Title

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Journal

Arthritis Care & Research, 71(10)

ISSN

2151-464X

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Publication Date

2019-10-01

DOI

10.1002/acr.24025

Peer reviewed

HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2020 October 01.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2019 October ; 71(10): 1285–1299. doi:10.1002/acr.24025.

2019 Update of the American College of Rheumatology/ Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis

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Abstract

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Financial Conflict: Forms submitted as required.

IRB approval: This study did not involve human subjects and, therefore, approval from Human Studies Committees was not required.

ADDITIONAL DISCLOSURE

Dr. Majithia had no conflicts of interest during the time of guideline development, but just before publication became the site principal investigator for clinical trials for systemic lupus erythematosus by Bristol-Myers Squibb and Janssen. Dr. Wang had no conflicts of interest during the time of guideline development, but before publication became a consultant for Novartis, as well as a member of the medical education advisory board for Eli Lilly.

Objective: To update evidence-based recommendations for the treatment of patients with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA).

Methods: We conducted updated systematic literature reviews for 20 clinical questions on pharmacological treatment addressed in the 2015 guidelines, and for 26 new questions on pharmacological treatment, treat-to-target strategy, and use of imaging. New questions addressed the use of secukinumab, ixekizumab, tofacitinib, tumor necrosis factor inhibitor (TNFi) biosimilars, and biologic tapering/discontinuation, among others. We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method to assess the quality of evidence and formulate recommendations, and required at least 70% agreement among the voting panel.

Results: Recommendations for AS and nr-axSpA are similar. TNFi are recommended over secukinumab or ixekizumab as the first biologic to be used. Secukinumab or ixekizumab is recommended over use of a second TNFi in patients with primary non-response to the first TNFi. TNFi, secukinumab, and ixekizumab are favored over tofacitinib. Co-administration of low-dose methotrexate with TNFi is not recommended, nor is a strict treat-to-target strategy or discontinuation or tapering of biologics in patients with stable disease. Sulfasalazine is recommended only for persistent peripheral arthritis when TNFi are contraindicated. For patients with unclear disease activity, spine or pelvis magnetic resonance imaging could aid assessment. Routine monitoring of radiographic changes with serial spine radiographs is not recommended.

Conclusion: These recommendations provide updated guidance regarding use of new medications and axial imaging in the management of patients with AS and nr-axSpA.

Keywords

Axial spondyloarthritis; ankylosing spondylitis; non-radiographic axial spondyloarthritis; nonsteroidal anti-inflammatory drugs; tumor necrosis factor inhibitors; interleukin-17 inhibitors; biologics; biosimilars

INTRODUCTION

Axial spondyloarthritis (axSpA), comprised of ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA), is the main form of chronic inflammatory arthritis affecting the axial skeleton [1]. AS affects 0.1–0.5% of the population, and is characterized by inflammatory back pain, radiographic sacroiliitis, excess spinal bone formation, and a high prevalence of HLA-B27 [2,3]. While nr-axSpA shares several features with AS, advanced sacroiliac joint damage and spine ankylosis are absent [4]. The severity of arthralgia, stiffness, and limited flexibility varies widely among patients and over the course of axSpA. Skeletal disease may be accompanied by uveitis, psoriasis, and inflammatory bowel disease (IBD). AxSpA can impose substantial physical and social burdens on patients, and can interfere with work and schooling [5,6]. The goals of treatment are to alleviate symptoms, improve functioning, maintain work ability, decrease disease complications, and forestall skeletal damage as much as possible.

In 2015, the American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN)

published recommendations for the treatment of adults with AS and nr-axSpA [7]. Recommendations were provided for pharmacological treatment, rehabilitation, use of surgery, management of selected comorbidities, disease monitoring, patient education, and preventive care. The recommendations were tailored to patients with either active or stable disease, and focused on the most common decisions confronting clinicians when treating these patients.

The advent of new medications to treat axSpA warranted this update. We did not re-examine all of the 2015 recommendations, but rather focused on those questions for which consequential new evidence was present. We added several new recommendations on how the newly available medications should fit in treatment strategies, and on the use of imaging. The target populations are adults with AS or nr-axSpA. The target users of these recommendations are rheumatologists, primary care clinicians, physiatrists, physical therapists, and others providing care to patients with axSpA.

METHODS

These recommendations followed ACR and GRADE methodology, as described in Supplementary Appendix 1 [8,9]. Briefly, systemic literature reviews were done for pre-specified clinical Patient-Intervention-Comparator-Outcome (PICO) questions. The resulting evidence was reviewed, and recommendations formulated and voted on, by an expert voting panel. Key definitions, including for active and stable disease, are provided in Table 1. Clinical trials of ixekizumab became available during the time the manuscript was in preparation, after the voting panel had met [10,11]. The data from these trials was provided to the voting panel, and revised recommendations that included ixekizumab were reviewed and voted on by the panel.

RESULTS

Here we present the recommendations that were reviewed in this update, whether a new recommendation (designated “new”) or reevaluation of an existing recommendation. Tables 2 and 3 provide all current recommendations, including those from the 2015 report that were not newly reviewed. The order of recommendations here does not imply priority for use or recommended sequencing of different interventions. PICO numbers following each recommendation can be used to locate related evidence in Supplemental Appendix 6.

A. Recommendations for the Treatment of Patients with Active AS.

In adults with active AS, we conditionally recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs (*PICO 1*).—The efficacy of NSAIDs for symptom improvement in active AS has been established in many controlled trials. Evidence that continuous NSAID use results in less spinal fusion on radiographs over two years compared to on-demand use is inconsistent, with one trial of celecoxib suggesting less progression with continuous use, and one trial of diclofenac indicating no difference in progression (Supplementary Appendix 6)[12,13]. Despite the uncertainty regarding potential disease-modifying effects, the committee conditionally favored continuous use of NSAIDs in patients with active AS, primarily for controlling disease activity. The decision to use

NSAIDs continuously may vary depending on the severity of symptoms, patient preferences, and comorbidities, particularly gastrointestinal, kidney, and cardiovascular disease.

