CLINICAL PRACTICE GUIDELINE

on the

Treatment of Axial Spondyloarthritis and Psoriatic Arthritis

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Update of ESPOGUÍA

Espoguía

Sociedad Española de Reumatología

This clinical practice guideline serves to support decision-making in primary care. Adherence is not mandatory and the guideline does not replace the clinical judgment of health professionals.

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Spanish Society of Rheumatology (SER)

Contents

Foreword

The Spanish Society of Rheumatology (SER), a nonprofit organisation, recognised the need for this clinical practice guideline (CPG) and has supported its development, deciding on the initial group of researchers to be involved in its development and the timetable for the work. It also signed agreements with the funding bodies which safeguard the editorial independence of the guideline in terms of its contents.

The SER Research Unit oversaw the selection of the principal investigator and panel members, developed the methodology, and coordinated the meetings and work on the CPG including the systematic reviews (SRs) of the literature.

The ESPOGUÍA gathers together the evidence available up to 2023 and some studies published in 2024. Depending on advances in knowledge and the emergence of new evidence, it is envisaged that the guideline will be updated again in 4 years.

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Collaborating organisations

Spanish Society of Rheumatology (SER)

Spanish Society of Ophthalmology (SEO)

Acción Psoriasis

Coordinator of Spanish Spondyloarthritis Associations (CEADE)

Members of these organisations have participated in the drafting of this CPG.

Declaration of interests:

All the members of the ESPGUIA working group have declared potential conflicts of interest as documented in Appendix 6.

Public scrutiny:

These guidelines were made available for public scrutiny. Information concerning this process is available in the Clinical Practice Guidelines section (under Research) on the SER website (https://www.ser.es/wp-content/uploads/2023/03/230321-Normativa-para-la-Elaboraci%C3%B3n-de-Documentos-Basados-en-la-Evidencia-SER.pdf).

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Clinical practice guideline recommendations

Treatment of Axial Spondyloarthritis (axSpA)

Biologic disease-modifying antirheumatic drugs (bDMARDs) or Janus kinase (JAK) inhibitors compared to placebo

Clinical question: In axSpA, what is the efficacy of IL-17 and JAK inhibitors compared to placebo?	**Strength of recommendation**
Recommendation 1: In patients with active axSpA who have an inadequate response and/or intolerance to nonsteroidal anti-inflammatory drugs, treatment options should include IL-17A and IL-17A/F and JAK inhibitors. The line of treatment in which they are used should depend on patient clinical characteristics*. *Appendix 2 contains the recommendations made in the previous guideline as complementary information.	*Strong, in favour*[N]

Important clinical considerations:

- Subgroups to be considered:
  - *Patients ≥65 years old:* Prioritise options other than JAK inhibitors in ≥65-year-olds, patients who are active smokers (or have a history of heavy smoking), and those who have an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible dose.
  - *Patients with non-radiographic axSpA*: These patients should also be assessed for objective signs of inflammation, such as elevated C-reactive protein (CRP) and positive magnetic resonance imaging (MRI) findings.
  - *Drug groups:* Although there are some differences between different IL-17 inhibitors (A and A/F) and different JAK inhibitors, the guideline development group (GDG) believes that recommendations should be made by drug group, as it is not currently possible to demonstrate that small differences in the mechanism of action between drugs in the same group lead to significant differences in efficacy or safety profile (given a lack of head-to-head clinical trials of different drugs in the same group for treating axSpA).

Predictors of prognosis

Clinical question: In axSpA, does pharmacological treatment with bDMARDs or JAK inhibitors slow the progression of structural damage?	**Strength of recommendation**
Recommendation 2: The GDG considers that there is insufficient good-quality evidence available to make a definitive recommendation on the use of bDMARDs or JAK inhibitors for slowing the progression of structural damage in patients with axSpA; however, the group does suggest assessing predictors of the progression of structural damage when considering prescribing these drugs.	*Good clinical practice*[A]

Clinical question: In axSpA, what are the predictors of response to IL-17 and JAK inhibitors?	**Strength of recommendation**
Recommendation 3: In patients with active axSpA starting treatment with IL-17A, or IL-17A/F inhibitors, assess predictors of good response, such as being male, and elevated CRP.	*Weak, in favour*[N]
Recommendation 4: In patients with active axSpA starting treatment with IL-17A, or IL-17A/F inhibitors, assess predictors of radiographic progression, such as being male, older age, smoking, elevated CRP, HLA-B27 positivity and spinal bone marrow oedema on MRI.	*Weak, in favour*[N]
<u>Important clinical considerations:</u> • Monitoring and assessment: - Based on the literature reviewed, it may be useful to measure CRP at each follow-up visit, to identify axSpA patients at a higher risk of structural damage progression. Further, in these patients, smoking should be assessed regularly and smoking cessation encouraged. - To date, no studies have provided evidence of the value of predictors of response to JAK inhibitors.	

Treatment failure

Clinical question: In patients with axSpA who have an inadequate response to a first tumour necrosis factor (TNF) inhibitor, what is the efficacy of a different TNF inhibitor or targeted therapy?	**Strength of recommendation**
Recommendation 5: After an inadequate response to a first TNF inhibitor in patients with axSpA, use another TNF inhibitor, an IL-17A or IL-17A/F inhibitor or a JAK inhibitor.	*Strong, in favour*[U]
Important clinical considerations: • Subgroups to be considered: - *Patients ≥65 years old:* Prioritise options other than JAK inhibitors in ≥65-year-olds, patients who are active smokers (or have a history of heavy smoking), and those who have an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest dose.	

Treatment optimisation

Clinical question: In axSpA, can bDMARD therapy be tapered or withdrawn?	**Strength of recommendation**
Recommendation 6: In patients with axSpA who have achieved low disease activity or sustained remission (for at least 6 months), assess the possibility of tapering bDMARD therapy, once the patient has agreed and under clinical monitoring.	*Strong, in favour*[N]
Recommendation 7: In patients with axSpA who have achieved low disease activity or sustained remission, bDMARD therapy should not be withdrawn systematically due to the increased risk of disease reactivation.	*Strong, in favour*[N]
Important clinical considerations: • Implementation-related factors to consider when reducing the total dose administered: - In the case of intravenous bDMARDs (infliximab [IFX] being the most widely used), the dose given in a day hospital can be reduced based on the patient's weight. - In the case of bDMARDs administered subcutaneously using a prefilled pen or syringe, the dosing interval can be increased.	

Extra-musculoskeletal manifestations

Clinical question: In axSpA, what is the efficacy of bDMARDs and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) in treating extra-musculoskeletal manifestations (uveitis, psoriasis and inflammatory bowel disease [IBD])?	**Strength of recommendation**
Recommendation 8: In patients with axSpA and uveitis, use monoclonal TNF inhibitors and certolizumab pegol (CZP) for preventing anterior uveitis episodes. **Recommendation 8.1:** TNF inhibitors, especially adalimumab (ADA), are also recommended for treating refractory or recurrent anterior uveitis when conventional therapies have failed. **Recommendation 8.2:** In axSpA, do not use etanercept for the prevention or treatment of anterior uveitis.	*Strong, in favour*[N] *Good clinical practice*[N] *Good clinical practice*[N]
Recommendation 9: In axSpA, the GDG considers that there is no evidence for recommending the use of IL-17 or JAK inhibitors for the prevention or treatment of anterior uveitis.	*Strong, in favour*[N]
Recommendation 10: In patients with axSpA and active IBD, use monoclonal TNF inhibitors* or JAK inhibitors** for the management of IBD. **Approved: IFX and ADA for ulcerative colitis and Crohn's disease; golimumab (GOL) only for ulcerative colitis* ***Approved: Upadacitinib (UPA) for ulcerative colitis and Crohn's disease; tofacitinib (TOFA) for ulcerative colitis.*	*Strong, in favour*[N]
Recommendation 11: In patients with axSpA and IBD, do not use IL-17 inhibitors.	*Strong against*[N]
Recommendation 12: Given the lower incidence of psoriasis in axSpA, there is less evidence of the efficacy of the different treatments for psoriasis in this context; therefore, the GDG suggests following the recommendations for psoriatic arthritis (PsA).	*Good clinical practice*[N]
<u>Important clinical considerations:</u> • Subgroups to be considered: - *Patients ≥65 years old:* Prioritise options other than JAK inhibitors in ≥65-year-olds, patients who are active smokers (or have a history of heavy smoking), and those who have an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible dose,	

especially in patients with IBD, a condition in which the doses given are higher than those used in axSpA. • Implementation-related factors to consider: - The majority of bDMARDs indicated for treating axSpA (TNF and IL-17 inhibitors) are also indicated for treating moderate-to-severe psoriasis. In the case of JAK inhibitors (UPA and TOFA), no indication in plaque psoriasis is mentioned in their summary of product characteristics, and therefore, their use in patients with axSpA and moderate-to-severe plaque psoriasis should be assessed jointly with dermatologists.

Exercise

Clinical question: In axSpA, what type of exercise programme is most effective in improving clinical and functional outcomes?	**Strength of recommendation**
Recommendation 13: In adult patients with axSpA, exercise programmes should be used to improve symptoms, quality of life and health-related physical fitness as part of the treatment of the disease.	*Weak, in favour*^{U}
Recommendation 14: Such programmes should include aerobic exercises and be performed in a group under the supervision of a physiotherapist.* * Appendix 5 provides more detailed information to guide patients concerning this type of exercise.	*Weak, in favour*^{U}

Obesity and smoking

Clinical question: In axSpA, do obesity and/or smoking increase disease activity, accelerate radiographic progression of structural damage and impair treatment response?	**Strength of recommendation**
Recommendation 15: In axSpA, encourage smoking cessation and recommend maintaining a BMI between 18.5 and 25 kg/m^2 to improve disease control.	*Strong, in favour*^{N}
<u>Important clinical considerations:</u> • Subgroups to be considered: - *Patients who smoke*: these patients should be offered referral to smoking cessation services or their general practitioner, to receive information about such services.	

