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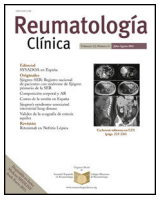

Special Article

2021 clinical practice guidelines for the diagnosis, treatment, and follow-up of patients with peripheral spondyloarthritis. Colombian Association of Rheumatology☆,☆☆

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ABSTRACT

Background: Peripheral spondyloarthritis is a chronic inflammatory disease in which clinical presentation is related to the presence of arthritis, enthesitis and/or dactylitis. This term is used interchangeably with some of its subtypes such as psoriatic arthritis, reactive arthritis, and undifferentiated spondyloarthritis.
Objective: To develop and formulate a set of specific recommendations based on the best available evidence for the diagnosis, treatment and monitoring of adult patients with peripheral spondyloarthritis.
Methods: A working group was established, clinical questions were formulated, outcomes were graded, and a systematic search for evidence was conducted. The guideline panel was multidisciplinary (including patient representatives) and balanced. Following the formal expert consensus method, the GRADE methodology "Grading of Recommendations Assessment, Development and Evaluation" was used to assess the quality of the evidence and generate the recommendations. The Clinical Practice Guideline includes ten recommendations; related to monitoring of disease activity (n = 1) and treatment (n = 9).
Results: In patients with peripheral spondyloarthritis, the use of methotrexate or sulfasalazine as the first line of treatment is suggested, and local injections of glucocorticoids is recommended conditionally. In patients with failure to cDMARDs, an anti TNFα or an anti IL17A is recommended. In case of failure to bDMARDs, it is suggested to use another bDMARD or JAK inhibitor. In patients with peripheral spondyloarthritis associated to inflammatory bowel disease, it is recommended to start treatment with cDMARDs; in the absence of response, the use of an anti TNFα over an anti-IL-17 or an anti-IL-12-23 is recommended as a second line of treatment. In patients with psoriatic arthritis, the combined use of methotrexate with bDMARD is conditionally recommended for optimization of dosing. To assess disease activity in Psoriatic Arthritis, the use of DAPSA or MDA is suggested for patient monitoring.
Conclusions: This set of recommendations provides an updated guide on the diagnosis and treatment of peripheral spondyloarthritis.

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Guía de práctica clínica 2021 para el diagnóstico, el tratamiento y el seguimiento de pacientes con espondiloartritis periférica. Asociación Colombiana de Reumatología

Palabras clave:
Espondiloartritis
Guía de práctica clínica
Tratamiento
Seguimiento

R E S U M E N

Antecedentes: La espondiloartritis periférica es una patología inflamatoria crónica cuya presentación clínica está determinada por la presencia de artritis, entesitis y/o dactilitis. Este término se utiliza indistintamente con algunos de sus subtipos como artritis psoriásica, artritis reactiva y espondiloartritis indiferenciada.
Objetivo: Desarrollar y formular un conjunto de recomendaciones específicas basadas en la mejor evidencia disponible para el diagnóstico, tratamiento y seguimiento de pacientes adultos con espondiloartritis periférica.
Métodos: Se constituyó un grupo desarrollador, se formularon preguntas clínicas, 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. Siguiendo el método de consenso formal de expertos, se utilizó la metodología GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) para para evaluar la calidad de la evidencia y generar las recomendaciones. La guía de práctica clínica incluye diez recomendaciones; una sobre seguimiento de la actividad de la enfermedad y nueve sobre tratamiento.
Resultados: En pacientes con espondiloartritis periférica se sugiere usar metotrexato o sulfasalazina como primera línea de tratamiento y se recomienda en forma condicional la inyección local de glucocorticoides. En los pacientes que fallan a cDMARDs, se recomienda iniciar un anti TNFα o un anti IL17A. Ante falla terapéutica a la primera línea con bDMARDs, se sugiere usar otro bDMARD o un inhibidor JAK. En pacientes con espondiloartritis periférica y enfermedad inflamatoria intestinal asociada, se recomienda iniciar tratamiento con cDMARDs; en ausencia de respuesta, se recomienda el uso de un anti TNFα sobre un anti IL-17 o un anti IL-12-23 como segunda línea de tratamiento. En pacientes con artritis psoriásica se recomienda de forma condicional el uso combinado de metotrexato con bDMARD para favorecer la optimización de la dosis de estos. Para evaluar la actividad de la enfermedad en artritis psoriásica, se sugiere el uso del DAPSA o MDA para el seguimiento de los pacientes.
Conclusiones: Este conjunto de recomendaciones proporcionan una guía actualizada sobre el diagnóstico y tratamiento de espondiloartritis periférica.

Introduction

Spondyloarthritis (SpA) is a generic term comprising a group of underlying inflammatory conditions that share clinical, genetic, epidemiological, pathophysiological and therapeutic response characteristics. Based on their clinical presentation, these conditions may be peripheral or axial; the age of onset is usually before 45 years old. Peripheral spondyloarthritis (pSpA), as a subtype of spondyloarthritis, is a chronic inflammatory condition clinically characterized by the presence of arthritis (oligoarthritis predominantly of the lower extremities), enthesitis (site of attachment of a tendon, ligament, or joint capsule to the bone) and/or dactylitis (sausage fingers). The classification criteria *Assessment of SpondyloArthritis International Society* substantially changed the phenotypical approach, also referred to as the "SpA concept", by a more accurate classification for the peripheral presentation associated with the predominant symptomatology[1]. However, the ESSG classification criteria may also be useful in various clinical settings[2].

The term SpA is used indistinctively with some of its subtypes, such as psoriatic arthritis (PsA), reactive arthritis and undifferentiated SpA. However, the hallmark of pSpA is the presence of peripheral symptoms (arthritis, enthesitis and dactylitis) but it is not pathognomonic, since these may also be present in patients with axial SpA[3].

Several studies in Colombia have reported different clinical presentation patterns in pSpA and their more frequent manifestations, assessing the performance of the different classification criteria and using the rheumatologists clinical diagnosis as the external standard[4].

The data associated with the clinical presentation patterns in pSpA, in contrast to the data extrapolated from PsA studies, are limited. The diagnostic delay is shorter than axial SpA because patients with peripheral manifestations usually present with clinically objective inflammatory signs (arthritis and/or dactylitis). The age of onset of symptoms is delayed as compared against axial spondyloarthritis and the gender distribution is the same[5]. Among the typical manifestations of pSpA, dactylitis is a hallmark of PsA[6].

Among the extra-articular manifestations, psoriasis is the most common one (43%–53%), followed by inflammatory bowel disease (4%–17%) and acute anterior uveitis (2%–6%). Inflammatory lumbar pain which is a prevalent characteristic in patients with axial SpA has also been reported in 12.5% of the patients with PsA and in up to 21% in pSpA[7].

The prevalence of SpA in Latin America has been estimated at about 0.14 (95% CI: 0.05–0.34)[8]. A recent study conducted in Colombia using the Copcord methodology, estimated a prevalence of 0.11% for SpA and of 0.28% for undifferentiated SpA[9].

In addition to the extra-articular manifestations (uveitis, psoriasis and inflammatory bowel disease), the associated comorbidities in these patients increase the total burden of the disease, particularly in terms of cardiovascular and infectious diseases[10].