In adults with active AS despite treatment with NSAIDs: we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications (new; *PICO 7*). Sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNFi are not available.—Treatment with sulfasalazine is recommended primarily for patients with prominent peripheral arthritis and few or no axial symptoms. However, TNFi may provide a better option for these patients. Evidence for the efficacy of sulfasalazine is based on eight older controlled trials which reported benefit for peripheral arthritis (Supplementary Appendix 6). Although a recent placebo-controlled trial of sulfasalazine reported improvement in axial symptoms, and modest clinical and imaging responses were seen in a second trial, the preponderance of evidence indicates that sulfasalazine has little benefit for axial symptoms [14,15]. Sulfasalazine may have a role in treating patients who have contraindications to TNFi, those who decline treatment with TNFi, or those with limited access to TNFi.

Three negative trials of methotrexate tested doses of 10mg or less weekly, and the lack of benefit may reflect the low doses used [16–18]. One uncontrolled study of methotrexate 20mg weekly reported no improvement in axial symptoms, but a decrease in swollen joint count [19]. Treatment with methotrexate may be considered for patients with predominately peripheral arthritis, although among non-biologics, there is more evidence supporting the use of sulfasalazine.

A phase II study of tofacitinib showed benefit in both clinical and imaging outcomes of axial disease over 12 weeks [20]. Use of tofacitinib could be another option, although the results of phase III trials are not available.

Leflunomide, apremilast, thalidomide, and pamidronate are not recommended (Supplementary Appendix 6).

In adults with active AS despite treatment with NSAIDs: we strongly recommend treatment with TNFi over no treatment with TNFi (*PICO 6*); we do not recommend any particular TNFi as the preferred choice (*PICO 5*).—The efficacy of TNFi in patients with active AS has been demonstrated in 24 randomized controlled trials, most of which were short-term (6 months or shorter) placebo-controlled studies. Improvements were shown in patient-reported outcomes, composite response criteria, and spine and sacroiliac inflammation on magnetic resonance imaging (MRI) (Supplementary Appendix 6). The panel judged that the evidence justified a strong recommendation for use of TNFi, in patients whose AS remained active despite treatment with NSAIDs. The panel recommended that lack of response (or intolerance) to at least two different NSAIDs at maximal doses over one month, or incomplete responses to at least two different NSAIDs over two months, would be adequate trials with which to judge NSAID responsiveness prior to escalating to treatment with TNFi.

Indirect comparisons in network meta-analyses of clinical trials have not reported clinically meaningful differences in short-term efficacy among TNFi in the treatment of active AS (Supplementary Appendix 6)[21]. Direct comparisons among these medications are limited to a trial of infliximab versus its biosimilar, and a very small open-label trial of infliximab versus etanercept [22,23]. The panel judged that the evidence did not support preference of one TNFi over any other for the typical patient. Important exceptions apply to patients with recurrent uveitis or coexistent IBD (see PICO 29 and 32 below). Patients treated with infliximab may have increased risks of tuberculosis and of infections generally [24,25]. TNFi other than infliximab should be considered for patients at higher risk of tuberculosis exposure (either through travel or household contacts) or with a history of recurrent infections. Patient preferences regarding the frequency of dosing and route of administration should be weighed when selecting a specific TNFi.

In adults with active AS despite treatment with NSAIDs: we strongly recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab (new; *PICO 58*); we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab (new; *PICO 59*); we conditionally recommend treatment with TNFi over treatment with tofacitinib (new; PICO 60). we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib (new; *PICO 61)*.—Use of secukinumab and ixekizumab in patients with active AS is supported by data from large placebo-controlled trials (Supplementary Appendix 6). The panel recommended use of TNFi over secukinumab or ixekizumab based on greater experience with TNFi and familiarity with their long-term safety and toxicity. Similarly, the panel judged that TNFi, secukinumab or ixekizumab should be used over tofacitinib, given their larger evidence base. In patients with coexisting ulcerative colitis, if treatment with TNFi is not an option, tofacitinib should be considered over secukinumab or ixekizumab. IL-17 inhibitors have not been shown to be efficacious in inflammatory bowel disease, while tofacitinib is an approved treatment for ulcerative colitis [26,27].

In adults with active AS despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib (new; *PICO 8*).—No studies have directly compared the risks and benefits of treatment alternatives in patients who have contraindications to treatment with TNFi. The panel favored treatment with secukinumab or ixekizumab over treatment with sulfasalazine or methotrexate based on a higher likelihood of benefit, but this recommendation was conditional on the specific contraindication. If the contraindication to TNFi use was the presence of congestive heart failure or demyelinating disease, secukinumab or ixekizumab was preferred, since these medications have not been shown to worsen these conditions. If the contraindication to TNFi use was tuberculosis, other chronic infection, or high risk of recurrent infections, sulfasalazine was preferred over secukinumab, izekizumab, and tofacitinib. In these cases, efforts to mitigate the infectious contraindications should be undertaken so that TNFi might safely be used. Treatment with rituximab, abatacept,

ustekinumab, or interleukin-6 inhibitors is not recommended, even in patients with contraindications to TNFi, due to lack of effectiveness.

In adults with active AS despite treatment with the first TNFi used: we conditionally recommend treatment with secukinumab or ixekizumab over treatment with a different TNFi in patients with primary non-response to TNFi (new; *PICO 10*); we conditionally recommend treatment with a different TNFi over treatment with a non-TNFi biologic in patients with secondary non-response to TNFi (new; *PICO 10*); we strongly recommend against switching to treatment with a biosimilar of the first TNFi (new; *PICO 62*); we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of switching to a new biologic (*PICO 9*).—Direct comparisons of treatment strategies for patients who do not have or sustain adequate responses to their first TNFi have not been reported, and the recommendations are based on the panel's consideration of indirect comparisons among the available treatment options (Supplementary Appendix 6). Data from observational studies suggest that 25–40% of patients who switch from one TNFi to another will have a meaningful response (e.g. 50% improvement in Bath AS Disease Activity Index) to the second TNFi [28–30]. However, not all patients in these studies switched TNFi because of ineffectiveness.

