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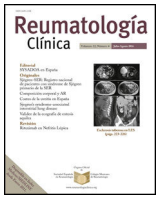

Special Article

2021 clinical practice guideline for the early detection, diagnosis, treatment, and monitoring of patients with axial spondyloarthritis. Colombian Association of Rheumatology☆,☆☆

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ABSTRACT

Background: Axial Spondyloarthritis is a rheumatic condition affecting young patients with social and occupational consequences. Diagnosis delay is associated with functional impairment and impact on quality of life, requiring a multidisciplinary approach.
Objective: To develop a set of recommendations based on the best available evidence for early detection, diagnosis, treatment and monitoring adult patients with axial spondyloarthritis.
Methods: A working group was established, questions were developed, outcomes were graded, and a systematic search for evidence was conducted. A multidisciplinary panel of members was established (including patient representatives), minimizing bias in relation to conflicts of interest. The GRADE approach "Grading of Recommendations Assessment, Development and Evaluation" was used to assess the quality of the evidence as well as the direction and strength of recommendations. In total, 11 recommendations with regard to diagnosis (n = 2), pharmacological treatment (n = 6), non-pharmacological treatment (n = 2) and monitoring (n = 1) are presented.
Results: Sacroiliac joint radiography as the first diagnostic method, and the use of disease activity scales for patient monitoring (ASDAS or BASDAI), are recommended. Nonsteroidal anti-inflammatory drugs are the first treatment option; in case of intolerance or residual pain, acetaminophen or opioids are recommended. In patients with axial involvement, it is recommended not to use conventional disease-modifying antirheumatic drugs or systemic or local glucocorticoids. In patients with failure to non-steroidal anti-inflammatory drugs, anti-TNF or anti-IL17A is recommended. In those patients presenting with anti-TNF failure, starting an anti-IL17A is recommended. Exercise, physical and occupational therapy are recommended as part of treatment. It is recommended not to use unconventional therapies as the only treatment option.

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Conclusions: This set of recommendations provides an updated guide on the diagnosis, treatment and monitoring of patients with axial spondyloarthritis.

Palabras clave:
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Guía de práctica clínica
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Tratamiento
Seguimiento

Guía de práctica clínica 2021 para la detección temprana, el diagnóstico, el tratamiento y el seguimiento de los pacientes con espondiloartritis axial. Asociación Colombiana de Reumatología

R E S U M E N

Antecedentes: La espondiloartritis axial es una enfermedad reumatológica que afecta a individuos jóvenes y tiene una gran repercusión sociolaboral. El retraso en el diagnóstico y el tratamiento se asocia con un mayor deterioro funcional y un impacto negativo en la calidad de vida, por lo que requiere un abordaje multidisciplinario.
Objetivo: Desarrollar y formular un conjunto de recomendaciones específicas basadas en la mejor evidencia disponible para la detección temprana, el diagnóstico, el tratamiento y el seguimiento de los pacientes adultos con espondiloartritis axial.
Métodos: Se configuró un grupo desarrollador, se formularon preguntas clínicas contestables, se graduaron los desenlaces y se realizó la búsqueda sistemática de la evidencia. El panel de la guía fue multidisciplinario (incluyendo representantes de los pacientes) y balanceado, minimizando el sesgo por conflictos de interés. Se utilizó la aproximación Grading of Recommendations Assessment, Development and Evaluation (GRADE) para evaluar la calidad de la evidencia, al igual que la dirección y la fortaleza de las recomendaciones. Se presentan 11 recomendaciones relacionadas con diagnóstico (n = 2), tratamiento farmacológico (n = 6), tratamiento no farmacológico (n = 2) y seguimiento (n = 1).
Resultados: Se recomienda la radiografía de articulaciones sacroilíacas como primer método diagnóstico, y el uso de escalas de actividad para el seguimiento de los pacientes (ASDAS o BASDAI). Los antiinflamatorios no esteroideos son la primera opción de tratamiento; en caso de intolerancia o dolor residual se recomienda acetaminofén u opioides. En pacientes con compromiso axial se recomienda abstenerse de utilizar medicamentos antirreumáticos modificadores de la enfermedad convencionales ni glucocorticoides sistémicos o locales. En pacientes con falla a los antiinflamatorios no esteroideos, se recomienda un anti-TNFα o un anti-IL17A. En pacientes con falla a anti-TNFα, se recomienda iniciar un anti-IL17A. El ejercicio, la terapia física y ocupacional se recomiendan como parte del tratamiento. Se recomiendan no utilizar las terapias no convencionales como única opción de tratamiento.
Conclusiones: Este conjunto de recomendaciones proporcionan una guía actualizada sobre el diagnóstico y tratamiento de espondiloartritis axial.