The main treatment objective in SpA is to maximize the long-term health-related quality of life by controlling signs and symptoms (pain, morning stiffness, and fatigue) and inflammation (disease activity), in addition to the prevention of progressive structural damage (osteo-proliferative and osteo-destructive changes in the peripheral joints), preserving function (spinal mobility) and social participation (activity and productivity)[11]. However, the treatment of patients with pSpA represents a challenge to the clinician because of the heterogenous nature of the clinical manifestations and the subtypes included in the definition, which significantly influence the therapeutic decisions for each individual patient[3].

This is the first clinical practice guideline (CPG) developed, published and implemented in Colombia, for patients with pSpA; its objective is to make specific recommendations on the diagnosis, treatment and follow-up of these patients. The CPG are addressed to all healthcare professionals involved with the care of patients with pSpA, decision-makers, healthcare payers and government institutions developing health policies. The complete version of the CPG (included the methodology developed, the systematic search for scientific information and the detailed presentation of the evidence) is available in the supplemental material and may be accessed through the website of the Colombian Association of Rheumatology (Asoreuma) and the webpage of the scientific societies of the Ministry of Health and Social Protection of Colombia, following the publication of this document.

Materials and methods

The main purpose of this CPG is to develop and design specific recommendations supported by the best available evidence associated with the diagnosis and treatment of adult patients with pSpA. The intent is to standardize diagnostic and monitoring approaches, to create awareness of the medical practitioners about the identification and clinical suspicion of the disease, reduce the treatment variability by rationalizing expenditure, optimizing timely referral of patients to the rheumatologist, and improving quality of life and occupational and social performance of these patients.

In accordance with the formal consensus methodology suggested by the *Methodological Guidelines for the development of comprehensive care guidelines of the Colombian General Healthcare System*[12], the experts panel approach was selected to produce the recommendations.

The Guidelines Development Team (GDT) assessed the accuracy of the evidence, developed and graded the recommendations, pursuant to the approach suggested by the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE [GRADEwg]) work group[13–16].

Organization, planning and coordination of the clinical practice guidelines

The GDT comprised 9 expert rheumatologists and one immunology bacteriologist, members of the Asoreuma Spondyloarthritis Study Group, 2 representatives of patients one anthropologist as the civil society representative. All the panel sessions were joined by representatives of the Ministry of Health and Social Protection and of the Institute for the Assessment of Health Technologies (IETS). The leader of the GDT was a rheumatologist representing the Asoreuma study group. The development of the CPG was under the methodological oversight of an external independent consulting firm - Evidentias SAS. The CPG were developed according to the recommendations of the Methodological Guidelines for Preparing Clinical Practice Guidelines and economic evaluation of the Colombian Social Security system[12]. The work of the GDT was conducted using IT tools, on-site meetings, and virtual meetings. Evidentias assisted the process for the development of the guidelines, including the identification of the methodology, the preparation of the agendas for the meetings, the materials, moderating the discussion panel sessions, in addition to summarizing and assessing the evidence to systematically respond to each question of the guidelines and producing the final documents.

Sponsorship of the clinical practice guidelines and addressing conflicts of interest

The development of the CPG was possible due to the unrestrictive support of the following organizations which together funded the project: Abbvie, Amgen, Janssen, Novartis and Pfizer. The technical work for the development process of these CPG was independently conducted by the GDT.

The disclosure of possible conflicts of interest by each GDT member was explicitly made at the beginning of the process for the development of the CPG, and also before the start of the meetings to produce the recommendations suggested by all of the participants. No conflict of interests was disclosed which preventing the participation or vote of any of the GDT members.

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

Outcomes of questions assessing treatment interventions	Significance
Disease control - remission/low symptom activity	Critical
Disease control – improvement in functional scales	Critical
Improved quality of life	Critical
Severe adverse events (defined for each specific treatment)	Critical
Disease control – radiographic progression	Important
Chronic structural changes and acute inflammatory radiographic	Important
Outcomes of questions assessing diagnostic tests and scales	Significance
Diagnostic accuracy (sensitivity, specificity, positive predictive value, negative predictive value, odds ratio)	Critical
Reliability, sensitivity to change, discriminative ability	Critical

Drafting of clinical questions and definition of outcomes

The questions of the guidelines were designed via open consultation to all the GDT members and then prioritized by the GDT, pursuant to the Delphi methodology. A total of 2 rounds of virtual consultation were needed via e-mail to reach consensus (more than 80% of the GDT membership). The methodology suggested by the GRADEwg was used to grade the relevant outcomes for each question[13]. The process was conducted virtually. The outcomes are shown in Table 1 and were considered critical and important for the total number of questions to be answered by the GDT, using in the definition the selection criteria of the evidence supporting each recommendation (supplemental material [protocols per question available at: https://www.asoreuma.org]).

Review and assessment of previous clinical practice guidelines

After defining the questions to be answered by the guidelines, a search was conducted to identify any CPG on pSpA, in order to assess the relevance of adapting and adopting some of their recommendations, according to the *Adolopment* strategy[17]. A total of 10 CPG[18–28] published over the past 5 years were identified as pre-established criterion, including the pSpA recommendation. These CPG were fully reviewed by 3 members of the GDT and an expert in methodology from Evidentias, using *The Appraisal of Guidelines for Research & Evaluation Instrument* (AGREE-II)[29,30]. The results of this assessment are shown in Table 2.

None of the CPGs approached all of the questions designed by the GDT to be answered as part of this guidelines. The CPGs that rigorously complied (based on the assessment by AGREE-II) were taken into consideration to adapt their recommendations for the questions for which no evidence was found to provide an answer.

Review of the evidence and development of the recommendations

The Evidentias team conducted a systematic literature review following the international standards suggested by the Cochrane collaboration[31], to respond to each question and report on the

Table 2
Assessment of the clinical practice guidelines in peripheral Spondyloarthritis according to AGREE-II[15,16].

AGRE-II domains	Average score (%)	Range (%)
Scope and purpose	86	67–96
Participation of 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 the guideline recommend?[a]	62	0–100[a]

[a] 0%–24%: will not recommend; 25%–75%: recommends with amendments; 76%–100%: recommends.

effects (benefits and damages) of the interventions, the use of resources (profitability), values and preferences (relative importance of the results), potential impact on fairness, acceptability, and feasibility of implementing the potential recommendation.

Initially, a highly sensitive search strategy was developed to identify any publications associated with "Spondyloarthritis". Based on this strategic definition of the condition, specific search strategies were developed for each question, considering the interventions and relevant comparators according to the structure «Patient, Intervention, Comparator and *Outcome*» (PICO) of each question. The necessary changes were introduced to the strategies defined (Ex. use of high-sensitivity filters for the identification of the relevant type of study) so that 3 complementary searches were conducted per each question: (1) one focusing on the identification of evidence to assess the effect of the intervention or diagnostic test; (2) another focused on the identification of cost studies and economic assessments to inform on the potential economic impact of the intervention; and (3) identification of studies on values and preferences of patients. The searches were designed by a bio-IT expert from Evidentias.

The searches were conducted using the OVID search engine, including PubMed/Medline, Embase, Epistemonikos and LILACs-SciELO. If the search failed to produce any relevant evidence to answer the question, a manual search was conducted reviewing references, accessing pages of scientific societies, and consultation with GDT experts.