The panel judged that treatment should differ for patients who had a primary non-response to TNFi and those with secondary non-response to TNFi. Switching to secukinumab or ixekizumab was recommended in most patients who had a primary non-response to the first TNFi, under the assumption that TNF was not the key inflammatory mediator in these patients. Continuing treatment with the first TNFi could be considered if additional time was believed important to assess the response fully, or if a higher dose or shorter dosing interval was thought to be beneficial.

In patients who relapse after an initial response (i.e. secondary non-response), the panel judged that treatment with a different TNFi held a reasonable prospect of benefit and should be used in most patients, rather than immediately switching to a different class of biologics. Although ixekizumab is efficacious among TNFi non-responders, trials have not directly compared responses to ixekizumab (or secukinumab) to responses to a second TNFi in patients with a secondary non-response to the first TNFi [11]. Given that options for biologics are limited, treatment with a second TNFi was recommended in these patients.

In cases of non-response (primary or secondary), the panel recommended against switching to the biosimilar of the first TNFi (e.g., switching from originator infliximab to infliximab-dyyb), as the clinical response would not be expected to be different. The panel also recommended against the addition of sulfasalazine or methotrexate to TNFi in cases of non-response to TNFi, judging any benefit would likely be marginal. Addition of sulfasalazine could be considered in the rare patient whose axial symptoms are well-controlled on TNFi but who has active peripheral arthritis.

In adults with either active or stable AS on treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate

(new; *PICO 64*).—In rheumatoid arthritis, the likelihood of TNFi discontinuation is lower among patients who receive co-treatment with methotrexate, perhaps by reducing the development of anti-drug antibodies [31]. In AS, it is less clear if the duration of TNFi use, and by inference their effectiveness, is similarly prolonged [32]. Data from observational studies are conflicting, although some studies, primarily of infliximab, reported longer TNFi treatment when methotrexate was co-administered (Supplementary Appendix 6). Clinical responses were not larger among patients who received co-treatment with methotrexate. In the absence of convincing evidence of benefit, and due to greater burden for patients, the panel recommended against routine co-administration of methotrexate with TNFi, although its use could be considered in patients treated with infliximab.

B. Recommendations for the Treatment of Patients with Stable AS.

In adults with stable AS, we conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs (*PICO 1*).—This recommendation applies to patients who have been stable on no pharmacological treatment. In this group, the panel considered the potential toxicities of continuous NSAID treatment outweighed the uncertain benefit of less radiographic progression. On-demand treatment should be considered for short-term symptom recurrences (flares).

In adults with stable AS receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone over continuing both medications (*PICO 11*). In adults with stable AS receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing both medications (*PICO 12*).—No new studies directly compared outcomes between patients who continued combination treatment and those who discontinued either NSAIDs or a conventional synthetic antirheumatic drug (csARD). The NSAID-sparing potential of etanercept was demonstrated in a recent trial [33]. The panel judged these recommendations primarily based on symptom control, rather than on any potential effect of combination therapy on future spine fusion. In stable patients, a trial of withdrawing either NSAIDs or the csARD should be considered, due to the likelihood of greater toxicity with the chronic use of more than one medication. However, on-demand NSAIDs for control of intermittent symptoms is recommended for patients with good responses to previous NSAID courses.

In adults with stable AS on treatment with a biologic: we conditionally recommend against discontinuation of the biologic (new; *PICO 66)*; we conditionally recommend against tapering of the biologic dose as a standard approach (new; *PICO 65*).—Data from several observational studies suggest that discontinuation of TNFi after achieving either remission or low disease activity results in relapses in 60–74% of patients, occasionally within a few weeks to months of discontinuation (Supplementary Appendix 6). Although the data only concerned TNFi discontinuation, the panel judged that a similar recommendation would also apply to other biologics. In general, treatment with a biologic should be planned to be continued long-term, barring toxicities. Discontinuation might be considered in patients in sustained remission

(i.e. several years), with the anticipation that only one-third of patients would not relapse. Patient preferences should help guide this decision.

Tapering of TNFi could entail a change in either the dose or frequency of administration. Two controlled unblinded trials of tapering etanercept to 25mg weekly versus maintaining the dose at 50mg weekly in patients with stable AS reported that remission or partial remission was somewhat less likely among those who were tapered [34,35]. In small observational studies, 53–70% of patients were still on their reduced dose at 2 years, but there is little evidence regarding maintenance of long-term remission after tapering of TNFi (Supplementary Appendix 6). Therefore, the panel recommended against tapering of biologics as a standard approach. One condition in which tapering could be considered would be in patients with prolonged stable AS, if patient and provider engage in shared decision-making.

In adults with stable AS on an originator TNFi, we strongly recommend continuing treatment with the originator TNFi over mandated switching to its biosimilar (new; *PICO 63*).—While the efficacy of originator and biosimilar TNFi are comparable, and while either could be chosen to initiate new courses of TNFi treatment, it was the opinion of the panel to recommend against mandated switching to a biosimilar during the course of treatment, in the absence of evidence of interchangability. Medication changes can increase the risk of destabilizing a patient, and the panel judged that additional data were needed to understand the frequency of potential problems and concerns associated with switching patients who were stable on an originator TNFi to its biosimilar. Given these concerns, the panel judged that there should be a compelling rationale to switch medications, particularly in light of the marginal cost savings apparent for U.S. patients [36].