Introduction

Spondyloarthritis (SpA) is a generic term that integrates a group of interrelated inflammatory conditions, which share clinical, genetic, epidemiological, pathophysiological and radiographic characteristics, as well as therapeutic options. According to the clinical presentation pattern, they may be predominantly axial or peripheral. The onset of symptoms usually occurs before 45 years of age. Axial spondyloarthritis (axSpA), as a subtype of SpA, is a chronic inflammatory disease that mainly affects the axial skeleton (spine and sacroiliac joints), but can also affect peripheral joints (oligoarthritis predominantly in the lower limbs) and the enthesses (regions where a tendon, ligament or the articular capsule are inserted into the bone) both axial and peripheral. The term axSpA includes: 1) patients with structural damage of the sacroiliac joints or the spine visible on radiographs (radiographic axSpA, also called ankylosing spondylitis [AS]), and 2) patients without structural damage visible on plain radiography (non-radiographic axSpA [nr-axSpA])[1]. The prevalence of SpA in Latin America has been estimated in 0.52 (95% CI: 0.10–1.25) and that of AS in 0.14 (95% CI: 0.05–0.34)[2]. In Colombia, a recent study that used the Copcord methodology estimated a prevalence of 0.11% for AS and 0.28% for undifferentiated SpA[3].

Patients present with chronic back pain (more than 3 months of evolution) associated with morning stiffness, predominantly located in the lumbar region; however, any part of the spine can be affected. Low back pain is a frequent symptom in daily clinical practice and is one of the main causes of medical consultation, so it is important to define its approach, especially at the first level of healthcare. In addition to extra-articular manifestations (uveitis, psoriasis and inflammatory bowel disease), the associated comorbidities in these patients increase the total burden of the disease, especially those related to cardiovascular and infectious diseases[4]. The diagnosis of axSpA, as well as its therapeutic approach, present important challenges for the clinician, given the variability and heterogeneity of its clinical manifestations. One of the most important manifestations is the presence of inflammatory low back pain. Different criteria have been developed for the classification of inflammatory low back pain, which overlap to a large extent[5,6]. The ASAS criteria that define the inflammatory characteristics of low back pain have a sensitivity of 79.6% and a specificity of 72.4%[7]. These include the onset of pain before the age of 40, which is insidious and nocturnal, improves with exercise, and is also characterized by a lack of improvement with rest. Several studies in the country have reported the different patterns of clinical presentation in SpA and its most frequent manifestations[8,9], and have evaluated the performance of the different classification criteria using the clinical diagnosis of the rheumatologist as an external standard[10]. Likewise, additional studies in the country have explored the clinical variables that guide the rheumatologist to request additional

studies for the diagnosis of SpA[11], and have reported the frequency of the HLA-B27 allele in individuals with clinical signs suggestive of SpA[12] and in healthy individuals[13].

This is the first clinical practice guideline (CPG) aimed at patients with axSpA that is developed, published and implemented in Colombia, and is intended to have a favorable impact on the early diagnosis, treatment and follow-up of these patients. The CPG in axSpA joins and complements the most widely used international guides in the country for the diagnosis and treatment of this disease, such as the guide of the European League Against Rheumatism (EULAR)[14] and the guide of the American College of Rheumatology (ACR)[15].