The studies identified for each question were assessed by 2 clinical epidemiologists from Evidentias in terms of their methodological quality. The systematic reviews were assessed using the *Assessing the Methodological Quality of Systematic Reviews* tool[32]. The randomized clinical experiments were assessed using the Cochrane *Risk of Bias*[33], while the diagnostic studies and systematic reviews of diagnostic tests were assessed using the *Quality Assessment of Diagnostic Accuracy Studies* tool[34]. Cost studies were evaluated using the *Drummond* checklist, recommended for the appraisal of studies on economic analysis[35]. The quality assessment of the studies on values and preferences was conducted pursuant to the GRADEwg recommendations for this type of evidence[36]. The overall certainty of the evidence was assessed according to the GRAD[37] approximation for developing evidence profiles and summary tables of findings that included the principal outcomes considered to be relevant to each question.

A protocol was designed for each question, including: the PICO structure, rating of outcomes, search strategy, description of the search results, a brief outline of the studies identified for each relevant aspect and its methodological quality, in addition to the outcomes summary table GRADE, as well as the "Evidence to decision" (EtD) framework suggested by GRADEwg to collect the necessary information on each aspect to consider, in order to produce the recommendations and opinions of the GDT on each particular aspect[15].

The protocol for each question was reviewed by an expert rheumatologist of the GDT. Any comments and addenda suggested by the expert were taken into account to produce a new version of the protocol, which was finally submitted to all the GDT members for review. The articles sent by the experts as complementary information were assessed in terms of their methodological quality by the Evidentias team, and allocated to the columns "evidence" or "additional information" of the EtD framework.

The GDT members, representatives of patients and fairness experts were contacted by the CPG coordinators during the process of preparing the EtD, well in advance, in order to collect the relevant data to report on these 2 aspects.

At least 8 days prior to the meeting for the recommendations, all GDT members received all of the protocols developed for each question, via e-mail, encouraging them to read the information and prepare any additional information considered to be relevant and their opinion (vote) regarding each of the items under the EtD framework.

Two virtual meetings using *Google Meet* were held to generate the recommendations. In addition to the panel of experts, the representatives of patients, the representative of the society, the representatives of the Ministry of Health and Social protection, the IETS representatives and the experts in methodology participated in these meetings. The votes were casted using the *Mentimeter*® ^{x} electronic voting system. The recommendation was approved with 50% + 1 vote, of the total number of valid voters. The results of the ballot are available in the supplemental material (https://www.asoreuma.org). The meetings were video and audio recorded for future reference.

The final EtD was produced after the meeting, including the final opinions of the GDT, any amendments agreed and the recommendations submitted. The final protocols for each question were reviewed once again by the GDT in a virtual consult via e-mail (these protocols are part of the available supplemental material available at: https://www.asoreuma.org).

Interpretation of the recommendations

Each recommendation informs about the direction (in favor or against the intervention assessed and indicates the strength of a recommendation, which is expressed as strong— "the panel recommends. . ."— or conditional —"the panel suggests. . ."—). Occasionally, a strong recommendation is based on a low or very low certainty of the evidence. In such circumstances, the panel believes that additional enquiry on other aspects such as: economic impact, patient values, impact on fairness and acceptability of the intervention in the evaluation, contribute to the balance of the impact (beneficial or undesirable effects), and therefore alters the recommendations. The rationale of the considerations and the opinions of the panel support such recommendations.

Document review

The GDT conducted the activities leading to the inclusion of the various stakeholders and decision-makers: (1) dissemination of the scope, the objectives and the clinical questions included in the guidelines, via their publication in the Asoreuma webpage; (2) participation and ballot during the virtual meetings; (3) dissemination over the course of one month of the final CPG recommendations among the healthcare professionals and interested parties, via the Asoreuma webpage and social media posts; and (4) submission of the final document of the CPG for external peer review. The suggestion is to update this CPG every 2 years from the date of its publication, when there is evidence of any changes in the recom-

mendations initially made. In the absence of any new evidence, the guidelines shall be reviewed every three years.

Results

The recommendations – based on each question asked – are as follows, and include the summary of the evidence:

Question 1

In adult patients with pSpA should SNAID or conventional DMARDs (cDMARDs)[38] be used as the first line of drug therapy, based on effectiveness (disease control, remission/low symptoms activity, improvement in functional scales) and safety (adverse events)?

Recommendation: in adult patients with pSpA the suggestion as first line therapy is the use of cDMARDs. Conditional recommendation in favor of cDMARDs intervention. Certainty of the evidence low ⊕⊕◯◯.

Good practice point: the panel considers that methotrexate or sulfasalazine may be used indistinctively[38]. It is necessary to educate the patient about the treatment and its effects for improved treatment compliance and satisfaction[39,40].

Rationale: upon consideration of the evidence on effectiveness, safety, use of resources, costs, value for patients and impact on fairness, the panel considers that the balance of the effects favors the intervention with cDMARDs, based on its potential effect on the improvement of patients and the fact that there are no differences in terms of adverse events as compared to placebo[38–40].

Subgroup consideration: In patients with PsA, the suggestion is to use methotrexate as the first line therapy[38]. Conditional recommendation in favor of methotrexate. Certainty of the evidence low ⊕⊕◯◯.

Question 2

In adult patients with pSpA, should local or systemic glucocorticoids be used based on their effectiveness (disease control, remission/low symptom activity, improvement in function and quality of life scales, radiographic progression) and safety (adverse events)?

Recommendation: in patients with pSpA the recommendation is to avoid the use of systemic glucocorticoids. Strong recommendation against treatment. Certainty of the evidence low ⊕⊕◯◯.

Good practice point: prior to initiating glucocorticoid management in patients suspicious of pSpA, the recommendation is early referral to the rheumatologist to ensure management and diagnosis according to the highest quality standards.

Rationale: upon considering the evidence on effectiveness[41,42], safety[43–45], use of resources and costs[46,47], value for patients[48] and potential impact on fairness, the panel considers that the balance of the effects is against the use of glucocorticoids. This is due to the known undesirable effects of the systemic use of these medications, and the very low evidence of any benefits. The panel considers that despite the poor evidence, glucocorticoids are frequently used in these patients; this recommendation reduces the variability of the therapeutic approach of pSpA, optimizes and rationalizes healthcare costs.

Subgroup consideration: in patients with PsA the recommendation is to avoid the use of systemic glucocorticoids. Strong recommendation against the treatment. Certainty of the evidence low ⊕⊕◯◯.

Rationale: the panel considers that in patients with PsA treated with systemic glucocorticoids, the discontinuation of the medication may lead to a flare of the psoriatic skin lesions[48].

Question 3

In adult patients with pSpA and cDMARDs failure, the first choice for biologic therapy is an TNFα, an anti-IL-17, an anti IL12-23, or JAK inhibitors, based on their effectiveness (disease control, remission/low symptom activity, improvement if function scales) and safety (adverse events)?

Recommendation: in patients with pSpA who failed therapy or are cDMARDs intolerant, the recommendation is to initiate treatment with an anti TNFα or an anti IL17A. Strong recommendation in favor. Certainty of the evidence moderate ⊕⊕⊕◯.

Good practice point: during treatment with any of these biologic DMARDs (bDMARDS), strict patient follow-up is mandatory and regular assessment of the therapeutic response. Following a reasonable period of treatment, the medication should be discontinued to start therapy with a different class of molecule, in accordance with the individual patient characteristics.