C. Recommendations for adults with AS-related comorbidities

In adults with AS and recurrent uveitis, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics *(PICO 29)*.—Evidence for this recommendation is limited to indirect comparisons of the rates of acute uveitis episodes in clinical trials or observational studies, rather from direct comparisons (Supplementary Appendix 6). Many studies reported overall rates of uveitis without separately reporting recurrences as opposed to incident episodes [37]. Rates were generally lower for adalimumab and infliximab compared to etanercept. For example, a large observational study reported rates (per 100 patient-years) on adalimumab, infliximab, and etanercept of 13.6, 27.5, and 60.3, compared to pre-treatment rates of 36.8, 45.5, and 41.6, respectively [38]. Adalimumab or infliximab are preferred over etanercept for the treatment of AS in patients with recurrent uveitis. Certolizumab or golimumab may also be considered, although supporting data are less substantial [39,40]. Data from clinical trials suggest that rates of uveitis flares were not different between patients with AS treated with secukinumab and placebo, but more evidence is needed. Secukinumab was not efficacious in the treatment of panuveitis or posterior uveitis [41]. Rates of uveitis flares among patients treated with ixekizumab have not been well-defined.

In adults with AS and inflammatory bowel disease, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics *(PICO 32)*.—This recommendation was based on limited indirect evidence on the risks of flares or new onset of IBD among patients with AS during treatment with biologics, and the much larger literature on the treatment of IBD in general. Patients with AS treated with infliximab or adalimumab have lower risks of IBD exacerbations than those treated with etanercept (Supplementary Appendix 6). Infliximab, adalimumab, and certolizumab are approved for the treatment of Crohn's disease, and infliximab, adalimumab, and golimumab are approved for the treatment of ulcerative colitis, while etanercept is not approved for either condition [42,43]. This evidence is the basis for the recommendation favoring TNFi monoclonal antibody use in patients with AS and coexisting IBD. Choice of the particular TNFi monoclonal antibody should be made in consultation with the patient's gastroenterologist. Secukinumab has been associated with the new onset, or exacerbation, of Crohn's disease [44–46]. Increased risks of IBD exacerbation appear to also occur with ixekizumab [47].

D. Recommendations for the Treatment of Patients with either Active or Stable Non-radiographic axial spondyloarthritis

Parallel questions on pharmacological treatment were investigated for patients with nr-axSpA. There were no relevant published data for 19 questions. There was high quality evidence only for the use of TNFi in nr-axSpA, which was examined in several clinical trials. Low quality or very low quality evidence from single studies suggested no differences in outcomes among different TNFi in nr-axSpA, high likelihood of relapse following discontinuation of TNFi, and no association between co-treatment with nonbiologics and TNFi persistence (Supplementary Appendix 6). Therefore, the recommendations for nr-axSpA were largely extrapolated from evidence in AS (Table 3). The recommendations were identical in both patient groups with one notable exception: treatment with secukinumab or ixekizumab was strongly recommended over no treatment with secukinumab or ixekizumab in patients with AS, while use of these medications was conditionally recommended in patients with nr-axSpA, because trials in nr-axSpA have not been reported. Evidence on tofacitinib in nr-axSpA has not been reported.

E. Disease Activity Assessment and Imaging

In adults with active AS, we conditionally recommend against using the treat-to-target strategy, which aims at a target of ASDAS < 1.3 (or 2.1), over a treatment strategy based on physician assessment (new; *PICO 67*).—The concept of treat-to-target strategies is well-founded in chronic disease management for conditions that have an accurate measure of disease activity (often one that is asymptomatic, as in blood pressure or glycosylated hemoglobin), a tight link between this disease activity measure and future health outcomes, and evidence that maintaining a particular target in the disease activity measure is closely associated with better long-term health [48]. The treat-to-target approach in AS is indirectly supported by associations between levels of AS activity and future radiographic progression, but lacks robust direct evidence. Because adoption of this strategy would place additional burden on patients and providers, the panel judged that more convincing evidence of benefit should be present before endorsing this change in

practice. There was also concern that focus on a specific target could lead to rapid cycling through all currently available treatments in some patients. As reflected in the 2015 guidelines, quantifying disease activity is important to help guide treatment decisions.

In adults with AS of unclear activity while on a biologic, we conditionally recommend obtaining a spinal or pelvis MRI to assess activity *(*new; *PICO 69)*. In adults with nr-axSpA of unclear activity while on a biologic, we conditionally recommend obtaining a pelvis MRI to assess activity *(*new; *PICO 82)*.—Because physical and laboratory measures are often normal despite active axSpA, and because symptoms may be non-specific, it may be difficult to know if a patient is experiencing inflammation that warrants a change in treatment. Limited evidence suggests that knowledge of MRI findings of the spine and sacroiliac joints may alter treatment recommendations. However, the degree of inflammatory change on MRI may not correlate with treatment responses, and the location of MRI inflammation may not correlate with the location of pain [49] (Supplementary Appendix 6). The panel judged that MRI could provide useful information in cases where the level of disease activity was unclear and where this information would influence treatment decisions. For patients with nr-axSpA, the imaging should focus on the sacroiliac joints. In interpreting MRI results, it is important to keep in mind the range and frequency of abnormalities, including bone marrow edema lesions, that may occur in individuals without axSpA and which may not represent inflammation due to axSpA [50,51]. MRI is not recommended in patients who are either clearly clinically active or clinically stable, or when the results would not be expected to change treatment.

In adults with stable AS, we conditionally recommend against obtaining a spinal or pelvis MRI to confirm inactivity (new; *PICO 68*). In adults with stable nr-axSpA, we conditionally recommend against obtaining a spine or pelvis MRI to confirm inactivity (new; *PICO 81*).—Because the clinical assessment of inflammation is axSpA has many limitations, questions may arise about whether subclinical inflammation is being “missed” by either the physical examination, symptoms, or laboratory studies that could be detected by MRI. Given the lack of evidence that obtaining an MRI in stable patients improves clinical outcomes, the only moderate sensitivity and specificity of MRI abnormalities for measurement of activity in axSpA, the burden of testing, and concern for possible overtreatment, the panel recommended against obtaining an MRI in this setting. MRI could be considered in circumstances where the clinician and patient differ in their assessment of whether the disease is stable.