- *Patients with overweight/obesity:* these patients should be offered referral to weight management services, when available in the health service, or their general practitioner, to receive information about such services.

Treatment of psoriatic arthritis

Early intervention

Clinical question: In PsA, does early detection and pharmacological treatment improve functional capacity, slow radiographic progression of structural damage and enhance quality of life?	**Strength of recommendation**
Recommendation 16: In patients with peripheral PsA and predictors of poor prognosis*, start pharmacological treatment as soon as possible with conventional synthetic DMARDS (csDMARDS) and/or bDMARDs, to improve signs and symptoms, functional capacity and quality of life, by suppressing inflammation. * Polyarthritis, structural damage, elevated CRP, dactylitis or nail disease	*Weak, in favour*^{U}

Conventional synthetic disease-modifying antirheumatic drugs

Clinical question: In PsA, what is the efficacy of csDMARDs in treating axial and peripheral disease, enthesitis and dactylitis?	**Strength of recommendation**
Recommendation 17: In patients with active peripheral PsA, use csDMARDs (methotrexate [MTX], leflunomide [LFN] and sulfasalazine [SSZ]) as the first-line treatment.	Strong, in *favour*^{U}
Recommendation 17.1: Among csDMARDs, MTX is considered the treatment of choice, given its effects on arthritis and psoriasis.	*Weak, in favour*^{U}
Recommendation 17.2: Do not use csDMARDs for treating axial disease.	*Weak, in favour*^{U}

Treatment with biologic disease-modifying antirheumatic drugs and targeted synthetic disease-modifying antirheumatic drugs

Clinical question: In PsA, what is the efficacy of IL-23 and IL-17 inhibitors and tsDMARDs (JAK inhibitors and apremilast) in treating axial and peripheral disease, enthesitis and dactylitis?	**Strength of the recommendation**
Recommendation 18: In patients with active PsA, after an inadequate response and/or intolerance to a csDMARD or a bDMARD (TNF inhibitor), use IL-17A, IL-17A/F or JAK inhibitors for treating axial or peripheral disease, enthesitis and dactylitis.* *Appendix 2 contains the recommendations in the previous guidelines as complementary information.	*Strong, in favour*[N]
Recommendation 19: In patients with active PsA, after inadequate response and/or intolerance to a csDMARD or a bDMARD (TNF inhibitor), use IL-23 inhibitors for treating peripheral disease, enthesitis and dactylitis.* *Appendix 2 contains the recommendations in the previous guidelines as complementary information.	*Strong, in favour*[N]
Recommendation 20: In patients with active PsA, after inadequate response and/or intolerance to a csDMARD or a bDMARD (TNF inhibitor), use IL-17A, IL-17A/F, IL-12/23 or IL-23 or JAK inhibitors for controlling structural damage.* *Appendix 2 contains the recommendations in the previous guidelines as complementary information.	*Strong, in favour*[N]
Recommendation 21: In patients with active PsA who have an inadequate response and/or intolerance to a csDMARD, consider using apremilast for treating peripheral disease, enthesitis and dactylitis.	Weak, in favour[N]
Important clinical considerations: • Subgroups to be considered: - *Patients ≥65 years old:* Prioritise options other than JAK inhibitors in ≥65-year-olds, patients who are active smokers (or have a history of heavy smoking), and those who have an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible dose. - *Patients with axial psoriatic arthritis (axPsA):* the only agent shown to be effective for treating axPsA in a randomised controlled trial (RCT) is secukinumab (SEC), an IL-17A inhibitor. Indirect evidence suggests that TNF inhibitors or other IL-17A and IL-17A/F inhibitors, as well as JAK inhibitors, may be good treatment options for the axial domain of PsA.	

- *Drug groups*: Although there are some differences between different IL-17 inhibitors (A and A/F) and different JAK inhibitors, the GDG believes that recommendations should be made by drug group, as it is not currently possible to demonstrate that small differences in the mechanism of action between drugs in the same group lead to significant differences in efficacy or safety profile (given a lack of head-to-head clinical trials of different drugs in the same group for treating PsA).
- There are, however, two types of IL-17 inhibitors with different mechanisms of action: 1) inhibition of IL-17A (SEC and ixekizumab [IXE]), and 2) inhibition of both IL-17A and IL-17F (bimekizumab [BZK]). Therefore, for the purposes of ESPOGUÍA, all of them are grouped as IL-17 inhibitors.
- tsDMARDs: 1) phosphodiesterase 4 (PDE4) inhibitors (apremilast), and 2) JAK inhibitors (TOFA and UPA).

Treatment with biologic or targeted synthetic disease-modifying antirheumatic drugs compared to TNF inhibitors

Clinical question: In PsA, what is the efficacy, effectiveness and safety of IL-17, IL-23, IL-12/23 and JAK inhibitors compared to TNF inhibitors?	**Strength of recommendation**
Recommendation 22: In patients with active PsA, use any bDMARD (TNF, IL-17A or 17A/F, IL-23, or IL-12/23 inhibitors) or a JAK inhibitor, given that there is no evidence that there is a significant difference between them in terms of efficacy, effectiveness or safety, apart from a difference in efficacy in treating extra-musculoskeletal manifestations.	*Strong, in favour*[N]

<u>Important clinical considerations:</u>

- Subgroups to be considered:
  - *Patients ≥65 years old:* Prioritise options other than JAK inhibitors in ≥65-year-olds, patients who are active smokers (or have a history of heavy smoking), and those who have an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible dose.
  - *Patients with axPsA:* the only agent shown to be effective for treating axPsA in an RCT is SEC, an IL-17A inhibitor. Indirect evidence suggests that TNF inhibitors or other IL-17A and IL-17A/F inhibitors, as well as JAK inhibitors, may be good treatment options for the axial domain of PsA.

Treatment with a biologic or targeted disease-modifying antirheumatic drug monotherapy

Clinical question: In PsA, is combination therapy with MTX and bDMARDs or tsDMARDs more effective than using bDMARD or tsDMARD monotherapy?	**Strength of recommendation**
Recommendation 23: Use IL-17A, IL-17A/F, IL-23 or IL-12/23 inhibitors alone to treat all manifestations of peripheral PsA. Monoclonal TNF inhibitors, especially IFX, should be used in combination with MTX. **Recommendation 23.1:** Combination therapy with MTX can increase drug survival of monoclonal TNF inhibitors, especially that of chimeric TNF inhibitors.	*Strong, in favour*[U] *Weak, in favour*[U]

Extra-musculoskeletal manifestations

Clinical question: In PsA, what is the efficacy of bDMARDs and tsDMARDs in treating extra-musculoskeletal manifestations (uveitis, psoriasis and IBD)?	**Strength of recommendation**
Recommendation 24: Use TNF, IL-17A, IL-17A/F, IL-12/23 and IL-23 inhibitors for treating psoriasis in patients with PsA and active psoriasis. **Recommendation 24.1:** In patients with PsA and moderate-to-severe psoriasis, the treatments of choice are IL-17A, IL-17A/F, IL12/23 or IL-23 inhibitors, rather than TNF inhibitors.	*Strong, in favour*[N] *Good clinical practice*[N]
Recommendation 25: In patients with PsA and active psoriasis, the use of JAK inhibitors can be considered. Patients with moderate-to-severe psoriasis should be assessed jointly by rheumatologists and dermatologists.	*Good clinical practice*[N]
Recommendation 26: In patients with PsA and active psoriasis, the use of apremilast can be considered, recalling that it has lower efficacy than bDMARDs or JAK inhibitors.	*Good clinical practice*[N]
Recommendation 27: In patients with PsA, do not use abatacept for treating psoriasis, as it has not shown efficacy in this clinical domain.	*Strong, against*[N]
Recommendation 28: In patients with PsA and IBD, use monoclonal TNF* and IL-12/23, IL-23** and JAK*** inhibitors for managing gut inflammation. **Approved: IFX and ADA in ulcerative colitis and Crohn's disease; GOL only for ulcerative colitis*	*Strong, in favour*[N]

*** At the time of drafting the CPG, the only IL-23 inhibitor approved for IBD and Crohn's disease is risankizumab (RIS).* **** Approved: UPA for ulcerative colitis and Crohn's disease; TOFA only for ulcerative colitis*	
Recommendation 29: In patients with PsA and IBD, do not use IL-17 inhibitors.	*Strong, against*[N]
Recommendation 30: Given the lower incidence of uveitis in PsA, there is less evidence of the efficacy of these drugs in the treatment of uveitis in this context, and therefore, the GDG suggests following the recommendations given for axSpA.	*Good clinical practice*[N]
Important clinical considerations: • Subgroups to be considered: - *Patients ≥65 years old:* Prioritise options other than JAK inhibitors in ≥65-year-olds, patients who are active smokers (or have a history of heavy smoking), and those who have an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible dose.	

Obesity and smoking

Clinical question: In PsA, do obesity and/or smoking increase disease activity, accelerate radiographic progression of structural damage and impair treatment response?	**Strength of recommendation**
Recommendation 31: In PsA, encourage smoking cessation and recommend maintaining a BMI between 18.5 and 25 kg/m^2 to improve disease control.	*Strong, in favour*[N]
Important clinical considerations: • Subgroups to be considered: - *Patients who smoke*: these patients should be offered referral to smoking cessation services or their general practitioner, to receive information about such services. - *Patients with overweight/obesity:* these patients should be offered referral to weight management services, when available in the health service, or their general practitioner, to receive information about such services.	