Rationale: upon consideration of the evidence on effectiveness[49–59], safety[60,61], use of resources and costs[62–64], patient values and the potential impact on fairness, the panel considers that the balance of the effects favors the start of biologic therapy with an TNFα or an anti IL17A.

Subgroup considerations: in patients with psoriatic arthritis and treatment failure or cDMARDs intolerance, the recommendation is to initiate therapy with an anti TNFα or anti IL17A, anti-IL 12-23, anti PDE4 or a JAK inhibitor (tofacitinib). Strong recommendation in favor. Certainty of the evidence moderate ⊕⊕⊕◯

In patients with PsA and significant skin involvement who failed therapy of are intolerant to cDMARDs, the recommendation is to initiate treatment with an agent exhibiting a stronger effect on these manifestations such as ixekizumab or secukinumab[65,66]. Strong recommendation in favor. Certainty of the evidence, moderate ⊕⊕⊕◯.

Implementation considerations: among the various anti-IL17A, the use of secukinumab or ixekizumab is suggested, based on their higher probability of being cost-effective versus the various thresholds of willingness to pay in the countries in which they have been assessed, in contrast to other medications of the different subclasses considered[67,68].

Question 4

In adult patients with pSpA and failure to first line therapy with bDMARDs (anti TNFα, anti-IL-17, anti-IL 12-23) or JAK inhibitors, which DMARD should be used as the next treatment option, considering effectiveness (disease control, remission/low symptom activity, improvement if function scales) and safety (adverse events)?

Recommendation: in adult patients with pSpA and failure to first line therapy with bDMARDs, the suggestion is the use of another bDMARD as the next treatment option (whether with the same or with a different mechanism of action) or a JAK inhibitor. Conditional recommendation in favor of the intervention. Certainty of the evidence, moderate ⊕⊕⊕◯.

Good practice point: the decision to change or discontinue therapy with the first bDMARD shall be made based on the objective analysis of the disease activity, using valid clinimetric tools. Expert consensus.

Rationale: upon consideration of the evidence on effectiveness and safety[69–71] and use of resources and costs, the panel considered that the balance of effects is favorable for the continuation of treatment with another bDMARD. The panel acknowledges that the current evidence is only relevant for psoriatic arthritis, there is no evidence about all of the potential comparisons, and some are the result of a subgroup analysis with a small number of participants;

in every case, the safety analyses of the treatments assessed are adequate.

Question 5

In the treatment of adult patients with pSpA and associated uveitis as an extra-articular manifestation, cDMARDs should be used based on their effectiveness (disease control, remission/low symptom activity, improvement in functional scales (and safety (adverse events)?

Recommendation: in adult patients with pSpA and anterior uveitis (associated as an extra-articular manifestation) the suggestion is to use methotrexate or sulfasalazine with a view to reducing flares. Conditional recommendation in favor of the use of cDMARDs. Certainty of the evidence ⊕⊕◯◯.

Subgroup consideration: in adult patients with pSpA and anterior uveitis that fails to respond to management with immune-modulators, the suggestion is to use azathioprine to control the ocular inflammation. Conditional recommendation in favor of the intervention. Certainty of the evidence is low ⊕⊕◯◯.

Rationale: the panel considers that there is currently a lack of strong evidence about the use of immune-modulators in patients with SpA and anterior uveitis; however, the available evidence shows the potential effectiveness of methotrexate and of sulfasalazine to prevent acute manifestations of anterior uveitis and improve visual acuity, in addition to being safe in these patients. Upon consideration of the specific evidence on effectiveness and safety[72,73], and of the use of resources and costs[74], the patients' values and preferences[75], and the potential impact on fairness, the panel considered that the balance of effects is in favor of cDMARDs treatment.

Question 6

In the treatment of adult patients with pSpA and associated uveitis as an extra-articular manifestation, should bDMARDs (anti TNFα, anti-IL-17, anti IL 12-23) or JAK inhibitors be used, based on their effectiveness (disease control, remission/low symptom activity, improvement in functional scales) and safety (adverse events)?

Recommendation: in adult patients with pSpA and associated uveitis (as an extra-articular manifestation), with indication of bDMARDs, the use of an anti TNFα is suggested in order to reduce the rate of acute anterior uveitis. Conditional recommendation in favor of the intervention. Certainty of the evidence very low ⊕◯◯◯.

Rationale: there is currently poor solid evidence to answer this question; the few experimental studies identified were placebo controlled and the most recent studies are observational or case series. Upon consideration of the evidence on effectiveness and safety, use of resources and costs, patient values and potential impact on fairness, the panel considered that the balance of the effects favors the intervention with anti TNFα (its potential benefits exceed the risks). Additionally, the panel considered that anti TNFα monotherapy does not show any clinically relevant differences in terms of undesirable effects (severe infections or hepatic events) when compared against combined methotrexate and anti TNFα therapy[76–83].

Question 7

In the treatment of adult patients with pSpA and associated inflammatory bowel disease, should cDMARDs be used in terms of their effectiveness (disease control, remission/low symptom activity, improvement in functional scales) and safety profile (adverse events)?

Recommendation: in patients with pSpA and associated inflammatory bowel disease, the suggestion is to initiate treatment with cDMARDs. Conditional recommendation in favor of the intervention. Certainty of the evidence very low ⊕◯◯◯.

Rationale: the literature search analyzed failed to identify any study assessing the intervention of interest in these patients; hence a review of the *Guidelines for the treatment of psoriatic arthritis* of the American College of Rheumatology and the National Psoriasis Foundation published in 2018[84] was conducted and made recommendations for adult patients with active PsA and active inflammatory bowel disease, who were *naive* both to cDMARD and biologic therapy. The intent was to identify potential sources of information and assess the relevance of adopting some of their recommendations regarding this question. Upon considering the recommendations given in the guidelines and the supporting evidence, as well as the evidence on patient values and preferences, the panel decided to recommend by consensus the use cDMARDs, based on the fact that the balance of the effects favors the use of this intervention due to its potential moderate benefits, and the few undesirable effects observed with these therapies in multiple other treatment approaches (indirect evidence).

Question 8

In the treatment of adult patients with pSpA and associated inflammatory bowel disease, should bDMARDs (anti TNFα, anti-IL-17, anti IL 12-23) or JAK inhibitors be used, based on their effectiveness (disease control, remission/low symptom activity, improvement in functional scales) and safety profile (adverse events)?

Recommendation: in patients with pSpA and associated inflammatory bowel disease that do not respond to cDMARDs management, the recommendation is the use of an anti TNFα over treatment with other bDMARDs such as anti IL-17 or anti IL 12-23. Strong recommendation in favor of the use of anti TNFα. Certainty of the evidence: on anti-IL-17 moderate ⊕⊕⊕◯; on anti-IL 12-23 very low ⊕◯◯◯

Good practice point: when choosing the anti TNFα in these patients, the suggestion is to prefer the use of monoclonal antibodies over soluble receptor bDMARDS[85–88]. Certainty of the evidence: moderate ⊕⊕⊕◯

There is need to regularly monitor patients receiving this therapy to identify any adverse events in the long term.