In adults with active or stable AS on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach (new; *PICO 70*). In adults with active or stable nr-axSpA on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach (new; *PICO 83*).—Spinal radiographs are useful for the diagnosis of axSpA, in evaluating the extent of spinal fusion, and for investigating new spinal pain in patients with established AS. In research studies, small changes in the extent

of spine damage can be detected in 20–35% of patients with AS over a two-year interval (Supplementary Appendix 6). There is no evidence that monitoring serial changes in spine radiographs at a regular interval leads to better patient outcomes, and data balancing a clinical benefit with the risk of radiation exposure are absent. Therefore, the panel recommended against repeating spine radiographs as a standard approach. In the absence of clinical indications, repeat spine radiographs could be considered on an ad hoc basis for counseling patients on the progression of their disease, which may help in career and life planning.

F. Summary of Recommendations

Figures 1 and 2 present a diagram of the main treatment recommendations for active and stable AS, integrating the new recommendations with the 2015 recommendations that were not updated in this review.

DISCUSSION

This update was primarily motivated by the availability of new treatment options, notably secukinumab, ixekizumab, tofacitinib, and TNFi biosimilars, for patients with axSpA. Providers and patients have questions on where these new medications fit in the pharmacological strategy, and how originator TNFi, sulfasalazine, and NSAIDs should be used given these new options. Based on the current evidence and the considerations of the panel, NSAIDs and TNFi remain the primary classes of medications for the treatment of AS and nr-axSpA. Secukinumab or ixekizumab is recommended for patients with active disease who have heart failure or demyelinating disease as a contraindication to TNFi, and in primary non-responders to TNFi. Secukinumab and ixekizumab are not recommended in patients with IBD or recurrent uveitis, as TNFi monoclonals are better options. Tofacitinib is a potential second-line option for patients with contraindications to TNFi other than infections. Recommendations regarding tofacitinib may change pending the results of larger clinical trials.

Several of the 2015 recommendations were modified in this update. The current recommendation is conditionally in favor of use of sulfasalazine in limited clinical circumstances, whereas the 2015 recommendations had this as an exception to the general recommendation against the use of conventional synthetic anti-rheumatic drugs. In the 2015 recommendations, sulfasalazine and pamidronate were suggested as alternatives for the treatment of patients with active disease and contraindications to TNFi, while the current recommendations suggest use of secukinumab or ixekizumab in most of these cases (except patients with high risk of infections). In cases of failure of TNFi, the 2015 guidelines included a conditional recommendation for a trial of a second TNFi and against use of a non-TNFi biologic, whereas the current guidelines differentiate treatment recommendations based on whether there was primary or secondary non-response to the TNFi. For the treatment of patients with recurrent uveitis, the previous guidelines specified conditional use of infliximab or adalimumab, while the update broadened this recommendation to include TNFi monoclonal antibodies generally. Similarly, for patients with coexisting IBD, the update includes a conditional recommendation for TNFi monoclonal antibodies over other

biologics, rather than over only etanercept. Finally, the recommendation for use of TNFi in patients with active nr-axSpA was changed from conditional to strong.

New questions on the treatment of patients with stable disease were addressed in this update. Discontinuation of biologics is not recommended due to the likelihood for symptom recurrence. If tapering is considered, patients should be counseled regarding the potential for increased disease activity. Co-treatment with low-dose methotrexate is not generally recommended, but ongoing studies will shed further light on this question. Switching to a biosimilar during the course of treatment with TNFi is also not recommended, echoing the concerns previously expressed by the ACR [52].

Imaging remains a central tool in the diagnosis of patients with axSpA, but its role in monitoring patients is less well-defined. Spine and/or pelvis MRI could aid in the evaluation of patients whose degree of active inflammation is uncertain, and especially in those for whom the findings would change management. MRI is not recommended to seek sub-clinical inflammation in stable patients. However, MRI could be considered in circumstances where it may inform shared decision-making. We recommend against obtaining spine radiographs on scheduled intervals to monitor progression. This entails radiation exposure and would not alter treatment in most cases.

We used the GRADE method to develop these treatment recommendations in a way that was transparent, systematic, and explicit, and that was informed by the medical evidence as well as patient preferences. The major limitation of these guidelines is the very low quality of evidence for many recommendations, which necessitated reliance on the clinical expertise of the panel. For nr-axSpA, most recommendations were based on extrapolation of results from studies in AS. We tried to identify the most common and consequential treatment questions, so that the recommendations would be useful in guiding clinical decision-making. The low quality of evidence for many questions is an indication that research has not yet tackled many of the most important treatment questions. As more treatment options become available, this problem will grow. Importantly, failure to recommend a particular medication does not imply that it is contraindicated. Key evidence gaps include the comparative effectiveness and safety of different biologics, the optimal sequencing of treatments, and the role of NSAIDs.

This update addressed only a subset of treatment questions. The 2015 recommendations that were not re-examined are to be considered extant. Recommendations are meant to describe the approach to treatment of the typical patient, and cannot anticipate all possible clinical scenarios. Application of these recommendations must be individualized, and requires careful assessment, sound clinical judgment of each patient’s circumstances, and consideration of patient’s preferences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This work was supported by the ACR and the SAA. We thank Cassie Shafer and Elin Aslanyan of the SAA for their partnership on this project. We thank the SPARTAN for its partnership on this project. We thank our patient representatives for adding valuable perspectives. We thank the ACR staff, including Ms. Regina Parker for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project, and Ms. Robin Lane for assistance in manuscript preparation. We thank Ms. Janet Waters for help in developing the literature search strategy and performing the literature search and updates, and Ms. Janet Joyce for peer-reviewing the literature search strategy.

Grant support:

This material is the result of a project supported by the American College of Rheumatology (ACR), Spondylitis Association of America (SAA) and Spondyloarthritis Research and Treatment Network (SPARTAN).

Dr. Ward was supported by the Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health. The views expressed do not represent those of the National Institutes of Health or the U.S. Department of Veterans Affairs.