Treatment of axial spondyloarthritis and psoriatic arthritis

Health education

Clinical question: In PsA and axSpA, is nurse-led health education beneficial?	**Strength of recommendation**
Recommendation 32: Nurse specialists should participate in follow-up consultations for patients with axSpA or PsA, face-to-face or over the phone, as this increases patient satisfaction.	*Weak, in favour*[U]
Recommendation 33: Patients with axSpA or PsA who smoke may benefit from nurse-led smoking cessation programmes, as these can increase smoking cessation rates.	*Weak, in favour*[U]
Recommendation 34: Nurse-led educational workshops may be offered before starting subcutaneous treatments, as they help improve treatment adherence.	*Weak, in favour*[U]
Recommendation 35: Nurses should be involved in addressing patient concerns and helping them complete self-report questionnaires; provided that they avoid influencing patients' opinions and preferences.	*Weak, in favour*[U]
Recommendation 36: Patients with PsA would benefit from educational programmes, preferably in groups, led by clinical nurse specialists. This would improve self-management of the disease and treatment adherence.	*Weak, in favour*[U]

General recommendations on patient management	**Strength of recommendation**
The management of patients with axSpA or PsA should take into account individual patient characteristics.	*Good clinical practice*[V]
Before the early initiation of treatment for axSpA or PsA, patients should be appropriately informed about the pharmacological properties of the proposed drugs, treatment duration, expected benefits and potential adverse effects, and patient preferences should be taken into account.	*Good clinical practice*[V]
When prescribing treatment, health professionals should consider: age, previous treatments, tolerance, adverse effects, risk of pregnancy and cost-effectiveness, as well as patient preferences.	*Good clinical practice*[V]
Patients and their families should be trained in joint self-care and self-administration of any biological therapy.	*Good clinical practice*[V]

Health professionals should provide personalised information to patients with axSpA regarding the most suitable type of exercise.	*Good clinical practice*[V]
Health professionals should provide patients with axSpA with information about smoking cessation programmes.	*Good clinical practice*[V]
Given the involvement of multiple organs and tissue in PsA, rheumatologists should closely work with other medical specialists (dermatologists, ophthalmologists, and gastroenterologists) to achieve appropriate control of the corresponding extra-musculoskeletal manifestations (psoriasis, uveitis, and IBD). Close collaboration with dermatologists is essential to achieve early diagnosis and treatment of PsA.	*Good clinical practice*[V]

[N] Recommendations related to a new question

[U] Recommendation related to an updated question

[V] Recommendation in the previous ESPOGUÍA considered to be still valid

1. Introduction

Spondyloarthritis is a family of chronic inflammatory rheumatic diseases involving the musculoskeletal system with similar epidemiological, clinical, immunopathological, genetic, and radiographic characteristics and treatment response. This group includes axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA). In turn, axSpA can be classified into two subgroups: ankylosing spondylitis, now known as radiographic (r-axSpA), and non-radiographic (nr-axSpA).

In axSpA, there is involvement of sacroiliac joints and the spine. Traditionally, the diagnosis was based on the 1984 modified New York Criteria for ankylosing spondylitis[1]. These criteria require there to be some irreversible structural damage in the sacroiliac joints visible on X-ray, which implies a major delay in diagnosis. For this reason, in 2009, the *Assessment of SpondyloArthritis International Society* (ASAS) published classification criteria for axSpA[2], which additionally consider sacroiliac MRI findings, allowing early detection of acute changes in the sacroiliac joints[3], and not requiring radiographic structural damage to be apparent. Based on the ASAS criteria for axSpA, we currently distinguish two subgroups of patients with axSpA: 1) those with r-axSpA (previously known as ankylosing spondylitis), in whom a certain degree of structural damage is already visible on plain radiographs, and 2) those with nr-axSpA, in whom no such changes are seen on X-ray. In this guideline, we address each clinical question for r-axSpA and nr-axSpA separately.

PsA is a chronic inflammatory disease of the skin and the musculoskeletal system that can involve peripheral joints, the axial skeleton (sacroiliac joints and spine), entheses (sites where a tendon, ligament, joint capsule or fascia attaches to bone), tendon sheaths (dactylitis), skin, nails and other organs (gut and eye). Epidemiological studies and specific clinical trials are difficult to conduct due to the clinical heterogeneity of the disease. Further, the wide range of presentations and manifestations, both musculoskeletal and extra-musculoskeletal (skin, gut and eye), make its management more complex, requiring collaboration between medical specialists, particularly rheumatologists and dermatologists[4, 5].

To reduce the variability in clinical practice and improve care and quality of life for people with axSpA and PsA, the Spanish Society of Rheumatology (SER) has driven the development of this clinical practice guideline (CPG) with the participation of a multidisciplinary team of professionals involved in the care of these patients. A CPG consists of a set of recommendations

that seek to optimise patient care based on a systematic review of the evidence and evaluation of the risks and benefits of available treatment options[6].

Internationally, the recommendations of the *European League Against Rheumatism* (EULAR) and the *American College of Rheumatology* (ACR) for the diagnosis and treatment of these rheumatic diseases are the most widely followed. In Spain, the reference guideline is ESPOGUÍA, first developed under the auspices of the SER in 2009[4] and updated in 2015 and 2018[7, 8].

The significant advances in recent years, especially in the area of therapeutic interventions, made it necessary to update the guideline content again. Hence, the production of this document, ESPOGUÍA 2024, a Clinical Practice Guideline on the Treatment of Axial Spondyloarthritis and Psoriatic Arthritis, which aims to provide users with up-to-date guidance on the best approaches to managing these diseases, as well as an assessment of their effectiveness.

1.1 2024 Update

The development and approval of new treatment options for axSpA and PsA since the publication of ESPOGUÍA 2018 prompted the SER to update the CPG. In particular, it was necessary to include new biological therapies for treating PsA, such as IL-23 and IL-17A/F inhibitors, and JAK inhibitors (JAK1,3 and JAK1); new therapies for nr-axSpA (IL-17A and IL-17A/F inhibitors); new data on efficacy and safety of IL-17A inhibitors in axPsA; the results of head-to-head trials comparing IL-17A and TNF-alpha inhibitors; and the findings of a study suggesting that methotrexate (MTX) is effective for treating enthesitis and dactylitis associated with PsA. Further, it was important to document the new evidence available from retrospective studies suggesting that psoriasis treatments, especially those based on biologics, may prevent or delay the onset of PsA; and bring the debate on whether axSpA and axPsA are the same disease or not up-to-date.

The new 2024 CPG is fruit of the work of a large number of health professionals, from across Spain, involved in the management of patients with axSpA or PsA. This guideline is organised into chapters, which state each clinical question followed by the associated recommendations and then summarise the supporting evidence.

As the sponsor of these guidelines, the SER aspires to help health professionals achieve effective, safe and coordinated decision-making on therapeutic interventions for axSpA and PsA, focused on patients with these conditions.

2. Scope and objectives

2.1. Scope

This guideline focuses on the care provided to people with axSpA or PsA. It applies only to adult patients, and the clinical area addressed is the treatment of these diseases.

The following are therefore beyond the scope of the guideline:

- People under 18 years old
- Recommendations on diagnosis, prevention, monitoring and prognosis.

This guideline covers various aspects of treatment:

- Pharmacological treatments
- Considerations related to treatment at early stages of these diseases
- Non-pharmacological interventions involving rehabilitation exercise programmes
- The influence of obesity and/or smoking on disease activity, progression and treatment response
- Usefulness of health education programmes
- Management of extra-musculoskeletal manifestations.

2.2. Guideline objectives

Primary objective: to guide rheumatologists and other health professionals caring for patients with these conditions, by selecting scientific evidence-based recommendations on therapeutic interventions for the management of adult patients with axSpA or PsA. When there is insufficient evidence, the recommendations are based on consensus reached among the members of the working group.

Specific objectives:

- To strengthen the clinical skills of health professionals involved in caring for people with axSpA and PsA, to improve the quality of the care provided
- To reduce variability in clinical practice regarding the therapeutic management of these conditions
- To assess the efficacy, safety and effectiveness of the different pharmacological and non-pharmacological treatment options proposed

- To summarise the scientific evidence to facilitate knowledge transfer to all health professionals, seeking to optimise care, and hence, improve the quality of life of their patients
- To establish recommendations to standardise the care provided to patients with axSpA or PsA
- To promote collaboration between specialities involved in the management of patients. In the case of PsA, collaboration between dermatologists and rheumatologists is essential for appropriate patient management. It is also important to work with ophthalmologists and gastroenterologists.
- Preparation of general information for people with axSpA or PsA and their relatives and caregivers, to help them better understand these conditions and the key factors that influence the course of the disease.

2.3. Target users of the guideline

Seeking to achieve integrated patient care, the target audience of the guideline is not only rheumatologists but also other health professionals who may be involved in the management of patients with axSpA or PsA working in specialised or primary care: dermatologists, gastroenterologists, ophthalmologists, physiotherapists, nurses, and general practitioners, among others. In addition, it is aimed at patients and their relatives who attend consultations with these health professionals. For them, it is a tool for learning about treatment strategies and options for these conditions, to help them avoid treatment regimens not supported by scientific evidence or a strong consensus among experts.

3. Development methods

In the development of this Clinical Practice Guideline on the Treatment of Axial Spondyloarthritis and Psoriatic Arthritis, a series of steps were followed, as described below. The updating process has been based on the Spanish National Health System's methodology manual for updating CPGs[6].

1. Establishment of the guideline development group

A multidisciplinary working group was set up, composed of professionals involved in care delivery, technical staff of the SER Research Unit and representatives of patients. All participants are listed in the authors and collaborations section. The composition of the group, hereon called the guideline development group (GDG), is outlined below:

- *Coordinators*: one specialist in rheumatology, as the principal investigator, and one methodological expert, a member of the technical staff of the SER Research Unit, were responsible for coordinating the clinical and methodological aspects of the CPG and supporting the GDG.

