during discussions and while drafting and refining recommendations.

4.2 | Expert guidance on issues for which evidence is lacking

Some clinical questions were not directly addressed because relevant evidence to inform a strong recommendation were not identified, including questions on the use of csDMARDs, adjustment or tailoring of NSAID and bDMARD treatment, vaccination, and surgery. Rather than forego stating a recommendation, the working group recognized the need for practical guidance in these clinical situations. Recommendations were proposed by consensus, to

provide reasonable advice on therapy. Areas where current evidence is lacking may be addressed in future updates to this consensus document as new information and new therapies become available. The group deems these topics to be important foci of future research, and enjoins APLAR to consider devoting resources to generating evidence-based answers to these research questions.

4.3 | Treatment-access considerations

In the Asia-Pacific region, there are some differences in genetic predisposition, disease subtypes and clinical features of SpA associated with certain ethnicities;[189,190] nonetheless, in general, clinical features, HLA-B27 association and management of SpA are similar comparing Asia and other regions of the world.[53,192,193] Asian physicians regard non-pharmacological management such as physical therapy as important as pharmacological treatment, the cornerstone of which is NSAIDs.[193] Importantly, the use of TNFi, which have been reported to be effective in Asians, mainly in studies of Chinese patients,[194,195] is increasing with the availability of cheaper biosimilar TNFi. However, the high cost of branded and (even less costly) biosimilar TNFi make them relatively inaccessible to many patients in the region, compelling clinicians to utilize less expensive alternatives.[189,192,193,197] Recommendations 4 (on short-term use of corticosteroids) and 5 (on use of csDMARDs) were formulated in recognition of treatment-access limitations in the many resource-poor settings across the region.

4.4 | Soliciting patient feedback

Important to the optimal management of axial SpA is the patient-clinician partnership. The group plans to obtain patients' perspectives on these recommendations through the methodology employed by Dr Andrew Harrison and colleagues for the Patient Opinion Real-Time Anonymous Liaison System (PORTAL) project for RA.[198] The PORTAL project was set up in 2014; it deployed multiple short, patient-directed surveys to elicit patients' values and preferences in relation to RA management. The group will utilize this approach for axial SpA, to include contributions of patients from the Asia-Pacific for future updates of these recommendations.

5 | CONCLUSION

This document provides an up-to-date guide for treatment of axial SpA to meet the needs of patients and clinicians in the Asia-Pacific region. Clinicians implementing these current recommendations will need to consider both the individual needs and values of their patients, and the differences in each country's practice setting.

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CONFLICTS OF INTEREST

LST has received research grants and/or served as member of advisory boards and speaker bureaus of AbbVie, Eli Lilly, Celltrion, Janssen, Novartis, Pfizer, Roche and Sanofi. JCCW has received research grants or consultation fees from AbbVie, BMS, Celgene, Chugai, Eisai, Janssen, Novartis, Pfizer, Sanofi-Aventis, TSH Taiwan and UCB. HJB has received consulting and/or speaker fees from Novartis, AbbVie, Astellas, JW and Pfizer, and unrestricted research grants from Celltrion and Hanlim, and has been a participant in clinical trials of Eli Lilly, Celltrion, LG Chem, Yungin, Sanofi-Aventis, Janssen, Novartis, Centocor, AbbVie, Celgene and Pfizer. PC is a member of advisory boards for Novartis and Pfizer. NH has received honoraria from, and/or is on the speaker bureaus of AbbVie, Tanabe Mitsubishi Pharm, Takeda Pharm, Ayumi Pharm, Ono Pharm, Chugai Pharm and Asahi Kasei Pharm. MK has received honoraria from, and/or is on the speaker bureaus of AbbVie, Tanabe Mitsubishi Pharm, Ayumi Pharm, Ono Pharm, Chugai Pharm, Novartis and Eli Lilly. SS has received educational grants from AbbVie and Pfizer, and speaker's honoraria from AbbVie and Janssen. SSY is a member of advisory boards for Novartis and Eli Lilly. CSL is a member of the Janssen CollAboRatE Coalition and a consultant for UCB. AA, PPC, LD, JG, HMR, SS and SW report no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of the manuscript. All authors were involved in formulating the research questions that framed the literature search, as well as in the literature search proper and GRADE assessments. All authors were responsible for drafting of the manuscript and participated in revising it critically for intellectual content. All authors gave the final approval of the version to be published and agree to be accountable for all aspects of the work. LST and JCCW contributed equally.

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