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SIGNIFICANCE & INNOVATION

- An update to the 2015 recommendations is provided, which includes recommendations on new medications and imaging.
- In adults with active AS despite treatment with NSAIDs, treatment with TNFi over treatment with secukinumab or ixekizumab is conditionally recommended.
- In adults with stable AS receiving treatment with a biologic, conditional recommendation against discontinuation of the biologic.
- Conditional recommendation against obtaining repeat spine radiographs at a scheduled interval as a standard approach.

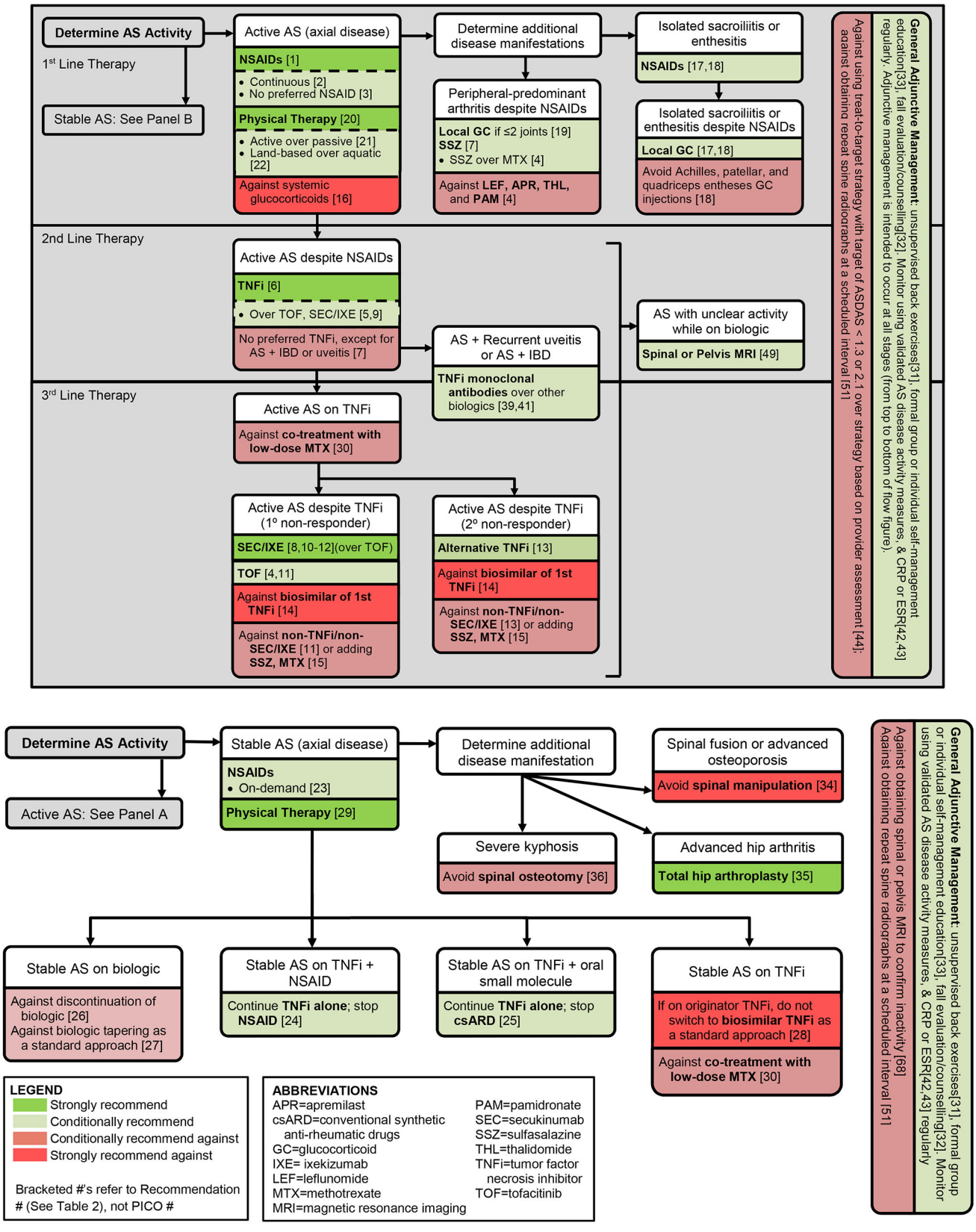

Figure 1.

Summary of the main recommendations for the treatment of patients with active ankylosing spondylitis (panel A) and stable ankylosing spondylitis (panel B).

Table 1.

Definitions of key terms.

Active disease	Disease causing symptoms at an unacceptably bothersome level to the patient and judged by the examining clinician to be due to inflammation.
Stable disease	Disease that was asymptomatic or causing symptoms but at an acceptable level as reported by the patient. A minimum of six months was required to qualify as clinically stable.
Primary non-response	Absence of a clinically meaningful improvement in disease activity over the three to six months after treatment initiation, not related to toxicity or poor adherence.
Secondary non-response	Recurrence of AS activity, not due to treatment interruption or poor adherence, after having a sustained clinically meaningful improvement on treatment (generally, beyond the initial 6 months of treatment).
Conventional synthetic anti-rheumatic drug (csARD)	Sulfasalazine, methotrexate, leflunomide, apremilast, thalidomide, pamidronate
Biosimilar	Biopharmaceuticals that are copies of an original biologic medication and tested to be of the same purity and potency as the original. In these recommendations, we refer only to TNFi biosimilars. Examples include infliximab-dyyb, etanercept-szzs, and adalimumab-atto.
TNFi	Infliximab, etanercept, adalimumab, certolizumab, golimumab, and their biosimilars.
TNFi monoclonal antibodies	Infliximab, adalimumab, certolizumab, golimumab
Biologic	TNFi, abatacept, rituximab, sarilumab, tocilizumab, ustekinumab
High quality evidence	Studies that provide high confidence in the effect estimate, and new data from future studies are thought unlikely to change the effect.
Moderate quality evidence	Studies that provide confidence that the true effect is likely to be close to the estimate, but could be substantially different.
Low quality evidence	Studies that provide limited confidence about the effect, and the true effect may be substantially different from the estimate.
Very low quality evidence	Studies that provide very little certainty about the effect, and the true effect may be quite different from the estimate.
Strong recommendation	Action should be favored in almost all patients, usually requiring high quality evidence, high confidence that future research will not alter the conclusion, **and** an assessment that the desirable effects of the intervention outweigh the undesirable effects. Should not be taken to imply that the intervention has large clinical benefits.
Conditional recommendation	Action should be followed in only selected cases, often limited by low quality evidence, **or** when the desirable and undesirable consequences of an intervention are more balanced, **or** if patients' preferences for the intervention are thought to vary widely.
Patient preferences	Beliefs and expectations regarding potential benefits and harms of treatment and how these relate to an individual's goals for health and life.
Shared decision-making	The process by which a patient and clinician arrive at an individualized treatment decision based on an understanding of the potential benefits and risks of available treatment options and of a patient's values and preferences.