- *Expert panel*: specialists in rheumatology, dermatology, ophthalmology, and gastroenterology and nurse specialists were selected through a call for experts or contacting the corresponding scientific societies. As members of the expert panel, these people were responsible for formulating the recommendations in the CPG.

- *Reviewers of the scientific evidence*: several rheumatologists, members of the SER reviewer working group and others external to the society, were responsible for systematically reviewing the available scientific evidence.

- *Patients*: as well as clinical professionals, two patients participated in the GDG itself, from the early stages of the updating process.

A work plan was established outlining the different stages in the guideline updating process and deadlines for their completion.

2. Review of earlier ESPOGUÍA CPGs and planning of the updating process

This guideline is a partial update of the 2015 and 2018 ESPOGUÍA CPGs. The process for reviewing these previous versions and deciding which aspects needed updating involved the following steps:

i. Before updating the content of the guideline, a survey was carried out regarding the topics included in the earlier versions.

ii. A list was drawn up of clinical questions that potentially needed updating based on the aforementioned survey and consensus was reached on what new content to include in the guideline.

iii. A review and formal prioritisation process was conducted, involving face-to-face and online discussion, and in the end, nearly all the questions contained in the earlier guidelines were included in this new version.

3. Definition of the scope and objectives

The time since the publication of the earlier versions and the new evidence that has emerged during that time warrant updating of the guideline. The new scope and objectives were defined by consensus based on the clinical experience and knowledge of the participating health professionals.

4. Formulation of the clinical questions

The GDG reviewed and analysed the clinical questions in the earlier versions of the guideline to decide which to prioritise for revising and take a decision on whether they needed to be updated. Having agreed on the criteria for deciding which questions should be kept in the new guideline with no changes in the associated recommendations, which needed to be modified and whether new questions should be included, the GDG agreed on the following categories of questions:

- Questions addressed in the earlier versions (the 2015 and 2018 ESPOGUÍA CPGs) that did not need updating as, to the GDG's knowledge, there was no new evidence to justify changing the direction, strength/certainty or wording of the associated recommendations; two questions were identified in this category

- Questions that might be still valid, but that were going to be updated to confirm the hypothesis that the associated recommendations would not change compared to the earlier versions of the guideline. The updating process was based on a new narrative review of the evidence, conducting a restricted literature search or search for secondary evidence (prioritising SRs and CPGs, among other publications with characteristics outlined in the aforementioned methodology manual); seven such questions were identified

- New questions, identified and agreed on by the GDG members and redrafted using the Patient, Intervention, Comparison and Outcome (PICO) framework, for which a systematic literature review was required; seven such questions were identified

- Clinical research questions that did not need reformulating using the PICO framework and would be addressed by narrative reviews; four questions were identified.

5. Literature search, evaluation and synthesis of the evidence

A literature search was carried out in the following databases: Medline (through PubMed), Embase (Elsevier), Cochrane Library (Wiley Online Library) and the Cumulative Index to Nursing & Allied Health Literature (EBSCOhost). These databases were selected because they are the main sources of biomedical information to which we had access.

In the case of questions for which recommendations remained valid, the literature search was updated using the same strategy as for the 2015 and 2018 ESPOGUÍA CPGs, seeking to retrieve studies published after the previous guidelines, that is, from the beginning of 2015 or 2018 respectively. For the newly developed questions, no restriction was placed on publication date and searches were performed up to the end of August 2023. Initially, all the search strategies were prepared to retrieve only primary studies from the abovementioned databases; however, when this approach yielded few or irrelevant results, it was supplemented by a manual search performed using reference lists of the key documents selected for the review. References proposed by researchers and reviewers consulted were also included. In this way, we identified studies published in 2024, that is, after the initial literature search. Studies included were published in Spanish, English or French.

The references retrieved were managed using EndNote X7.

Study inclusion criteria

Studies were included if they had the characteristics described below:

Study population: adult patients diagnosed with r-axSpA, nr-axSpA or PsA

Intervention/exposure: early treatment, disease-modifying antirheumatic drugs (DMARDs: conventional synthetic DMARDs [csDMARDs], biologic DMARDs [bDMARDs], or targeted synthetic DMARDs [tsDMARDs]), predictors of prognosis, treatment tapering or withdrawal, health education programmes, treatment failure, smoking, and obesity.

Outcome measures: Efficacy in terms of disease activity as measured by usual clinical parameters; axial and peripheral symptoms, radiographic structural damage, markers of inflammation, flare rates, dactylitis, enthesitis, uveitis, psoriasis, inflammatory bowel disease (IBD) and treatment response.

Study design: SRs of RCTs, double-blind phase 3 or 4 RCTs, sub-analysis of clinical trials and observational studies.

Study exclusion criteria

The following were excluded: studies in children, adolescents or pregnant women; studies that did not fit into the PICO framework, due to the sample size, intervention, comparator, outcome(s) or study design; and abstracts, posters, narrative reviews, and editorials, as well as any type of unpublished material.

Analysis and synthesis of the scientific evidence

Studies likely to be relevant were selected based on the aforementioned selection criteria. The quality of the evidence was assessed by the methods developed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[9] working group. For determining the quality of evidence or certainty in evidence, as well as the design and methodological quality of individual studies, the GRADE system implies assessing other factors that influence the confidence in the estimates reported. Specifically, the following were analysed: the consistency of results between studies, the direct/indirect nature of the evidence (indirect comparison of the interventions of interest and/or differences in the population, the intervention, the comparator and/or the results of interest with regards to the objectives of this report), the accuracy of the estimates and publication bias. As shown in Table 1, considering a combination of these elements, the quality of the evidence for each critical or important outcome was classified and defined as high ⨁⨁⨁⨁ (very unlikely that new studies would change the estimate), moderate ⨁⨁⨁⊖ (likely that new studies would change the confidence in the estimate), low ⨁⨁⊖⊖ (very likely that new studies would have an effect on the confidence in the estimate and might change it) or very low ⨁⊖⊖⊖ (any outcome estimated is highly uncertain). The outcomes considered in each question and their importance can be consulted in the supplementary material (Appendix 6).

Table 1. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[9] approach to rating the quality of evidence

Quality	Study design	Factors that can reduce the quality of the evidence*	Factors that can increase the quality of the evidence**
High ⨁⨁⨁⨁	RCT	• Limitations in study quality (design): Large (-1) Very large (-2) • Inconsistency: Large (-1) Very large (-2)	Association: • Scientific evidence of a strong association (RR>2 or <0.5 based on observational studies with no plausible confounders) (+1)
Moderate ⨁⨁⨁⊖	--		

Low ⊕⊕⊖⊖ Very low ⊕⊖⊖⊖	Observational studies Studies with other designs	• Indirectness of evidence: Large (-1) Very large (-2) • Imprecision: Large (-1) Very large (-2) • High risk of publication bias: (-1)	• Scientific evidence of a very strong association (RR>5 or <0.2 based on studies with a low risk of bias) (+2) • Dose-response gradient (+1) • All plausible confounding would reduce the demonstrated effect (+1)

* In the case of RCTs, the rating of the quality of the scientific evidence may decrease

** In the case of observational studies, the rating of the quality of the evidence may increase

RCT: randomised controlled trial; RR: relative risk.

With the aim of standardising the visual presentation of the quality of the evidence, in the case of the questions from the earlier ESPOGUÍA CPGs for which the recommendations were considered still valid and which were updated through a restricted literature search or search for secondary evidence, the Oxford Centre for Evidence-based Medicine levels of evidence have been transformed to the GRADE system[10-12].

Formulation of recommendations

After the critical reading, the GDG formulated specific recommendations based on the scientific evidence. In the case of the quantitative evidence, the recommendations were based on formal assessment or 'considered judgement', after having summarised the evidence for each of the clinical questions. To this end, to aid in the process of moving from evidence to recommendations, the panel used an Evidence to Decision framework that evaluates the following:

1) The quality or certainty of the scientific evidence identified

2) Patient values and preferences

3) The balance between the desirable and undesirable effects of the interventions

4) Considerations such as equity, acceptability and feasibility of implementing the interventions

5) Other factors.

The direction and strength of the recommendations were also rated using the GRADE system. (Table 2).

Table 2. Implication of the strength of recommendations in the GRADE system[9]

Recommendation	Patients	Clinicians	Managers / Policymakers
Strong	Most people would agree with the recommended action, and only a small proportion would not.	Most patients should receive the recommended intervention.	The recommendation can be adopted as a healthcare policy in most situations.
Weak or Conditional	The majority of people would agree with the recommended action, but many would not.	Recognise that different choices will be appropriate for different patients and that you (the doctor) must help each patient make the decision that is most consistent with their values and preferences.	There is a need for considerable debate and the involvement of stakeholders.

On some occasions, the GDG identified important practical issues it wanted to highlight but related to which there was unlikely to be any supporting evidence. In general, these issues concern aspects of treatment considered good clinical practice and which are not commonly questioned. Such issues have been evaluated as recommendations for good clinical practice.
The recommendations associated with the questions from earlier ESPOGUÍA CPGs which were still considered valid have also been transformed from the Oxford Centre for Evidence-based Medicine system for grading recommendations to the GRADE system[10-12].

Patients' perspective

This CPG also brings up-to-date literature searches for the chapter on the patients´ perspective and information for the versions of the guideline for patients, their relatives and caregivers.
This information is written in language and formatted in a style that is tailored to the target audience and covers the topics related to these diseases that may be most useful to them. To update this information, some health professionals and patients in the GDG reviewed the versions based on the previous ESPOGUÍA and included the relevant changes.

External review and editing of the final guideline document

Once the previous phases had been completed, an advanced draft of the CPG was produced and this was then reviewed by the working group. Each section of the guideline was analysed, and using a comprehensive approach, any changes considered necessary were proposed.

Subsequently, the guideline was externally reviewed by professionals selected for their knowledge about the disease in question and guideline development methodology.