Rationale: No studies were identified that assessed the intervention of interest in these patients; hence the recommendation made in this regard by the *Guidelines for the Treatment of Psoriatic Arthritis* of the American College of Rheumatology and the National Psoriasis Foundation published in 2018 was reviewed[84]. After assessing the additional evidence on the values and preferences of patients, the panel decided to adopt this recommendation by consensus, notwithstanding the lack of studies in the population of interest (pSpA and associated inflammatory bowel disease), the indirect evidence supports the effectiveness and safety of the biologic therapy with an antiTNFα in patients with Spondyloarthritis.

Question 9

Is the use of clinimetric scales helpful to assess the activity of the disease in adult patients with pSpA (operating characteristics of the test): *Disease Activity Score-28* vs. *Disease Activity for Psoriatic Arthritis* (DAPSA) vs *Minimal Disease Activity*?

Recommendation 9: in patients with PsA, the recommendation is to assess the activity of the disease using DAPSA based on its adequate ability to discriminate the activity of the disease. Conditional recommendation in favor. Certainty of the evidence, moderate ⊕⊕⊕◯.

Good practice point: the suggestion is to complement the DAPSA assessment with the *Minimal Disease Activity* scale – if possible – keeping in mind that the evidence prevents the identification of superiority of one index over another, but they may complement each other when assessing different domains. Certainty of the evidence: moderate ⊕⊕⊕◯.

Rationale: upon assessing the evidence with regards to precision and operating characteristics of the tests[89–91], patient values, use of resources and costs[92–96], the panel considered that the balance of the effects favors the use of the DAPSA clinimetric scale. However, this scale focuses mostly in peripheral joint disease and is able to accurately reflect any changes in this domain, but fails to measure other domains of the disease; this may neglect to document the disease activity (high disease activity on the skin).

Question 10

In the treatment of adult patients with pSpA, is the use of combined methotrexate and bDMARDs therapy (anti TNFα, anti-IL-17, anti-IL 12-23) or JAK inhibitors more effective (disease control, remission/blow symptom activity, improvement in functional scales) and safer (adverse events) that the use of monotherapy with bDMARDs (anti TNFα, anti-IL-17, anti-IL 12-23) or JAK inhibitors?

Recommendation: in paients with PsA the combined use of methotrexate with bDMARDS (anti TNFα, anti-IL-17, anti-IL-12-23) is suggested. Conditional recommendation in favor of the intervention. Certainty of the evidence, low ⊕⊕◯◯.

Rationale: upon assessing the evidence of the effectiveness and safety of the patients and the use of resources and costs, the panel considered by consensus that the balance of the effects favors the combined therapy intervention. The use of methotrexate may be associated with higher retention of the biologic, and may additionally favor the dose optimization of the agent[97–100].

Discussion

This CPG provide the recommendations for the early diagnosis and treatment of adult patients with pSpA, and are addressed to the healthcare professionals involved with patient care, decision-makers, healthcare payers, and government agencies making health policies. These recommendations are intended to describe the treatment approach for typical patients and hence fail to anticipate every possible clinical scenario. Hence, the implementation of these recommendations should be individualized. This academic initiative is designed to reduce the variability in clinical practice and support decision-making for the management of patients with pSpA.

Limitations

The evidence identified to answer most of the questions included in these guidelines is indirect, since no comparative studies were found among the assessment options studying patients with pSpA.

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Conflict of interests

The disclosures of each GDT member were submitted at the beginning of the development process of the CPG and before the start of the meetings to produce the recommendations by the rest of the participants. No conflict of interest was disclosed that prevented the participation or vote of any member.

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Appendix A. Supplementary data

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References

1. Rudwaleit M, van der Heijde D, Landewe R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70:25–31, http://dx.doi.org/10.1136/ard.2010.133645.
2. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum. 1991;34:1218–27.
3. Carron P, de Craemer AS, van Den Bosch F. Peripheral spondyloarthritis: a neglected entity — State of the art. RMD Open. 2020;6:e001136, http://dx.doi.org/10.1136/rmdopen-2019-001136.
4. Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global prevalence of spondyloarthritis: a systematic review and meta-regression analysis. Arthritis Care Res (Hoboken). 2016;68:1320–31.
5. del Río-Martínez P, Navarro-Compán V, Díaz-Miguel C, Almodóvar R, Mulero J, De Miguel E. Similarities and differences between patients fulfilling axial and peripheral ASAS criteria for spondyloarthritis: Results from the Esperanza Cohort. Semin Arthritis Rheum. 2016;45:400–3, http://dx.doi.org/10.1016/j.semarthrit.2015.09.001.
6. Kaeley GS, Eder L, Aydin SZ, Gutierrez M, Bakewell C. Dactylitis: a hallmark of psoriatic arthritis. Semin Arthritis Rheum. 2018;48:263–73.
7. De Winter JJ, Paramarta JE, de Jong HM, van De Sande MG, Baeten DL. Peripheral disease contributes significantly to the level of disease activity in axial spondyloarthritis. RMD Open. 2019;5:1–8.