Table 2.

Recommendations for the treatment of adults with ankylosing spondylitis (AS). Recommendations with asterisks are from 2015 and were not reviewed in this update. The number preceding the recommendation is the recommendation number and is referenced as bracketed numbers in the figure.

Recommendations for adults with active AS	Level of evidence	PICO
1. We strongly recommend treatment with NSAIDs over no treatment with NSAIDs.*	Low	2
2. We conditionally recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs.	Low to moderate	1
3. We do not recommend any particular NSAID as the preferred choice.*	Low to moderate	3
4. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications. Sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNFi are not available.	Very low to moderate	7
5. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib.	Very low	60
6.In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi.	High	6
7. We do not recommend any particular TNFi as the preferred choice.	Moderate	5
8. In adults with active AS despite treatment with NSAIDs, we strongly recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab.	High	58
9. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab.	Very low	59
10. In adults with active AS despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib.	Very low	61
11. In adults with active AS despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib.	Low	8
12. In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with a different TNFi in patients with primary non-response to TNFi.	Very low	10
13. In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with a different TNFi over treatment with a non-TNFi biologic in patients with secondary non-response to TNFi.	Very low	10
14. In adults with active AS despite treatment with the first TNFi used, we strongly recommend against switching to treatment with a biosimilar of the first TNFi.	Very low	62
15. In adults with active AS despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of treatment with a new biologic.	Very low	9
16. We strongly recommend against treatment with systemic glucocorticoids.*	Very low	4
17. In adults with isolated active sacroiliitis despite treatment with NSAIDs, we conditionally recommend treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.*	Very low	13

Recommendations for adults with active AS	Level of evidence	PICO
18. In adults with stable axial disease and active enthesitis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided.*	Very low	14
19. In adults with stable axial disease and active peripheral arthritis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.*	Very low	15
20. We strongly recommend treatment with physical therapy over no treatment with physical therapy.*	Moderate	16
21. We conditionally recommend active physical therapy interventions (supervised exercise) over passive physical therapy interventions (massage, ultrasound, heat).*	Very low	17
22. We conditionally recommend land-based physical therapy interventions over aquatic therapy interventions.*	Moderate	18
Recommendations for adults with stable AS		
23. We conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs.	Low to moderate	1
24. In adults receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone compared to continuing both treatments.	Very low	11
25. In adults receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing both treatments.	Very low	12
26. In adults receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic.	Very low to low	66
27. In adults receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach.	Very low to low	65
28. In adults receiving treatment with an originator TNFi, we strongly recommend continuing treatment with the originator TNFi over mandated switching to its biosimilar.	Very low	63
29. We strongly recommend treatment with physical therapy over no treatment with physical therapy.*	Low	19
Recommendations for adults with active or stable AS		
30. In adults receiving treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate.	Low	64
31. We conditionally recommend advising unsupervised back exercises.*	Moderate	20
32. We conditionally recommend fall evaluation and counseling.*	Very low	51
33. We conditionally recommend participation in formal group or individual self-management education.*	Moderate	48
34. In adults with spinal fusion or advanced spinal osteoporosis, we strongly recommend against treatment with spinal manipulation.*	Very low	21
35. In adults with advanced hip arthritis, we strongly recommend treatment with total hip arthroplasty over no surgery.*	Very low	25
36. In adults with severe kyphosis, we conditionally recommend against elective spinal osteotomy.*	Very low	26
Recommendations for adults with AS-related comorbidities		

Recommendations for adults with active AS	Level of evidence	PICO
37. In adults with acute iritis, we strongly recommend treatment by an ophthalmologist to decrease the severity, duration, or complications of episodes.*	Very low	27
38. In adults with recurrent iritis, we conditionally recommend prescription of topical glucocorticoids over no prescription for prompt at-home use in the event of eye symptoms to decrease the severity or duration of iritis episodes.*	Very low	28
39. In adults with recurrent iritis, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics.	Low	29
40. In adults with inflammatory bowel disease, we do not recommend any particular NSAID as the preferred choice to decrease the risk of worsening of inflammatory bowel disease symptoms.*	Very low	31
41. In adults with inflammatory bowel disease, we conditionally recommend treatment with TNFi monoclonal antibodies over treatment with other biologics.	Very low	32
Disease activity assessment, imaging, and screening		
42. We conditionally recommend the regular-interval use and monitoring of a validated AS disease activity measure.*	Very low	54
43. We conditionally recommend regular-interval use and monitoring of the CRP concentrations or erythrocyte sedimentation rate (ESR) over usual care without regular CRP or ESR monitoring.*	Very low	55
44. In adults with active AS, we conditionally recommend against using a treat-to-target strategy using a target of ASDAS < 1.3 (or 2.1) over a treatment strategy based on physician assessment.	Low	67
45. We conditionally recommend screening for osteopenia/osteoporosis with dual x-ray absorptiometry (DXA) scan over no screening.*	Very low	49
46. In adults with syndesmophytes or spinal fusion, we conditionally recommend screening for osteoporosis/ osteopenia with DXA scan of the spine as well as the hips, compared to DXA scan solely of the hip or other non-spine sites.*	Very low	50
47. We strongly recommend against screening for cardiac conduction defects with electrocardiograms.*	Very low	52
48. We strongly recommend against screening for valvular heart disease with echocardiograms.*	Very low	53
49. In adults with AS of unclear activity while on a biologic, we conditionally recommend obtaining a spinal or pelvis MRI to assess activity.	Very low	68
50. In adults with stable AS, we conditionally recommend against obtaining a spinal or pelvis MRI to confirm inactivity.	Very low	69
51. In adults with active or stable AS on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach.	Very low	70

Table 3.