This CPG is addressed to health professionals involved in the care of patients with axSpA, decision makers, payers of health expenditures and government entities that generate health policies. The full version of this CPG (including the methodology developed, the systematic search for scientific information and the detailed presentation of the evidence) is found in Appendix A, Supplementary material, and will be available for consultation on the website of the Colombian Association of Rheumatology (Asoreuma) and on the website of Scientific Societies of the Ministry of Health and Social Protection of Colombia, after the publication of this document.

Materials and methods

The objective of the guideline is to develop a set of specific recommendations based on the best available evidence regarding the early diagnosis and treatment of adult patients with axSpA, establish the clinical parameters for the diagnostic approach of the patient with inflammatory low back pain, sensitize the medical staff on the identification and clinical suspicion of the disease, reduce the variability in treatment and, potentially, rationalize expenditures, optimize timely referral of patients to the rheumatologist and improve the quality of life and the occupational and social performance of the patients.

The Guideline Developer Group (GDG) assessed the certainty of the evidence, developed and graded the recommendations following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[16–19]. In the development of the CPG, the GDG has followed a series of steps that are described below.

Organization, planning and coordination of the clinical practice guideline

The GDG was composed of 9 expert rheumatologists and one immunology bacteriologist, members of the Asoreuma Spondyloarthritis Study Group, 2 patient representatives and one anthropologist as a representative of the civil society. All the panel sessions were accompanied by representatives from the Ministry of Health and Social Protection and the Institute of Evaluation of Technologies in Health (IETS). The leader of the CPG is a rheumatologist representing the Asoreuma Study Group and a member of the Assessment of Spondyloarthritis International Society (ASAS) group. The development of the CPG had the methodological accompaniment of an external and independent consulting firm. The CPG was carried out following the guidelines of the "Methodological Guide for the elaboration of clinical practice guidelines with economic evaluation in the Colombian General System of Social Security in Health"[20]. The work of the GDG was carried out using computer tools, face-to-face meetings, and virtual meetings. In addition to systematically synthesizing the evidence, the company Evidentias SAS supported the process of development of the CPG, including the determination of the methods, the preparation of agendas and meetings, the materials, and the facilitation of discussion panels.

Formulation of clinical questions and definition of the outcomes

The questions in the guide were formulated by open consultation with all members of the GDG, and were subsequently prioritized by the GDG itself, following the Delphi methodology, until a consensus was reached (greater than 80%). A total of 2 rounds of virtual consultation by email were carried out. The methodology proposed by the GRADE Working Group (GRADEwg) was followed for grading the outcomes of interest for each question[16]. The process was carried out virtually. The outcomes presented in Table 1 Table 1 were evaluated as critical and important for the total number of questions to be answered by the CPG, these outcomes were used to define the selection criteria of the evidence that supports each recommendation (Supplementary material: protocols by question available at https://www.asoreuma.org).

Review and evaluation of the previous clinical practice guidelines

After defining the questions to be answered by the guidelines, a search aimed to identified the CPGs in axSpA was carried out, in order to assess the pertinence of adapting or adopting some of their recommendations following the *Adolopment* strategy[21]. A total of 12 CPGs published in the past 5 years were identified[14,15,22–31], as a pre-established selection criterion. These CPGs were fully reviewed by three members of the GDG and a methodologist from Evidentias SAS, in accordance with The Appraisal of Guidelines for Research & Evaluation Instrument (AGREE-II)[32,33]. The results of this evaluation are presented in Table 2.

None of the 12 CPGs addressed the totality of questions defined by the GDG. Those that met the desired rigor (according to the evaluation of this domain by AGREE-II) were taken into account to adapt their recommendations on those questions for which no evidence that would allow giving an answer was found. In most cases, the questions were developed *de novo*.

Review of the evidence and development of the recommendations

The Evidentias SAS team carried out systematic reviews of the literature to resolve each question of the guideline and report on the effects (benefits and harms) of the interventions, the use of resources (cost-effectiveness), values and preferences (relative importance of the results), and the possible impact on the equity, acceptability and feasibility of the potential recommendation.