Public scrutiny

The draft of the complete version of this CPG was subjected to public scrutiny by members of the SER and other stakeholders (pharmaceutical industry, other scientific societies and patients´ associations). For this purpose, it was made available for 15 days on the SER website, with a form to submit comments, to gather data on people's opinions and scientific assessment of the CPG methodology and/or recommendations. More detailed information about this process is available in the Clinical Practice Guidelines section (under Research) on the SER website (https://www.ser.es/wp-content/uploads/2023/03/230321-Normativa-para-la-Elaboraci%C3%B3n-de-Documentos-Basados-en-la-Evidencia-SER.pdf).

As well as the SER itself, the following organisations were involved in the development of this guideline, through representation by their members on the GDG: the Spanish Academy of Dermatology and Venereology (AEDV), the Spanish Society of Ophthalmology (SEO), and two patients' associations: Acción Psoriasis and the Coordinator of Spanish Spondyloarthritis Associations (CEADE).

How to use this CPG

This CPG is organised in chapters. Each chapter referring to treatment states a PICO question and then provides a brief introduction to the question, a list of associated recommendations and a summary of the amount of evidence, its consistency, applicability, and relevance in our setting.

4. Epidemiological characteristics and clinical manifestations

Spondyloarthritis is a common reason for consultation in both specialised and primary care settings. This group of conditions affects patients' health, quality of life and psychosocial well-being, as well as their family, social and working lives. A better understanding of their epidemiology will increase the awareness of their clinical importance.

4.1 Incidence and prevalence

Spondyloarthritis is found worldwide, with incidence and prevalence rates that vary with ethnic group, geographical location, and above all, the frequency of human leukocyte antigen B27 (HLA-B27) positivity in the general population[4, 13-15]. The wide range of classification criteria for these conditions explains why studies in different countries have reported different results. The rates of prevalence generally range from 0.1% to 2.5% of the population, while the incidence has been estimated at between 0.84 and 77 cases per 100,000 person-years[4].

Similar figures are observed in Spain. A study using the *European Spondylarthropathy Study Group* (ESSG) criteria, considered the gold standard, estimated the annual incidence of spondyloarthritis to be 62.5 new cases per 100,000 persons[16].

Among the various forms of spondyloarthritis, axSpA and PsA are very common chronic inflammatory musculoskeletal diseases with a significant healthcare and social impact. A systematic review of the mean prevalence of axSpA by continent concluded that, although there are marked differences between continents, comparable figures are reported within these regions. Further, there are sufficient data to estimate that in Europe between 1.30 and 1.56 million people have axSpA[17]. The 2016 Prevalence of rheumatic diseases in the adult population in Spain (EPISER) study provides a robust estimation of the prevalence of axSpA in Spain of 0.26% (95% confidence interval [CI]: 0.14-0.49), in line with rates reported in neighbouring countries[18, 19].

In the case of PsA, incidence and prevalence estimates vary markedly between geographical areas and countries. In general, the available evidence suggests that psoriasis affects around 3.2% of the general population and that nearly a third of patients with psoriasis also have arthritis. It has been estimated that the prevalence of PsA may range between 0.3% and 1.0% [5].

Few studies have analysed the prevalence of this condition in Spain[20, 21]. Based on data on over-20-year-olds in Spain in 2016, the prevalence of PsA was estimated at 0.58% (95% CI: 0.38 to

0.87). Such a rate would be just below figures found in Scandinavian and Baltic studies (Norway: 0.67% and Lithuania: 0.64%) and slightly higher than that reported for a neighbouring country (Italy: 0.42%)[18,19].

The EPISER study estimated that there are between 142,000 and 325,200 people with PsA in Spain. Among the variables studied, only educational attainment was significantly associated with PsA in the bivariate analysis; however, in multivariate analysis, though disease prevalence was lower in individuals with a higher level of education, the difference did not reach significance. The condition was more common in men and over-40-year-olds, the prevalence peaking in the seventh and eighth decades of life, but these associations were also not statistically significant[18, 19].

4.2 Organisation and care for people with rheumatic and musculoskeletal diseases in the Spanish National Health System

For people with rheumatic diseases, the first point of contact with the health system is usually in primary care. At this level, it is decided whether patients should be referred to specialised care. Specialised care is most commonly provided through outpatient appointments, this type of care activity growing due to improvements in diagnostic techniques and the possibility of resolving problems without the need for hospital admission. Preventive and health promotion activities in primary care are essential for improving the status quo in terms of the incidence and prevalence of rheumatic diseases, as well as the quality of life of many people with these conditions. Good coordination and communication between levels of care and other social and healthcare services enable more efficient provision of care that is patient-centred, facilitating integrated and continuous care[22].

In this conceptual framework, more efficient management of rheumatic diseases requires the participation and coordination of different health professionals focusing on the specific needs of patients at given times, avoiding duplication of services but also insufficient provision. Chronic inflammatory immune-mediated diseases are prime examples of conditions that need this type of complex care[22].

According to the Spanish national strategy, care should be patient-centred, and two ways of achieving this are education in self-care and the management of medication-related risks. Given this, any initiative or programme focused on promoting and facilitating self-care (expert patient and patient education programmes and nursing and rehabilitation/physiotherapy clinics) will benefit patients, clinicians and the health system. Additionally, it is important to adopt measures

to safeguard patient safety, as these conditions are chronic, and over the disease course, patients tend to have to take multiple medications, often simultaneously[22].

The Spanish national strategy for rheumatic diseases establishes a set of objectives, recommendations, and indicators that seek to improve the quality of interventions and health outcomes for people with these diseases. This strategy should always be implemented in a realistic way, considering the resources available, the scope of competence of each Spanish region, and the available evidence[22].

The quality of the care provided to people with rheumatic diseases and their health outcomes are difficult to assess. The strategy proposes a set of indicators enabling the analysis of these diseases over time using data from nationwide databases. Other indicators should be provided by regional authorities or sometimes by the corresponding scientific societies and patients´ associations[22].

4.3 Clinical manifestations

Spondyloarthritis refers to a heterogeneous group of conditions that share similar clinical, immunogenetic and radiographic features that distinguish them from other conditions, namely: 1) familial clustering; 2) disease mechanisms; 3) associations with HLA-B27 status and infections, generally of the gastrointestinal and/or genitourinary tracts; 4) involvement of entheses (sites where a tendon, ligament, joint capsule or fascia attaches to bone, in peripheral joints and/or the spine), and 5) clinical signs and symptoms[23].

They are diseases characterised by chronic inflammation of the entheses and other musculoskeletal structures that tend to cause bone ankylosis. The most common and characteristic clinical features are: sacroiliitis, enthesitis, spondylitis, oligo and polyarthritis, uveitis (inflammation of the eye), psoriasis and gut inflammation. Other extraarticular signs and symptoms may occur but are generally less common.

Each type of spondyloarthritis has characteristic features. They should, therefore, be considered different entities, and their treatment and follow-up should be tailored to address these features[4].

Axial spondyloarthritis

This condition is closely associated with HLA-B27 positivity[24]. It is a chronic systemic inflammatory disease of unknown aetiology, mainly involving the axial skeleton (sacroiliac joints and spine) and the entheses, and the most common feature is sacroiliitis[25].

It is known that the inflammatory process may lead to endochondral ossification and fibrous ankylosis which progress to bony ankylosis, in advanced stages in as many as 30% of patients. A less common but equally important feature is the involvement of peripheral joints, especially the joints of the lower limbs, namely, those of the hips, knees, and feet, and patients may also have extra-articular manifestations such as uveitis and IBD[4, 26]. This type of spondyloarthritis is also associated with serious comorbidities such as cardiovascular disease and osteoporosis[27]. Other less common comorbidities include renal, neurological and pulmonary manifestations[28].

Psoriatic arthritis

This condition is a chronic inflammatory disease of the skin and the musculoskeletal system. Its clinical heterogeneity has made it difficult to conduct specific epidemiological studies and clinical trials[4, 5]. One type of cutaneous psoriasis may occur in combination with one or more of the distinct clinical features of PsA and this may explain the difficulty of genetically characterising patients with this condition[29]. In particular, the HLA-Cw6 allele has been associated with psoriasis, while HLA-B27, HLA-B38 and HLA-B39 alleles have been linked to PsA[30].

Environmental factors, such as human immunodeficiency virus infection, post-traumatic stress disorder and obesity, seem to increase susceptibility to PsA. Furthermore, certain forms of psoriasis, including nail dystrophy, and scalp or intergluteal/perianal lesions, have been associated with a higher likelihood of developing PsA[31].

Notably, PsA seems to exacerbate cardiovascular risk factors such as hypertension and dyslipidaemia, and specifically, is associated with a pro-atherogenic lipid profile, which increases the rate of subclinical atherosclerosis[32-35]. Further, there is a high prevalence of metabolic syndrome in PsA, especially in patients with moderate-to-severe cutaneous involvement, in whom the disease tends to have a major psychological impact[36]. All this implies impairment in patient quality of life.

4.4 General a priori considerations concerning the available treatments

Systemic medications available for psoriatic arthritis

Nonsteroidal anti-inflammatory drugs and corticosteroids

Nonsteroidal anti-inflammatory drugs (NSAIDs) tend to be used for treating headache and inflammation but do not modify the course of the disease. Systemic corticosteroids are not recommended and should only be used at low doses in certain patients in conjunction with DMARDs and for as short a time as possible. Corticosteroids may also be used in injections, for inflamed joints, tendon sheaths and entheses, taking appropriate precautions.