Recommendations for the treatment of adults with nonradiographic axial spondyloarthritis (nr-axSpA). Recommendations with asterisks are from 2015 and were not reviewed in this update.

Recommendations for adults with active nr-axSpA	Level of evidence	PICO
52. We strongly recommend treatment with NSAIDs over no treatment with NSAIDs.*	Very low	34
53. We conditionally recommend continuous treatment with NSAIDs over on-demand treatment with NSAIDs.	Very low	33
54. We do not recommend any particular NSAID as the preferred choice.*	Very low	35
55. In adults with active nr-axSpA despite treatment with NSAIDs, we conditionally recommend treatment with sulfasalazine, methotrexate, or tofacitinib over no treatment with these medications.	Very low	39
56. In adults with active nr-axSpA despite treatment with NSAIDs, we strongly recommend treatment with TNFi over no treatment with TNFi.	High	38
57. We do not recommend any particular TNFi as the preferred choice.	Very low	37
58. In adults with active nr-axSpA despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with tofacitinib.	Very low	73
59. In adults with active nr-axSpA despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over no treatment with secukinumab or ixekizumab.	Very low	71
60. In adults with active nr-axSpA despite treatment with NSAIDs, we conditionally recommend treatment with TNFi over treatment with secukinumab or ixekizumab.	Very low	72
61. In adults with active nr-axSpA despite treatment with NSAIDs, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with tofacitinib.	Very low	74
62. In adults with active nr-axSpA despite treatment with NSAIDs and who have contraindications to TNFi, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with sulfasalazine, methotrexate, or tofacitinib.	Very low	40
63. In adults with active nr-axSpA and primary nonresponse to the first TNFi used, we conditionally recommend switching to secukinumab or ixekizumab over switching to a different TNFi.	Very low	42
64. In adults with active nr-axSpA and secondary nonresponse to the first TNFi used, we conditionally recommend switching to a different TNFi over switching to a non-TNFi biologic.	Very low	42
65. In adults with active nr-axSpA despite treatment with the first TNFi used, we strongly recommend against switching to the biosimilar of the first TNFi.	Very low	75
66. In adults with active nr-axSpA despite treatment with the first TNFi used, we conditionally recommend against the addition of sulfasalazine or methotrexate in favor of treatment with a different biologic.	Very low	41
67. We strongly recommend against treatment with systemic glucocorticoids.*	Very low	36
68. In adults with isolated active sacroiliitis despite treatment with NSAIDs, we conditionally recommend treatment with local glucocorticoids over no treatment with local glucocorticoids.*	Very low	45
69. In adults with active enthesitis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids. Peri-tendon injections of Achilles, patellar, and quadriceps tendons should be avoided.*	Very low	46

Recommendations for adults with active nr-axSpA	Level of evidence	PICO
70. In adults with active peripheral arthritis despite treatment with NSAIDs, we conditionally recommend using treatment with locally administered parenteral glucocorticoids over no treatment with local glucocorticoids.*	Very low	47
71. We strongly recommend treatment with physical therapy over no treatment with physical therapy.*	Low	22
72. We conditionally recommend active physical therapy interventions (supervised exercise) over passive physical therapy interventions (massage, ultrasound, heat).*	Very low	23
73. We conditionally recommend land-based physical therapy interventions over aquatic therapy interventions.*	Very low	24
Recommendations for adults with stable nr-axSpA		
74. We conditionally recommend on-demand treatment with NSAIDs over continuous treatment with NSAIDs.	Very low	33
75. In adults receiving treatment with TNFi and NSAIDs, we conditionally recommend continuing treatment with TNFi alone compared to continuing both medications.	Very low	43
76. In adults receiving treatment with TNFi and a conventional synthetic antirheumatic drug, we conditionally recommend continuing treatment with TNFi alone over continuing treatment with both medications.	Very low	44
77. In adults receiving treatment with a biologic, we conditionally recommend against discontinuation of the biologic.	Low	79
78. In adults receiving treatment with a biologic, we conditionally recommend against tapering of the biologic dose as a standard approach.	Very low	78
79. In adults receiving treatment with an originator TNFi, we strongly recommend continuation of treatment with the originator TNFi over mandated switching to its biosimilar.	Very low	76
Recommendations for adults with active or stable nr-axSpA		
80. In adults receiving treatment with TNFi, we conditionally recommend against co-treatment with low-dose methotrexate.	Low	77
Disease activity assessment and Imaging		
81. We conditionally recommend the regular-interval use and monitoring of a validated AS disease activity measure.*	Very low	56
82. We conditionally recommend regular-interval use and monitoring of the CRP concentrations or erythrocyte sedimentation rate (ESR) over usual care without regular CRP or ESR monitoring.*	Very low	57
83. In adults with active nr-axSpA, we conditionally recommend against using a treat-to-target strategy using a target of ASDAS < 1.3 (or 2.1) over a treatment strategy based on physician assessment.	Very low	80
84. In adults with nr-axSpA of unclear activity while on a biologic, we conditionally recommend obtaining a spinal or pelvis MRI to assess activity.	Very low	81
85. In adults with stable nr-axSpA, we conditionally recommend against obtaining a spinal or pelvis MRI to confirm inactivity.	Very low	82
86. In adults with active or stable nr-axSpA on any treatment, we conditionally recommend against obtaining repeat spine radiographs at a scheduled interval (e.g., every 2 years) as a standard approach.	Very low	83