Search for evidence

Initially, a highly sensitive search strategy was generated to identify the publications related to the condition "spondyloarthritis". Based on this strategy for the definition of the condition, search strategies specific for each question were developed in the "Patient, Intervention, Comparator, and Outcome" (PICO) format.

For each question, at least 3 complementary search strategies were designed: a search focused on the identification of evidence to evaluate the effect of the intervention or diagnostic test and their safety, another search to identify cost studies and economic evaluations that would allow to inform the panel about the potential economic impact of the intervention and finally, and, finally, a search designed to identify studies on patient values and preferences. For each of these searches, the strategies initially defined for each PICO question were complemented with high-sensitivity filters to identify the study of interest (systematic reviews of clinical trials, studies of diagnostic tests, studies of costs and economic

Table 1
Grading of the outcomes for questions on therapy and diagnosis.

Outcomes in questions that assess therapeutic interventions	Importance
Outcomes in questions that assess therapeutic interventions	
Control of the disease — remission/low activity of symptoms	Critical
Control of the disease — improvement in functional scales	Critical
Better quality of life	Critical
Serious adverse events (defined for each specific treatment	Critical
Control of the disease — radiographic progression	Important
Chronic structural changes and acute inflammatory changes in radiography	Important
Outcomes in questions that assess diagnostic tests and scales	
Diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value, odds ratio	Critical
Reliability, sensitivity to change, discriminative ability	Critical

Table 2
Evaluation of the CPGs in axSpA according to the AGREE-II instrument.

AGREE-II	Average score (%)	Range (%)
Scope and purpose	86	67–96
Participation of the interested parties	71	22–93
Rigor in the development	61	29–82
Clarity of the presentation	79	68–86
Applicability	48	21–71
Editorial independence	72	19–92
Overall assessment	65	21–83
Would you recommend the guideline[a]?	62	0–100[a]

Source: Cañete Crespillo J[31] and AGREE Next Steps Consortium[32].
axSpA: axial spondyloarthritis; CPG: clinical practice guideline.
[a] From 0 to 24%: I would not recommend it, from 25 to 75%: I would recommend it with modifications and from 76 to 100%: I would recommend it.

analyses, studies of quality of life and evaluation of preferences). The searches were performed by an expert in bioinformatics.

The searches were performed using the OVID metasearch engine, including the PubMed/MEdline, Embase, Epistemonikos and LILACs — Scientific Electronic Library Online (SciELO) databases. When the search did not yield relevant evidence to answer the question, a manual search was carried out by reviewing references, consulting pages of scientific societies and consulting GDG experts.

Both the search and the processes of selection, evaluation and synthesis of evidence were carried out in accordance with the standards proposed by the Cochrane collaboration[34]. The studies identified for each PICO question were assessed for methodological quality by epidemiologists. The systematic literature reviews (SLR) were evaluated according to the Assessing the Methodological Quality of Systematic Reviews (Amstar 2) tool[35], the randomized clinical experiments were evaluated with the Cochrane Collaboration Risk of Bias (RoB) instrument[36], the diagnostic studies and systematic reviews of diagnostic tests were assessed with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS 2) tool[37], and the cost studies, with the Drummond checklist, recommended for the evaluation of studies of economic analysis[38]. The evaluation of the quality of the studies on values and preferences was carried out following the recommendations of the GRADEwg for this type of evidence[39]. The evaluation of the overall quality of evidence was carried out according with the GRADE approach[40].

Based on the evaluation of the evidence and following the guidelines of the GRADE approach, evidence profiles and summary tables of the findings that included the main outcomes defined as of interest for each question were prepared[17] (Supplementary material available at: https://www.asoreuma.org).

For each question, it was prepared a protocol that included: the PICO question, the rating of the outcomes, the search strategy, the description of the search results, a brief overview of the studies identified for each aspect of interest and their methodological quality, and the summary table of the GRADE findings. In addition, each protocol included the Evidence to Decision (EtD) format suggested by the GRADEwg to support the panel in the formulation of recommendations[18].