8. Bautista-Molano W, Landewé RBM, Londoño J, Romero-Sanchez C, Valle-Oñate R, van der Heijde D. Analysis and performance of various classification criteria sets in a Colombian cohort of patients with spondyloarthritis. Clin Rheumatol. 2016;35:1759–67.
9. Londoño J, Peláez Ballestas I, Cuervo F, Angarita I, Giraldo R, Rueda JC, et al. Prevalence of rheumatic disease in Colombia according to the Colombian Rheumatology Association (COPCORD) strategy. Prevalence study of rheumatic disease in Colombian population older than 18 years. Rev Colomb Reumatol. 2018;25:245–56.
10. Bautista-Molano W, Landewé R, Burgos-Vargas R, Maldonado-Cocco J, Moltó A, Van Den Bosch F, et al. Prevalence of comorbidities and risk factors for comorbidities in patients with spondyloarthritis in Latin america: a comparative study with the general population and data from the ASAS-COMOSPA study. J Rheumatol. 2018;45:206–12.
11. Heuft-Dorenbosch L, Van Tubergen A, Spoorenberg A, Landewé R, Dougados M, Mielants H, et al. The influence of peripheral arthritis on disease activity in ankylosing spondylitis patients as measured with the Bath Ankylosing Spondylitis Disease Activity Index. Arthritis Rheum. 2004;51:154–9.
12. Orden LY, Carrasquilla G, Director G, Médico DP, Cristina A, Alvarez P, et al. Guía metodológica para la elaboración de guías de práctica clínica con evaluación económica en el Sistema General de Seguridad Social en Salud colombiano; 2014, http://gpc.minsalud.gov.co/recursos/Documentos compartidos/Guia_Metodologica_Web.pdf.
13. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6 https://www.bmj.com/content/336/7650/924
14. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64:383–94 https://linkinghub.elsevier.com/retrieve/pii/S0895435610003306
15. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ. 2016:i2089, http://dx.doi.org/10.1136/bmj.i2089.
16. Schünemann HJ, Mustafa R, Brozek J, Santesso N, Alonso-Coello P, Guyatt G, et al. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. J Clin Epidemiol. 2016;76:89–98, http://dx.doi.org/10.1016/j.jclinepi.2016.01.032.
17. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017;81:101–10, http://dx.doi.org/10.1016/j.jclinepi.2016.09.009.
18. Smolen JS, Schöls M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis. 2018;77:3–17, http://dx.doi.org/10.1136/annrheumdis-2017-211734.
19. Duarte C, Sousa-Neves J, Águeda A, Ribeiro P, Daniel A, Eugénio G, et al. Portuguese recommendations for the use of biological therapies in patients with rheumatoid arthritis-2016 update. Acta Reumatol Port. 2017;42:112–26 http://www.ncbi.nlm.nih.gov/pubmed/28535544
20. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017;76:978–91 http://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2016-210770
21. Hamilton L, Barkham N, Bhalla A, Brittain R, Cook D, Jones G, et al. BSR and BHPR guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. Rheumatology. 2017;56:313–6 https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/kew223
22. Rohekar S, Chan J, Tse SML, Haroon N, Chandran V, Bessette L, et al. 2014 Update of the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada Treatment Recommendations for the Management of Spondyloarthritis. Part II: Specific Management Recommendations. J Rheumatol. 2015;42:665–81, http://dx.doi.org/10.3899/jrheum.141001.
23. Wendling D, Lukas C, Paccou J, Claudepierre P, Carton L, Combe B, et al. Recommendations of the French Society for Rheumatology (SFR) on the everyday management of patients with spondyloarthritis. Jt Bone Spine. 2014;81:6–14 https://linkinghub.elsevier.com/retrieve/pii/S1297319X13002881
24. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis Rheumatol. 2016;68:1060–71, http://dx.doi.org/10.1002/art.39573.
25. Tam LS, Wei JC, Aggarwal A, Baek HJ, Cheung PP, Chiowchanwisawakit P, et al. 2018 APLAR axial spondyloarthritis treatment recommendations. Int J Rheum Dis. 2019;22:340–56 https://onlinelibrary.wiley.com/doi/abs/10.1111/1756-185X.13510
26. Spondyloarthritis in over 16s: Diagnosis and Management. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553609/.
27. Reyes-Cordero G, Enríquez-Sosa F, Gomez-Ruiz C, Gonzalez-Diaz V, Castillo-Ortiz JD, Duran-Barragán S, et al. Recomendaciones del Colegio Mexicano de Reumatología para el manejo de las espondiloartritis. Reumatol Clín. 2019;17:37–45, http://dx.doi.org/10.1016/j.reuma.2019.03.010.
28. Cañete Crespillo J. Guía de Práctica Clínica para el Tratamiento de la Espondiloartritis Axial y la Artritis Psoriásica. Soc Esp Reumatol. 2015 https://www.ser.es/wp-content/uploads/2016/04/GPC_-Tratamiento_EspAax_APs_DEF.pdf
29. AGREE Next Steps Consortium. http://www.guiasalud.es, 2009.
30. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. Can Med Assoc J. 2010;182:E839–842, http://dx.doi.org/10.1503/cmaj.090449.
31. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane Handbook for Systematic Reviews of Interventions. 2nd edition Chichester (UK): John Wiley & Sons; 2019.
32. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008, http://dx.doi.org/10.1136/bmj.j4008.
33. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928, http://dx.doi.org/10.1136/bmj.d5928.
34. Higgins J, Sterne J, Savovic J, Page MJ, Hróbjartsson A, Boutron I, et al. A revised tool for assessing risk of bias in randomized trials. Cochrane Database Syst Rev. 2016;10:29–31 https://research.monash.edu/en/publications/a-revised-tool-for-assessing-risk-of-bias-in-randomized-trials
35. Wijnen B, van Mastrigt G, Redekop W, Majoie H, De Kinderen R, Evers SMAA. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: data extraction, risk of bias, and transferability (part 3/3). Expert Rev Pharmacoeconomics Outcomes Res. 2016;16:723–32, http://dx.doi.org/10.1080/14737167.2016.1246961.
36. Zhang Y, Coello PA, Guyatt GH, Yepes-Nuñez JJ, Akl EA, Hazlewood G, et al. GRADE guidelines: 20. Assessing the certainty of evidence in the importance of outcomes or values and preferences—inconsistency, imprecision, and other domains. J Clin Epidemiol. 2019;111:83–93, http://dx.doi.org/10.1016/j.jclinepi.2018.05.011.
37. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64:401–6 https://linkinghub.elsevier.com/retrieve/pii/S089543561000332X
38. Wilsdon TD, Whittle SL, Thynne TR, Mangoni AA. Methotrexate for psoriatic arthritis. Cochrane Database Syst Rev. 2019;1:Cd012722.
39. Nota I, Drossaert CHC, Taal E, Vonkeman HE, van de Laar MAFJ. Patient participation in decisions about disease modifying anti-rheumatic drugs: a cross-sectional survey. BMC Musculoskelet Disord. 2014;15:333.
40. Pasma A, van't Spijker A, Luime JJ, Walter MJ, Busschbach JJ, Hazes JM. Facilitators and barriers to adherence in the initiation phase of Disease-modifying Antirheumatic Drug (DMARD) use in patients with arthritis who recently started their first DMARD treatment. J Rheumatol. 2015;42:379–85.
41. D'Angiolella LS, Cortesi PA, Lafranconi A, Micale M, Mangano S, Cesana G, et al. Cost and cost effectiveness of treatments for psoriatic arthritis: a systematic literature review. Pharmacoeconomics. 2018;36:567–89, http://dx.doi.org/10.1007/s40273-018-0618-5.
42. Ash Z, Gaujoux-Viala C, Gossec L, Hensor EMA, FitzGerald O, Winthrop K, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2012;71:319–26.
43. Soriano ER, McHugh NJ. Therapies for peripheral joint disease in psoriatic arthritis. A systematic review. J Rheumatol. 2006;33:1422–30.
44. Hoes JN, Jacobs JWG, Verstappen SMM, Bijlsma JWJ, van der Heijden GJMG. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis. 2009;68:1833–8.
45. McDonough AK, Curtis JR, Saag KG. The epidemiology of glucocorticoid-associated adverse events. Curr Opin Rheumatol. 2008;20:131–7 http://journals.lww.com/00002281-200803000-00004
46. Zink A, Thiele K, Huscher D, Listing J, Sieper J, Krause A, et al. Healthcare and burden of disease in psoriatic arthritis. A comparison with rheumatoid arthritis and ankylosing spondylitis. J Rheumatol. 2006;33:86–90.
47. Pisu M, James N, Sampsel S, Saag KG. The cost of glucocorticoid-associated adverse events in rheumatoid arthritis. Rheumatology. 2005;44:781–8 http://academic.oup.com/rheumatology/article/44/6/781/1784792/The-cost-of-glucocorticoidassociated-adverse
48. Robson JC, Dawson J, Cronholm PF, Ashdown S, Easley E, Kellom KS, et al. Patient perceptions of glucocorticoids in anti-neutrophil cytoplasmic antibody-associated vasculitis. Rheumatol Int. 2018;38:675–82 http://link.springer.com/10.1007/s00296-017-3855-6
49. McInnes IB, Nash P, Ritchlin C, Choy EH, Kanters S, Thom H, et al. Secukinumab for psoriatic arthritis: comparative effectiveness versus licensed biologics/apremilast: a network meta-analysis. J Comp Eff Res. 2018;7:1107–23 http://www.epistemonikos.org/documents/77f6dddb4a9002993e26d9a70160bdedf51069a8
50. Song GG, Lee YH. Comparison of the efficacy and safety of tofacitinib and apremilast in patients with active psoriatic arthritis: a bayesian network meta-analysis of randomized controlled trials. Clin Drug Investig. 2019;39:421–8. Available from: http://www.epistemonikos.org/documents/beb0ad29c6f9ad143b8cf70717bade806549b4c2