Disease-modifying antirheumatic drugs

DMARDs have been shown to improve the course of the disease. In patients with PsA with peripheral joint involvement, csDMARDs are the first line of treatment, with a preference for MTX when there is notable skin involvement or the disease is having a major impact on the patient.

csDMARDs: methotrexate (MTX), leflunomide (LFN) and sulfasalazine (SSZ).

bDMARDs

- ***Tumour necrosis factor (TNF) inhibitors***: adalimumab (ADA), certolizumab pegol (CZP), etanercept (ETA), infliximab (IFX) and golimumab (GOL)
- ***IL-17 inhibitors***
  - **IL-17 A inhibitors**: ixekizumab (IXE), secukinumab (SEC)
  - **IL-17A/F inhibitor**: bimekizumab (BZK)
- ***IL-12/23 inhibitors***: ustekinumab (UST)
- ***IL-23-p19 inhibitors***: guselkumab (GUS), risankizumab (RIS)
- ***CTLA4-Ig* (T cell co-stimulatory inhibitors)**: abatacept (ABA)

tsDMARDs

- **Phosphodiesterase 4 (PDE4) inhibitors**: apremilast
- **Janus kinase (JAK) inhibitors**: tofacitinib (TOFA), upadacitinib (UPA).

Systemic medications available for axial spondyloarthritis

Non-steroidal anti-inflammatory drugs and corticosteroids

NSAIDs tend to be used for treating headache and inflammation but have not been shown to modify the course of the disease. Nonetheless, they are the recommended first-line treatment, and bDMARD/tsDMARD therapy should only be initiated after an inadequate response to treatment with two NSAIDs at the highest tolerated doses.

Systemic corticosteroids are not recommended for axSpA, but may be used in injections, for inflamed joints, tendon sheaths and entheses, taking appropriate precautions.

Disease-modifying anti-rheumatic drugs

csDMARDs: these drugs are not effective for axSpA

bDMARDs

TNF inhibitors: adalimumab (ADA), certolizumab (CZP), etanercept (ETA), infliximab (IFX) and golimumab (GOL)

IL-17 inhibitors

IL-17 A inhibitors: ixekizumab (IXE), secukinumab (SEC)

IL-17A/F inhibitor: bimekizumab (BZK)

tsDMARDs

Janus kinase (JAK) inhibitors: tofacitinib (TOFA), upadacitinib (UPA).

Note: the sequence in which these drugs should be used is indicated in the treatment algorithms set out in Chapter 13

5. Approach to Disease Burden in Axial Spondyloarthritis and Psoriatic Arthritis in Spain

In this chapter, we present the main results of the estimation of the disease burden associated with axSpA and PsA in Spain. First, the main concepts related to these types of health measures are briefly explained.

5.1. Indicators of disease burden. Global Burden of Disease Study

In countries with a high life expectancy and at an advanced stage of demographic and epidemiological transition, such as Spain, traditional measures of mortality do not accurately reflect the health status of the population. Much of the improvement in survival is achieved by trading avoided deaths for a higher prevalence of disability and poor health. That is, increases in life expectancy do not always go hand in hand with improvements in quality of life and decreases in the prevalence of poor health. On the other hand, longer survival implies that chronic conditions, that are not fatal but are very common and/or disabling, affect more people for longer.

For these reasons, indicators that reflect both fatal and nonfatal outcomes are more suitable for describing the real impact of health problems at the population level. This is particularly relevant in diseases that -by their nature- are rarely the direct cause of death, but which may have nonfatal effects that are very widely spread in the population and/or very severe for some people, as is the case of rheumatic diseases.

Burden of disease studies aim to gather and synthesise data on these two types of consequences of disease and injury; that is, their goal is to estimate and use a synthetic indicator to summarise the impact of diseases and injuries, in terms not only of death (as reflected in indicators of mortality), but also as causes of disability and ill health. This allows us to reconsider and appropriately measure the effects on population health of diseases and disorders that, as they do not appear in the statistics as the underlying cause of death, lack visibility in traditional mortality-based health indicators. Various publications have explored the overall idea behind disease burden studies in more depth[37-41].

For populations across the world, the Global Burden of Disease project seeks to obtain estimates of the impact of diseases and injuries that are as realistic as possible thanks to thousands of

experts and technicians collecting all the epidemiological and demographic data available. It uses national death registers -even if not exhaustive- if countries have them, and when such registers do not exist, other sources of information on mortality (for example, verbal autopsies). Regarding the nonfatal effects of diseases and injuries, it uses data gathered from other registers (primary care, hospital care) and information from the national health surveys, disability surveys and so-called demographic and health surveys carried out in countries with no reliable registers. It also processes evidence on the incidence, prevalence, stage, severity and sequelae of diseases and injuries reported in the scientific literature.

The indicator typically used in burden of disease studies is disability-adjusted life years (DALYs), which are the sum of a component measuring premature mortality (years of life lost [YLLs]) and another component quantifying loss of health (years lived with disability or poor health [YLDs]). Estimates for each indicator are calculated by age, sex, and cause of disease or death.

5.2. Burden of axial spondyloarthritis and psoriatic arthritis in Spain

Diseases of the musculoskeletal system and connective tissue (Chapter XIII of the International Classification of Diseases, ICD-10) are a significant health problem worldwide. According to the most recent Global Burden of Disease Study (GBD 2019), this group of diseases account for 6% of the total global burden of disease, causing more than 157 million DALYs. In Western Europe and Spain in particular, their weight is even higher, causing 12.9 million DALYs accounting for 9.8% of the disease burden in the region and 1.9 million DALYs, accounting for 9.1% of the disease burden in Spain in 2019. Almost all of the burden (98%) is due to non-fatal consequences of these diseases: both in Spain, as well as in Western Europe and worldwide, YLLs due to premature death account for just two out of every hundred DALYs caused by musculoskeletal and connective tissue diseases.

The most recent study, GBD 2019, breaks down results for musculoskeletal and connective tissue diseases, providing specific data for rheumatoid arthritis, osteoarthritis, back pain, neck pain and gout, with a residual category for other musculoskeletal disorders. On the other hand, regarding skin diseases, GBD 2019 only reports generic data for psoriasis. That is, GBD 2019 does not give specific estimates for either axSpA or PsA.

Hence, the burden of axSpA and PsA in Spain cannot be determined using GBD 2019 statistics. Further, to our knowledge, no specific studies have been published on the burden of disease due to these conditions in Spain. Below, we outline an approach for estimating disease burden

related to these conditions based on various sources, while maintaining consistency with the GBD 2019 findings.

5.2.1. Results

Musculoskeletal and connective tissue diseases (ICD-10 Chapter XIII) account for a substantial percentage of the overall burden of disease in the Spanish population, being responsible for nearly 10% of the DALYs. This percentage is slightly lower than the overall figure for European countries (10.2%), but much greater than the percentage worldwide (5.9%) (Table 3).

Table 3. Disability-adjusted life years attributable to all causes, all musculoskeletal disorders and other musculoskeletal disorders, globally, in Western Europe and in Spain, in 2019

	Global	Western Europe	Spain
ll causes	2,538,020,071	126,857,530	12,652,100
All musc.	150,075,330	12,955,640	1,220,569
Other musc.	40,423,359	2,249,717	247,676
All musc./All causes	5.9%	10.2%	9.6%
Other musc./All musc.	26.9%	17.4%	20.3%

Produced in-house based on GBD 2019 data

Note that axSpA and PsA are included in the "Other musculoskeletal disorders" category. In 2019, the burden of disease due to axSpA and PsA was estimated to be 19,352 and 26,752 DALYs, respectively. These figures represent 7.8% and 10.8% of the total for this category, and 1.6 and 2.2% of the total burden of disease due to musculoskeletal disorders, respectively (Table 4).

Table 4. Disability-adjusted life years attributable to all musculoskeletal disorders, other musculoskeletal disorders, psoriatic arthritis and axial spondyloarthritis in Spain (in 2019)

	All musc.	Other musc.	Psoriatic arthritis	Axial spondyloarthritis
Disability-adjusted life years	1,220,569	247,676	26,752	19,352
% of all musc.	100.0%	20.3%	2.2%	1.6%
% of other musc.		100.0%	10.8%	7.8%

Produced in-house based on GBD 2019 data

Musculoskeletal disorders have very different weights depending on the component of burden considered. Only 0.3% of deaths and all YLLs due to death in Spain in 2019 were attributable to

these diseases; the fact that they seldom cause death and, generally, develop at advanced ages explain the small relative weight of this indicator of premature death. In contrast, nearly 1 in 5 (19%) YLDs in 2019 were due to musculoskeletal disorders, reflecting the marked negative impact of these diseases on population health in Spain (Table 5).