Each protocol, once completed, was reviewed by an expert rheumatologist of the GDG. The comments and additions suggested by the expert were taken into account to create a new version of the protocol, which was finally sent to all members of the GDG for review. The articles sent by the experts as complementary information were evaluated for their methodological quality by the Evidentias SAS group and, according to this evaluation, the information obtained was assigned to the "evidence" or "additional information" columns of the EtD.

The members of the GDG, the representatives of the patients and the experts in equity were contacted by the coordinators of the CPG during the process of preparation of the EtD early enough to obtain from them the information pertinent to these 2 aspects for each question.

All members of the GDG received the total of protocols developed for each question of the CPG, in an email message that motivated them to read the information and prepare in advance both the additional information that they considered pertinent and the vote (judgment) that they would give to each aspect contemplated in the EtD format. This mail was sent 8 days before the meeting on recommendations.

In accordance with the formal consensus methodology of the Methodological Guide for the elaboration of guidelines of comprehensive care in the Colombian General Social Security Health System[20], the modality of expert panel was chosen, thus facilitating the discussion of the evidence for the construction of the recommendations. The panel of experts consisted of 10 members of the Asoreuma Spondyloarthritis Study Group. A leader and a coordinator for the CPGs on axSpA were designated.

In order to generate the recommendations, two virtual meetings were held using the Google Meet platform. In addition to the panel of experts, the meetings were attended by patient representatives, an anthropologist, representatives of the Ministry of Health and Social Protection, representatives of the Institute of Evaluation of Technologies in Health (IETS) and the methodologists. Voting was carried out through the Mentimeter® electronic voting system. The recommendation was accepted with a vote of 50% + 1 of the votes of the total number of people eligible to vote (votes in the Supplementary material available at: https://www.asoreuma.org). After the vote, the definitive EtD was generated, incorporating the agreed adjustments and the voted recommendations. The final protocols were reviewed again by the GDG. The meetings were recorded on audio and video for later reference.

Review of the document

The GDG carried out the activities that allowed the inclusion of opinions from the different actors and decision makers: 1) socialization of the scope, objectives and clinical questions contained in the guideline, through publication on the Asoreuma page; 2) par-

ticipation and voting in the virtual meetings; 3) socialization of the final recommendations of the CPG with the health professionals and interested parties during a month, through their publication on the Asoreuma page and announcements in social networks; 4) sending of the final document of the CPG for external peer review. It is proposed to update this CPG every two years from its publication, if there is new evidence that changes any of the initially proposed recommendations in one direction or another. If there is no new evidence, it will be reviewed again in 3 years.

Results

The recommendations according to each question asked are presented below, together with the summary of the evidence:

□ **Question 1.** In the detection of adult patients with axSpA and chronic low back pain in individuals under 45 years of age, which of the screening scales (1. Berlin algorithm; 2. ASAS criteria for inflammatory low back pain; 3. Calin criteria), should be used because of its operational characteristics and diagnostic performance?

Recommendation: in patients with low back pain of more than 3 months of evolution, the panel suggests the application of any of the 3 classification criteria for screening of inflammatory low back pain.

Conditional recommendation in favor. Quality of the evidence ⊕⊕◯◯ low.

Good practice point: the primary care physician can find more useful the use of the ASAS criteria for inflammatory low back pain for this purpose.

Summary of the evidence: no SLRs that compared the operating characteristics of the Calin, Berlin and ASAS screening scales were found. Three independent studies that comparatively evaluate some of these screening tests were identified: the Divers study,[41] the Arnbak 2016 study,[42] and the Solmaz study.[43]

Conclusion: the screening questionnaires for inflammatory low back pain have the advantages of being widely available and easy to perform. Sensitivity and specificity values varied widely, taking into account the reference standard that was used. In general, the diagnostic performance is acceptable. These tools should be complementary to clinical judgment.

□ **Question 2.** For the diagnosis of axSpA in adult patients, should magnetic resonance imaging (MRI) of the sacroiliac joints be performed instead of sacroiliac radiograph, due to its operative characteristics and diagnostic performance?