51. Song GG, Lee YH. Relative efficacy and safety of apremilast, secukinumab, and ustekinumab for the treatment of psoriatic arthritis. Z Rheumatol. 2018;77:1–8 http://www.epistemonikos.org/documents/d8e78fce605016ac11f35e0804beca8697b0e1d5
52. Kawalec P, Holko P, Moćko P, Pilc A. Comparative effectiveness of abatacept, apremilast, secukinumab and ustekinumab treatment of psoriatic arthritis: a systematic review and network meta-analysis. Rheumatol Int. 2018;38:189–201, http://dx.doi.org/10.1007/s00296-017-3919-7.
53. Cawson MR, Mitchell SA, Knight C, Wildey H, Spurden D, Bird A, et al. Systematic review, network meta-analysis and economic evaluation of biological therapy for the management of active psoriatic arthritis. BMC Musculoskelet Disord. 2014;15:26, http://dx.doi.org/10.1186/1471-2474-15-26.
54. Ungprasert P, Thongprayoon C, Davis JM. Indirect comparisons of the efficacy of biological agents in patients with psoriatic arthritis with an inadequate response to traditional disease-modifying anti-rheumatic drugs or to non-steroidal anti-inflammatory drugs: a meta-analysis. Semin Arthritis Rheum. 2016;45:428–38, http://dx.doi.org/10.1016/j.semarthrit.2015.09.004.
55. Ruyssen-Witrand A, Perry R, Watkins C, Braileanu G, Kumar G, Kiri S, et al. Efficacy and safety of biologics in psoriatic arthritis: a systematic literature review and network meta-analysis. RMD Open. 2020;6 http://www.epistemonikos.org/documents/fa6413d4c27f0128c82d9d05efe9a2c436a88577
56. Kingsley G, Scott D. Assessing the effectiveness of synthetic and biologic disease-modifying antirheumatic drugs in psoriatic arthritis – a systematic review. Psoriasis (Auckl). 2015;5:71–81, http://dx.doi.org/10.2147/PTT.S52893.
57. Dressler C, Eisert LPAPT, Nast A. Efficacy and safety of systemic treatments in psoriatic arthritis. A systematic review, meta-analysis and GRADE evaluation. J Eur Acad Dermatol Venereol. 2019;33:1249–60 http://www.epistemonikos.org/documents/246ddd52624a1e2b26a0531eb7850f0a66c5b6e6
58. Kerschbaumer A, Smolen JS, Dougados M, de Wit M, Primdahl J, McInnes I, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature research for the 2019 update of the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2020;79:778–86 http://www.epistemonikos.org/documents/3cad9e1d73378c022e7a39a4028a0532c0862c7d
59. Loft ND, Vaengebjerg S, Halling AS, Skov L, Egeberg A. Adverse events with IL-17 and IL-23 inhibitors for psoriasis and psoriatic arthritis: a systematic review and meta-analysis of phase III studies. J Eur Acad Dermatology Venereol. 2020;34:1151–60.
60. Olivieri I, de Portu S, Salvarani C, Cauli A, Lubrano E, Spadaro A, et al. The psoriatic arthritis cost evaluation study: a cost-of-illness study on tumour necrosis factor inhibitors in psoriatic arthritis patients with inadequate response to conventional therapy. Rheumatology. 2008;47:1664–70.
61. Aiello E, Bianculli PM, Bhattacharyya D, Gunda P, Citera G. Cost-effectiveness of secukinumab versus other biologics in the treatment of psoriatic arthritis: an argentinean perspective. Value Health Reg Issues. 2019;20:86–94, http://dx.doi.org/10.1016/j.vhri.2019.03.002.
62. Schweikert B, Storck C, Núñez M, Dilla T, Hartz S, Sapin C. Pmu66 - Cost-effectiveness analysis of ixekizumab versus secukinumab in patients with psoriatic arthritis and concomitant moderate-to-severe psoriasis in Spain. Value Health. 2018;21:S319.
63. Mease PJ, Smolen JS, Behrens F, Nash P, Liu Leage S, Li L, et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis. 2020;79:123–31, http://dx.doi.org/10.1136/annrheumdis-2019-215386.
64. McInnes IB, Behrens F, Mease PJ, Kavanaugh A, Ritchlin C, Nash P, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet. 2020;395:1496–505, http://dx.doi.org/10.1016/S0140-6736(20)30564-X. Erratum in: Lancet. 2020 May 30;395(10238):1694. PMID: 32386593.
65. Conti F, Ceccarelli F, Marocchi E, Magrini L, Spinelli FR, Spadaro A, et al. Switching tumour necrosis factor alpha antagonists in patients with ankylosing spondylitis and psoriatic arthritis: an observational study over a 5-year period. Ann Rheum Dis. 2007;66:1393–7, http://dx.doi.org/10.1136/ard.2007.073569.
66. Paccou J, Solau-Gervais E, Houvenagel E, Salleron J, Luraschi H, Philippe P, et al. Efficacy in current practice of switching between anti-tumour necrosis factor-agents in spondyloarthropathies. Rheumatology (Oxford). 2010;50:714–20.
67. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73:990–9, http://dx.doi.org/10.1136/annrheumdis-2013-204655.
68. Corbett M, Chehadah F, Biswas M, Moe-Byrne T, Palmer S, Soares M, et al. Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease-modifying antirheumatic drugs: a systematic review and economic evaluation. Health Technol Assess. 2017;21:1–326, http://dx.doi.org/10.3310/hta21560.
69. Gómez-Gómez A, Loza E, Rosario MP, Espinosa G, Morales JMGR, Herreras JM, et al. Efficacy and safety of immunomodulatory drugs in patients with anterior uveitis: a systematic literature review. Medicine (Baltimore). 2017;96:e8045.
70. Squires H, Poku E, Bermejo I, Cooper K, Stevens J, Hamilton J, et al. A systematic review and economic evaluation of adalimumab and dexamethasone for treating non-infectious intermediate uveitis, posterior uveitis or panuveitis in adults. Health Technol Assess. 2017;21:1–170, http://dx.doi.org/10.3310/hta21680.
71. Kelly A, Tymms K, Tunnicliffe DJ, Sumpton D, Perera C, Fallon K, et al. Patients' attitudes and experiences of disease-modifying antirheumatic drugs in rheumatoid arthritis and spondyloarthritis: a qualitative synthesis. Arthritis Care Res (Hoboken). 2018;70:525–32, http://dx.doi.org/10.1002/acr.23329.
72. Braun J, Baraliakos X, Listing J, Sieper J. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. Arthritis Rheum. 2005;52:2447–51.
73. Rudwaleit M, Rødevand E, Holck P, Vanhoof J, Kron M, Kary S, et al. Adalimumab effectively reduces the rate of anterior uveitis flares in patients with active ankylosing spondylitis: results of a prospective open-label study. Ann Rheum Dis. 2008;68:696–701, http://dx.doi.org/10.1136/ard.2008.092585 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2663712/
74. Mesquida M, Llorens V, Sainz de la Maza M, Espinosa G, Blanco R, Calvo V, et al. Effectiveness of certolizumab pegol in patients with uveitis refractory to other tumor necrosis factor inhibitors. Report of 22 cases [abstract]. Arthritis Rheum. 2016;68 Supl 10.
75. Yazgan S, Celik U, Işık M, Yeşil NK, Baki AE, Şahin H, et al. Efficacy of golimumab on recurrent uveitis in HLA-B27-positive ankylosing spondylitis. Int Ophthalmol. 2017;37:139–45, http://dx.doi.org/10.1007/s10792-016-0239-y.
76. Calvo-Río V, Blanco R, Santos-Gómez M, Rubio-Romero E, Cordero-Coma M, Gallego-Flores A, et al. Golimumab in refractory uveitis related to spondyloarthritis. Multicenter study of 15 patients - ScienceDirect. [Accessed 9 October 2020]. Available from: https://www.sciencedirect.com/science/article/pii/S0049017216000925.
77. Kim M, Won JY, Choi SY, Ju JH, Park YH. Anti-TNFα treatment for HLA-B27-positive ankylosing spondylitis-related uveitis. Am J Ophthalmol. 2016;170:32–40, http://dx.doi.org/10.1016/j.ajo.2016.07.016.
78. Lee S, Park YJ, Lee JY. The effect of tumor necrosis factor-alpha inhibitors on uveitis in patients with ankylosing spondylitis. J Korean Med Sci. 2019;34 [Accessed 21 November 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6823519/
79. El-Shabrawi Y, Hermann J. Anti-tumor necrosis factor-alpha therapy with infliximab as an alternative to corticosteroids in the treatment of human leukocyte antigen B27-associated acute anterior uveitis. Ophthalmology. 2002;109:2342–6.
80. Lie E, Lindström U, Zverkova-Sandström T, Olsen IC, Forsblad-d'Elia H, Askling J, et al. Tumour necrosis factor inhibitor treatment and occurrence of anterior uveitis in ankylosing spondylitis: results from the Swedish biologics register. Ann Rheum Dis. 2017;76:1515–21.
81. Bolge SC, Eldridge HM, Lofland JH, Ravin C, Hart PJ, Ingham MP. Patient experience with intravenous biologic therapies for ankylosing spondylitis, Crohn's disease, psoriatic arthritis, psoriasis, rheumatoid arthritis, and ulcerative colitis. Patient Prefer Adherence. 2017;11:661–9, http://dx.doi.org/10.2147/PPA.S121032.
82. Van Denderen JC, Visman IM, Nurmohamed MT, Suttorp-Schulten MSA, van der Horst-Bruinsma IE. Adalimumab significantly reduces the recurrence rate of anterior uveitis in patients with ankylosing spondylitis. J Rheumatol. 2014;41:1843–8.
83. Gao X, Wendling D, Botteman MF, Carter JA, Rao S, Cifaldi M. Clinical and economic burden of extra-articular manifestations in ankylosing spondylitis patients treated with anti-tumor necrosis factor agents. J Med Econ. 2012;15:1054–63.
84. Singh JA, Guyatt G, Ogdie A, Gladman D, Deal C, Deodhar A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. Arthritis Care Res. 2019;71:2–29, http://dx.doi.org/10.1002/acr.23789.
85. Narula N, Marshall JK, Colombel J-F, Leontiadis GI, Williams JG, Muqtadir Z, et al. Systematic review and meta-analysis: infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. Am J Gastroenterol. 2016;111:477–91.
86. Stidham RW, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG, et al. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. Aliment Pharmacol Ther. 2014;39:1349–62, http://dx.doi.org/10.1111/apt.12749.
87. Stidham RW, Lee TCH, Higgins PDR, Deshpande AR, Sussman DA, Singal AG, et al. Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis. Aliment Pharmacol Ther. 2014;39:660–71.
88. Williams JG, Alam MF, Alrubaiy L, Clement C, Cohen D, Grey M, et al. Comparison of iNfliximab and ciclosporin in steroid resistant ulcerative colitis: pragmatic randomised trial and economic evaluation (construct). Health Technol Assess. 2016;20:1–320.
89. Salaffi F, Ciapetti A, Carotti M, Gasparini S, Gutierrez M. Disease activity in psoriatic arthritis: comparison of the discriminative capacity and construct validity of six composite indices in a real world. Biomed Res Int. 2014;2014:528105, http://dx.doi.org/10.1155/2014/528105.
90. Gisondi P, Girolomoni G, Sampogna F, Tabolli S, Abeni D. Prevalence of psoriatic arthritis and joint complaints in a large population of Italian patients hospitalised for psoriasis. Eur J Dermatol. 2005;15:279–83.
91. Salaffi F, de Angelis R, Grassi W, MArche Pain Prevalence, Investigation Group (MAPPING) study. Prevalence of musculoskeletal conditions in an Italian pop-