Table 5. Deaths, years of life lost due to death (YLLs), years lived with disability (YLDs) and disability-adjusted life years (DALYs) due to all causes, all musculoskeletal disorders, psoriatic arthritis and axial spondyloarthritis in Spain (in 2019)

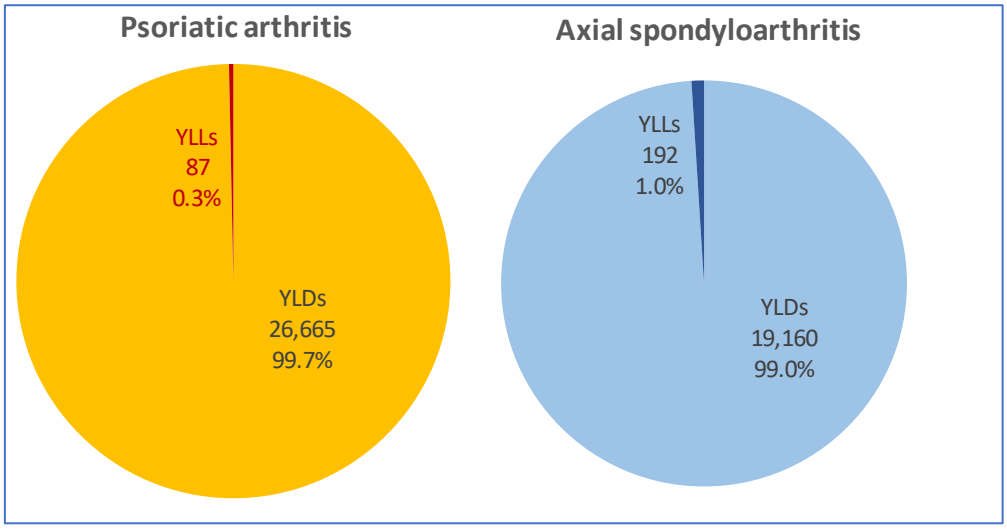
	Deaths	YLDs	YLLs	DALYs
All causes	428,577	6,321,961	6,330,140	12,652,100
All musc.	1,374	1,201,472	19,097	1,220,569
Psoriatic arthritis	5	26,665	87	26,752
Axial spondyloarthritis	11	19,160	192	19,352
All musc./All causes	0.3%	19.0%	0.3%	9.6%
Psoriatic arthritis/All musc.	0.4%	2.2%	0.5%	2.2%
Axial spondyloarthritis/All musc.	0.8%	1.6%	1.0%	1.6%

All musc.: all musculoskeletal disorders

Produced in-house based on GBD 2019 data

For both forms of spondyloarthritis of interest, the morbidity component (26,665 and 19,160 YLDs for PsA and axSpA, respectively) is responsible for nearly all the DALYs (99.7% and 99% for PsA and axSpA, respectively). Accordingly, premature death contributes little to the total burden in both diseases (0.3 and 1% for PsA and axSpA, respectively) (Figure 1).

Figure 1. Burden of disease due to psoriatic arthritis and axial spondyloarthritis. Percentage distribution of the years of life lost due to death (YLLs) and years lived with disability (YLDs) in Spain (in 2019).

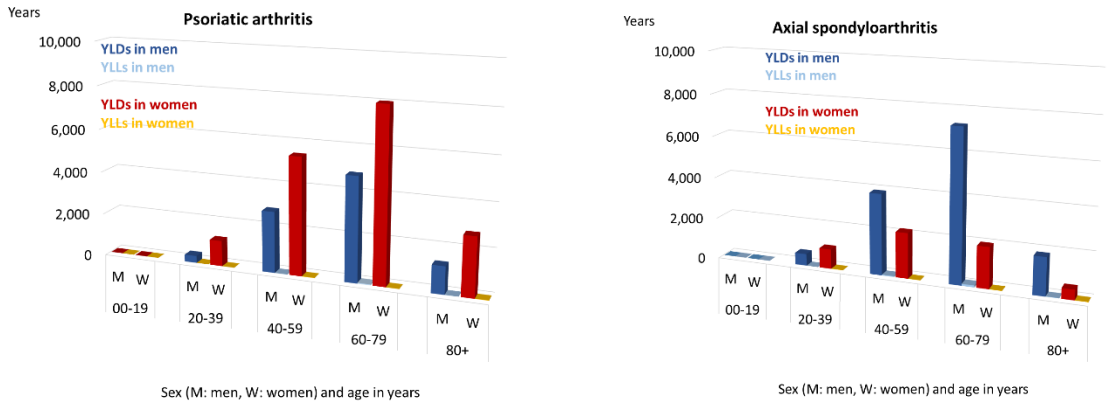


Estimates calculated and graphs produced in-house

The disease burden due to PsA and axSpA is very unevenly distributed by sex and age. For both diseases, the number of DALYs increases between 20 and 79 years of age, and then decreases

in the over-80-year-old group (Figure 2, Table 6). In relative terms (age- and sex-standardised rates per 100,000 persons), the small sample size for people at advanced ages distorts this indicator in this open age group, causing the rate to increase (Figure 3, Table 7). The burden of PsA is higher in women than men, while that of axSpA is higher in men than women.

Figure 2. Burden of disease due to psoriatic arthritis and axial spondyloarthritis. Years of life lost due to death (YLLs) and years lived with disability (YLDs) by age and sex in Spain (in 2019).



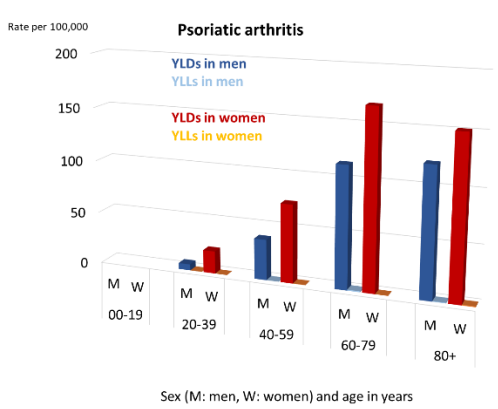
Estimates calculated and graphs produced in-house.

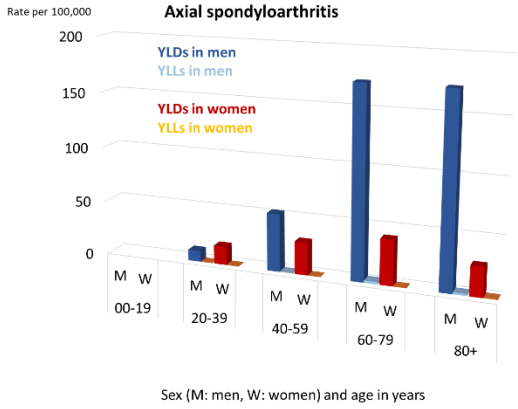
Table 5. Burden of disease due to psoriatic arthritis and axial spondyloarthritis. Years of Life lost due to death (YLLs), years lived with disability (YLDs) and disability-adjusted life years (DALYs) by age and sex in Spain (in 2019)

Years	Psoriatic arthritis						Years	Axial spondyloarthritis					
	Men			Women				Men			Women		
Age	YLDs	YLLs	DALYs	YLDs	YLLs	DALYs	Age	YLDs	YLLs	DALYs	YLDs	YLLs	DALYs
00-19	0	0	0	0	0	0	**00-19**	0	0	0	0	0	0
20-39	329	0	329	1,194	0	1,194	**20-39**	569	0	569	949	10	959
40-59	2,838	7	2,845	5,447	13	5,460	**40-59**	3,892	39	3,931	2,184	7	2,191
60-79	4,829	40	4,869	8,008	7	8,015	**60-79**	7,279	94	7,372	1,974	11	1,985
80+	1,279	6	1,285	2,741	13	2,755	**80+**	1,821	19	1,839	493	13	506
Total	**9,275**	**53**	**9,328**	**17,390**	**33**	**17,424**	**Total**	**13,560**	**151**	**13,712**	**5,599**	**41**	**5,640**

Estimates calculated and graphs produced in-house.

Figure 3. Burden of disease due to psoriatic arthritis and axial spondyloarthritis. Age- and sex-standardised rates (per 100,000 persons) of years of life lost due to death (YLLs) and years lived with disability (YLDs) in Spain (in 2019)





Estimates calculated and graphs produced in-house.

Table 7. Burden of disease due to psoriatic arthritis and axial spondyloarthritis. Age- and sex-standardised rates of years of life lost due to death (YLLs), years lived with disability (YLDs) and disability-adjusted life years (DALYs) in Spain (in 2019)

Rate per 100,000	Psoriatic arthritis						Rate per 100,000	Axial spondyloarthritis					
	Men			Women				Men			Women		
Age	**YLDs**	**YLLs**	**DALYs**	**YLDs**	**YLLs**	**DALYs**	**Age**	**YLDs**	**YLLs**	**DALYs**	**YLDs**	**YLLs**	**DALYs**
00-19	0	0	0	0	0	0	**00-19**	0	0	0	0	0	0
20-39	5.8	0.0	5.8	21.5	0.0	21.5	**20-39**	10.1	0.0	10.1	17.1	0.2	17.2
40-59	38.5	0.1	38.5	74.0	0.2	74.2	**40-59**	52.7	0.5	53.3	29.7	0.1	29.8
60-79	114.6	1.0	115.6	167.6	0.1	167.7	**60-79**	172.8	2.2	175.0	41.3	0.2	41.5
80+	121.5	0.6	122.1	151.3	0.7	152.0	**80+**	173.0	1.8	174.8	27.2	0.7	27.9
Total	**50.7**	**0.3**	**51.0**	**89.1**	**0.2**	**89.3**	**Total**	**74.1**	**0.8**	**74.9**	**28.7**	**0.2**	**28.9**

Estimates calculated and graphs produced in-house.

5.2.2. Conclusion

Both PsA and axSpA contribute substantially to the disease burden estimated for the other musculoskeletal disorders category. The mortality component, measured in years of potential life lost due to premature death, is very small, indicating that almost the entire burden of both diseases is due to their non-fatal consequences (YLDs). The disease burden is higher in women than men for PsA, while the reverse is true for axSpA. In both cases, the disease burden is largely concentrated in adults.

To be able to more accurately estimate the burden of disease due to PsA and axSpA, there is a need for more accurate up-to-date measures of prevalence of each disease, disaggregated by sex and age.