Recommendation: conventional radiography of the sacroiliac joints is suggested as the first imaging method to diagnose sacroiliitis as part of axSpA. If the diagnosis of axSpA cannot be established based on the clinical characteristics and the conventional radiography, and axSpA is still suspected, it is suggested to use a MRI of the sacroiliac joints. Conditional recommendation in favor of conventional radiography.

Quality of the evidence ⊕⊕◯◯ low.

Good practice point: the panel considers that it is not pertinent to request a bone scintigraphy for the study of patients with low back pain and suspected axSpA.

Summary of the evidence: no studies that comparatively evaluated the MRI vs. the lumbosacral radiography were identified. This summary is based on 4 studies: one SLR that evaluates the MRI in the diagnosis of axSpA,[44] one study that evaluates the performance of a MRI of sacroiliac and lumbar joints[45] and 2 cohort studies.[46,47].

Conclusion: it is suggested to perform conventional radiography of the sacroiliac joints as the first imaging method to diagnose sacroiliitis. Based on the ability of MRI to detect the disease early, it is considered pertinent to perform it in a young population with symptoms of few years of duration.

□ **Question 3.** In adult patients with axSpA, should non-steroidal anti-inflammatory drugs (NSAIDs) be used as the first option for pharmacological treatment due to their effectiveness (control of the disease, remission/low activity of symptoms, improvement in functionality scales) and safety (adverse events)?

Recommendation: in patients with axSpA, the use of NSAIDs is recommended as the first treatment option.

Strong recommendation in favor. Quality of the evidence ⊕⊕⊕⊕ high.

Good practice point: when prescribing NSAID-type medications, possible contraindications should be assessed. The panel considers that, in the case of active disease, 2 sequential NSAIDs at optimal doses should be used for at least 4 weeks.

Summary of the evidence: the systematic review of the literature (SLR) by Kroon 2015 which included 39 studies was selected. The methodological quality according to Amstar was good.

Conclusion: the balance between desirable and undesirable effects favors the use of the intervention, with a favorable impact on several outcomes and an adequate safety profile.

□ **Question 4.** In the treatment of adult patients with axSpA and axial manifestations, should conventional disease-modifying antirheumatic drugs (DMARDs) be used, due to their effectiveness (control of the disease, remission/low activity of symptoms, improvement in functionality scales) and safety (adverse events)?

Recommendation: in patients with axSpA and axial manifestations, it is recommended not to use conventional DMARDs as a therapeutic option.

Conditional recommendation against. Quality of the evidence ⊕⊕◯◯ low.

Summary of the evidence: no studies that comparatively assessed grouped conventional DMARDs vs. other therapies in axSpA were found. This summary is based on 2 RSLs from the literature.[48,49] The overall quality of the evidence was “low”

Conclusion: The use of conventional DMARDs is not recommended as a therapeutic strategy in patients with axSpA since the certainty of the evidence is low. In addition, there are no differences in the comparisons (methotrexate, sulfasalazine and leflunomide vs. placebo). There was a higher risk of adverse events with conventional DMARDs in studies that evaluated these medications in other autoimmune diseases.

□ **Question 5.** In the treatment of adult patients with axSpA, should conventional analgesics (acetaminophen, opioids) be used, due to their effectiveness (improvement in pain scales and quality of life) and safety (adverse events)?

Recommendation: in patients with axSpA who have intolerance and/or contraindication to NSAID therapy, or who have residual pain despite a properly established treatment, the use of acetaminophen or opioids is suggested for pain control.

Conditional recommendation in favor. Quality of the evidence ⊕⊕◯◯ low.

Good practice point: the panel suggests to avoid the continuous and prolonged use of opioid medications and rationalize their use, as well as starting acetaminophen-type analgesics before beginning opioid medications

Summary of the evidence: no study that evaluated this treatment only in patients with axSpA was identified, only one study conducted by Chang et al.[50] in ankylosing spondylitis was found.

Conclusion: patients with axSpA with a contraindication and/or intolerance to NSAIDs, or those with advanced disease or associated comorbidities, may benefit from the use of acetaminophen and/or opioids.