ulation sample: Results of a regional community-based study. I. The MAPPING Study. Clin Exp Rheumatol. 2005;23:819–28.
92. Van Mens LJJ, van de Sande MGH, van Kuijk AWR, Baeten D, Coates LC. Ideal target for psoriatic arthritis? Comparison of remission and low disease activity states in a real-life cohort. Ann Rheum Dis. 2018;77:251–7.
93. Wervers K, Vis M, Tchetveriko I, Gerards AH, Kok MR, Appels CWY, et al. Burden of psoriatic arthritis according to different definitions of disease activity: comparing minimal disease activity and the disease activity index for psoriatic arthritis. Arthritis Care Res. 2018;70:1764–70.
94. Helliwell PS, Kavanaugh A. Comparison of composite measures of disease activity in psoriatic arthritis using data from an interventional study with golimumab. Arthritis Care Res. 2014;66:749–56.
95. Fei JZ, Perruccio AV, Ye JY, Gladman DD, Chandran V. The relationship between patient acceptable symptom state and disease activity in patients with psoriatic arthritis. Rheumatology (Oxford). 2020;59:69–76, http://dx.doi.org/10.1093/rheumatology/kez202.
96. Kawalec P, Malinowski KP, Pilc A. Disease activity, quality of life and indirect costs of psoriatic arthritis in Poland. Rheumatol Int. 2016;36:1223–30 [Accessed 14 May 2020]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4983289/
97. Poole CD, Lebmeier M, Ara R, Rafia R, Currie CJ. Estimation of health care costs as a function of disease severity in people with psoriatic arthritis in the UK. Rheumatology (Oxford). 2010;49:1949–56, http://dx.doi.org/10.1093/rheumatology/keq182.
98. Behrens F, Cañete JD, Olivieri I, van Kuijk AW, McHugh N, Combe B. Tumour necrosis factor inhibitor monotherapy vs combination with MTX in the treatment of PsA: a systematic review of the literature. Rheumatology (Oxford). 2015;54:915–26.
99. Kavanaugh A, McInnes IB, Mease PJ, Krueger GG, Gladman DD, van der Heijde D, et al. Clinical efficacy, radiographic and safety findings through 2 years of golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of the randomised, placebo-controlled GO-REVEAL study. Ann Rheum Dis. 2013;72:1777–85.
100. Betts KA, Griffith J, Friedman A, Zhou Z-Y, Signorovitch JE, Ganguli A. An indirect comparison and cost per responder analysis of adalimumab, methotrexate and apremilast in the treatment of methotrexate-naïve patients with psoriatic arthritis. Curr Med Res Opin. 2016;32:721–9.