□ **Question 6.** In the treatment of adult patients with axSpA, should glucocorticoids (local or systemic) be used due to their effectiveness (control of the disease, remission/low activity of symptoms, improvement in the quality of life and functionality scales, radiographic progression) and safety (adverse events)?

Recommendation: in patients with axSpA, it is recommended not to use systemic or local glucocorticoids.

Strong recommendation against. Quality of the evidence ⊕◯◯◯ very low.

Summary of the evidence: the SLR of Ward et al.[51] was selected. The quality of the evidence was rated as very low. This SLR generated a strong recommendation against.

Conclusion: the low quality of the studies, the small number of patients and the high risk of bias prevented us from concluding in favor of the intervention. The indirect evidence regarding the safety profile of the use of systemic corticosteroids suggests that the risks outweigh the benefits.

□ **Question 7.** In adult patients with active axSpA in whom NSAIDs have failed, should the following: 1) anti-TNFα; 2) anti-IL-17; 3) anti-12−23 or 4) JAK inhibitors, be used as a second treatment option due to their greater effectiveness and safety?

Recommendation: In patients with axSpA who present therapeutic failure or pharmacological intolerance to NSAIDs, the initiation of therapy with anti-TNFα or anti-L17A is recommended.

Strong recommendation in favor. Quality of the evidence ⊕⊕⊕⊕ high.

Good practice point: In case of considering therapy with anti-IL17A, the panel preferably recommends the choice of secukinumab, for which there is more evidence that supports its use.

Summary of the evidence: no primary studies comparing in parallel the effect of iTNFa, anti-IL17A, anti-IL12−23 and iJAK were identified. One study that compared ixekizumab (anti-IL17A) at 2 different doses with adalimumab (iTNFa) and placebo was identified.[52] Several studies that individually evaluated drugs from the classes of interest vs. placebo were identified.[52–56] Secukinumab has been evaluated in several RCTs known as the Measure studies (1, 2 and 3) for the treatment of axSpA, and in the PREVENT study[54] for the treatment of nr-axSpA.

Conclusion: the balance of the desirable and undesirable effects based on the evidence evaluated favors the use of the intervention. The evidence on the benefit and safety of iTNFa is of high quality. The evidence on secukinumab regarding benefits is high, however, due to the imprecision in the measurement of adverse events (frequencies less than 1%), the quality of the evidence is considered moderate.

□ **Question 8.** In adult patients with axSpA in whom a first-line biological treatment with an anti-TNFα has failed, should another drug/biological agent (which one) be used as the next treatment option due to its effectiveness and safety?

Recommendation: in patients with axSpA, who present therapeutic failure or pharmacological intolerance to anti-TNFα, it is suggested to start an anti-IL17A. Conditional recommendation in favor. Quality of the evidence ⊕⊕◯◯ low.

Summary of the evidence: no study that has evaluated IL17A inhibitors in patients with axSpA in whom the initial anti-TNF therapy failed was identified. Phase III Measure 1–4 studies were conducted in order to evaluate the effect of secukinumab at different doses in patients with ankylosing spondylitis. In the Measure 2,[57,58] it was conducted a subgroup analysis that included 219 patients, of whom 85 (38.8%) had received anti-TNF treatment without response or intolerance.[58]

The Measure 3 study[59] included 226 patients, of whom 53 had presented therapeutic failure or pharmacological intolerance to management with an anti-TNF.

Conclusion: the balance between the desirable and undesirable effects favors the use of an anti-IL17A.

□ **Question 9.** In adult patients with axSpA, should non-pharmacological therapies, such as physical therapy and exercise, be used for the control of the disease, remission of symptoms, low disease activity, and improvement in quality of life and functionality scales?

Recommendation 9A: in patients with axSpA, the prescription of exercise and physical therapy is recommended as part of the usual treatment.

Strong recommendation in favor. Quality of the evidence ⊕⊕⊕◯ moderate.

Recommendation 9B: in patients with axSpA, the prescription of occupational therapy is suggested.

Conditional recommendation in favor. Quality of the evidence ⊕⊕◯◯ low.

Good practice point: the panel considers prioritizing the exercise on land over the exercise in water due to the feasibility of doing it for a long time. It considers that the prescription of physical therapy should ideally be carried out by professionals trained for this purpose (specialist in physical medicine and rehabilitation, specialist in sports medicine).

Summary of the evidence: no studies that comparatively evaluated all available physical therapies were identified, however, studies that evaluated some of them in comparison with others, or with the option of not doing physical therapy, were identified. An open-label controlled clinical trial[60] whose objective was to evaluate the effect of occupational therapy on the functional status of patients with AS treated with anti-TNF drugs was identified. An SLR[61] that evaluates the role of exercise on land or in water for the management of AS patients was identified. This review was rated with Amstar[62] and was considered of acceptable quality. For the exercise, the SLR of Pécourneau et al.[63] was identified as of acceptable quality according to Amstar.

Conclusion: the evidence from clinical trials and meta-analyses has shown the positive impact of physical therapy, exercise both on land and in water, and occupational therapy on the health status, the functional status, and the quality of life of patients with axSpA.

□ **Question 10.** In adult patients with axSpA, should non-pharmacological management with non-conventional therapies (1. Acupuncture; 2. Pilates; 3. Neural therapy; 4. Yoga; 5. Reiki) be used for the control of the disease, remission of symptoms, low disease activity, improvement in quality of life and functionality scales?

Recommendation: in patients with axSpA, it is recommended not to use non-conventional therapies as the önlÿtreatment option.

Conditional recommendation against. Quality of the evidence ⊕⊕◯◯low.

Summary of the evidence: 75 results were identified, of which 8 correspond to systematic reviews and meta-analyses: acupuncture, 3 SLR,[64–66]; Pilates, 2 SLR[66,67]; one meta-analysis[68], one

quasi-experimental study[69] and 2 clinical studies.[70,71] Neural therapy: only one study was identified[72]. Yoga: only one study was identified[73]. Reiki: the literature search did not yield any relevant article.

Conclusion: complementary therapies, generally with few contraindications and side effects, could be part of the pertinent multidisciplinary therapeutic arsenal in these diseases. However, they should not be used as the only treatment option.

□ **Question 11.** To assess disease activity in adult patients with axSpA, which of the clinimetry scales (ASDAS, BASDAI) should be used, according to the characteristics of the test (reliability, sensitivity to change, discriminative ability, internal consistency)?

Recommendation: in patients with axSpA, the use of the ASDAS or BASDAI scales is suggested for the evaluation of disease activity.

Conditional recommendation in favor. Quality of the evidence ⊕⊕⊕⊕ high.

Good practice point: the panel suggests to use preferably the ASDAS because it allows a better stratification of the disease activity.

Summary of the evidence: four studies that address this question were identified[74–77].

Conclusions: it is conditionally recommended in favor the evaluation of the activity with BASDAI and ASDAS, which showed a good discrimination ability and sensitivity to change.

Limitations

It is important to take into account that in some of the questions of this CPG, the evidence obtained did not respond directly, since no comparative studies between the strategies were found. This forced the use of indirect information for the recommendations. It is necessary in the future the design of RCTs that directly involve the comparisons of interest. The changing classification of the disease made it difficult the selection of the studies.

Discussion

This CPG presents the recommendations related to the early diagnosis and treatment of adult patients with axSpA, addressed to health professionals involved in patient care, decision makers, payers of health spending and government entities that generate health policies. These recommendations are intended to describe the treatment approach of the typical patient and cannot anticipate all possible clinical scenarios; therefore, their application must be individualized. This academic initiative aims to reduce variability in clinical practice and support decision-making in the management of patients with axSpA.

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Conflict of interest

The declaration of conflict of interest of each of the members of the GDG was made from the beginning of the process of elaboration of the CPG, and before starting the meetings for the generation of recommendations by all the other participants. No conflict of interest that prevented the participation or voting of any of the members was expressed.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.reumae.2021.09.003.

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