Complete data from GBD 2019 can be viewed and downloaded using the GBD tool provided by the Institute for Health Metrics and Evaluation (IHME) available from: https://vizhub.healthdata.org/gbd-results

6. Clinical research questions (in PICO format)

Treatment of Axial Spondyloarthritis

Biologic DMARD or JAK inhibitor therapy compared to placebo

1. In axSpA, what is the efficacy of IL-17 and JAK inhibitors compared to placebo?[N]

Predictors of prognosis

2. In axSpA, does pharmacological treatment with bDMARDs or JAK inhibitors slow the progression of structural damage?[A]

3. In axSpA, what are the predictors of response to IL-17 and JAK inhibitors?[N]

Treatment failure

4. In axSpA, what is the efficacy of treatment with a different TNF inhibitor or targeted therapy in patients who have an inadequate response to a first TNF inhibitor?[A]

Treatment optimisation

5. In axSpA, can bDMARD therapy be tapered or withdrawn?[N]

Extra-musculoskeletal manifestations

6. In axSpA, what is the efficacy of bDMARDs and tsDMARDs in treating extra-musculoskeletal manifestations (uveitis, psoriasis and IBD)?[N]

Exercise

7. In axSpA, what type of exercise programme is most effective in improving clinical and functional outcomes?[A]

Obesity and smoking

8. In axSpA, do obesity and/or smoking increase disease activity, accelerate radiographic progression of structural damage and impair treatment response?[N]

Treatment of psoriatic arthritis

Early intervention

9. In PsA, does early detection and pharmacological treatment improve functional capacity, slow radiographic progression of structural damage and enhance quality of life?[A]

Conventional synthetic disease-modifying antirheumatic drugs

10. In PsA, what is the efficacy of csDMARDs in treating axial and peripheral disease, enthesitis and dactylitis?[A]

Treatment with biologic and targeted synthetic disease-modifying antirheumatic drugs

11. In PsA, what is the efficacy of IL-23 and IL-17 inhibitors and tsDMARDs (JAK inhibitors and apremilast) in treating axial and peripheral disease, enthesitis and dactylitis?[N]

Treatment with biologic or targeted synthetic disease-modifying antirheumatic drugs compared to TNF inhibitors

12. In PsA, what is the efficacy, effectiveness and safety of IL-17, IL-23 and JAK inhibitors compared to TNF inhibitors?[N]

Treatment with a biologic or targeted disease-modifying antirheumatic drug monotherapy

13. In PsA, is combination therapy with MTX and bDMARD or tsDMARDs more effective than using bDMARD or tsDMARD monotherapy?[A]

Extra-musculoskeletal manifestations

14. In PsA, what is the efficacy of bDMARDs and tsDMARDs in treating extra-musculoskeletal manifestations (uveitis, psoriasis and IBD)?[N]

Obesity and smoking

15. In PsA, do obesity and/or smoking increase disease activity, accelerate radiographic progression of structural damage and impair treatment response?[N]

Treatment of axial spondyloarthritis and psoriatic arthritis

Health education

16. In PsA or axSpA, is nurse-led health education beneficial?[A]

[N] New question

[U] Updated question

7. Treatment

7.1 Treatment of axial spondyloarthritis (axSpA)

Clinical question 1 (New)

In axPsA, what is the efficacy of IL-17 and JAK inhibitors compared to placebo?

Context/Background

Since the publication of the previous ESPOGUÍA, progress has been made in the management of axSpA, including the development of advanced therapies based on two new mechanisms of action, approved by regulatory authorities: IL-17 and JAK inhibitors. Before, the only drugs available for use after an inadequate response and/or intolerance to NSAIDs all had the same mechanism of action, that is, they were all TNF inhibitors. It is necessary to assess and analyse the efficacy and safety of IL-17 and JAK inhibitors observed in clinical studies before recommending their use in patients with axSpA in clinical practice.

Recommendations

Recommendation 1: In patients with active axSpA who have an inadequate response and/or intolerance to NSAIDs, treatment options should include IL-17A and IL-17A/F and JAK inhibitors. The line of treatment in which they are used should depend on patient clinical characteristics.* (Strong recommendation in favour)[N]

*Appendix 2 contains the recommendations made in the previous guideline as complementary information.

[N] Recommendation related to a new question

Important clinical considerations:

- Subgroups to be considered:
  - *Patients ≥65 years old:* Prioritise options other than JAK inhibitors in ≥65-year-olds, patients who are active smokers (or have a history of heavy smoking), and those who have an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible dose.
  - *Patients with nr-axSpA*: These patients should also be assessed for objective signs of inflammation, such as elevated CRP and positive MRI findings.
  - *Drug groups:* Although there are some differences between different IL-17 inhibitors (A and A/F) and different JAK inhibitors, the GDG believes that recommendations should be made by drug group, as it is not currently possible to demonstrate that small differences in the mechanism of action between drugs in the same group lead to

significant differences in efficacy or safety profile (given a lack of head-to-head clinical trials of different drugs in the same group for treating axSpA).

Rationale

These recommendations have been made based on the results of double-blind placebo-controlled RCTs of IL-17 or JAK inhibitors in which the variables studied were primary or secondary endpoints, and the results have shown statistically significant differences compared to placebo. Both IL-17 and JAK inhibitors have shown greater efficacy than placebo in patients with r-axSpA or nr-axSpA and have an acceptable safety profile. There are, however, other factors that should be taken into account: first, the measures recommended by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (EMA) to minimise the risk of serious adverse effects associated with JAK inhibitors used in the treatment of various chronic inflammatory conditions; and second, the results of studies in patients with nr-axSpA, which only included patients with objective signs of inflammation (elevated CRP and/or positive MRI findings).

Detailed rationale

Interleukin-17 inhibitors

IL-17A

Secukinumab vs. placebo

One SR was found that included four RCTs assessing the efficacy and safety of secukinumab (SEC) compared to placebo over 16 weeks[42]. The MEASURE 3 trial[43] lasted for 52 weeks and included 226 patients with active r-axSpA who were randomised to receive iv SEC 150 mg/kg (weeks 0, 2 and 4) followed by subcutaneous (sc) SEC 150 or 300 mg every 4 weeks (q4w), or placebo. Across the groups, the mean age of participants was 42 to 43 years old and between 53% to 66% were male. Subsequently, the MEASURE 4 trial[44] lasted 104 weeks and included 350 patients (mean age: 41-45 years; 65%-70%, male) with active r-axSpA randomised to SEC 150 mg with or without a loading dose of 150 mg or placebo; and the MEASURE 5 trial[45] lasted 52 weeks and included 458 patients (mean age: 33-35 years; 83%-86%, male) with r-axSpA randomised to SEC 150 mg or placebo. Most recently, the PREVENT[46] trial included 555 patients (mean age: 39 to 40 years; 43%-49%, male) with active nr-axSpA randomly allocated to receive SEC 150 mg with or without a loading dose or placebo, and results were analysed at weeks 16 and 52. The overall quality of the evidence was rated as high, although the randomisation process was not clearly described for the MEASURE 3 trial.

Regarding the risk-benefit balance, the evidence identified shows that results with SEC differ significantly from those with placebo in terms of reducing key clinical disease scores. Further, these studies did not raise any concerns in relation to adverse effects.

Other considerations: The ASAS-EULAR recommendations for the management of patients with axSpA were also taken into account[47].

Based on the group's experience, the GDG considers that SEC may be used in patients with axSpA who have an inadequate response and/or intolerance to NSAIDs.

Ixekizumab vs. placebo

Regarding ixekizumab (IXE), the aforementioned SR by Webers et al. included the results of three RCTs, all with a 16-week follow-up. These trials compared IXE every 2 weeks (q2w) or q4w with placebo.

The COAST-V[48] study included 341 patients with active r-axSpA who were randomly allocated (1:1:1:1) to receive IXE 80 mg q2w or q4w, adalimumab (ADA) 40 mg q2w or placebo. The trial only included patients naïve to bDMARDs. The primary endpoint was ASAS 40 response at week 16. The mean age was 41 years in the IXE groups, 42 years in the ADA group and 43 years in the placebo group. In the ADA, IXE q2w and IXE q4w groups respectively, 81%, 77% and 84% of the patients were men vs. 83% in the placebo group, and 91%, 90% and 93% were HLA-B27 positive vs. 89% in the placebo group.

Subsequently, the COAST-W[49] included 316 patients with axSpA who had an inadequate response and/or intolerance to 1 or 2 TNF inhibitors. Patients were randomly allocated to receive IXE 80 mg q2w, IXE 80 mg q4w or placebo. As in the previous trial, the primary endpoint was ASAS 40 response at week 16. The mean age was 44 years old in the IXE q2w group and 47 years in the IXE q4w and placebo groups. In the IXE q2w and q4w groups respectively, 76.5% and 79.8% of trial participants were male vs. 83.7% in the placebo group. Regarding history of TNF inhibitor use, 68% and 61.4% of patients in the IXE q2w and q4w groups had received one TNF inhibitor vs. 59.6% in the placebo group; while 32% and 38.6% of participants had received two TNF inhibitors vs. 40.4% in the placebo group.

Lastly, the COAST-X[50] study included 303 patients with nr-axSpA randomly allocated to receive IXE 80 mg q2w (n=102), IXE 80 mg q4w (n=96) or placebo (n=105). Patients who met the radiographic criterion of the New York criteria or had previously received any bDMARDs were excluded. The primary endpoint was ASAS 40 at weeks 16 and 52. The mean age of patients was 40 years old in the IXE q2w and placebo groups, and 41 years old in the IXE q4w group. In the IXE q2w and q4w groups respectively, 52% and 48% of participants were male vs. 42% in the placebo group, and 75% and 72% were HLA-B27 positive vs. 72% in the placebo group.

Regarding the risk-benefit balance, the evidence identified shows that results with IXE differ significantly from those with placebo in terms of reducing key clinical disease scores. Further, these studies do not raise any concerns in relation to adverse effects.

Other considerations: The ASAS-EULAR recommendations for the management of patients with axSpA were also taken into account[47].

Based on the group's experience, the GDG considers that IXE may be used in patients with axSpA who have an inadequate response and/or intolerance to NSAIDs.

IL-17A and IL-17F

Bimekizumab vs. placebo

The SR by Webers included the BE AGILE[51] study that compared bimekizumab (BKZ) with placebo. This study included 303 patients with radiographic axSpA randomly allocated (1:1:1:1:1) to one of the following groups: BKZ 16 mg (n=61), 64 mg (n=61), 160 mg (n=60) or 320 mg (n=61) q4w, or placebo (n=60). The primary endpoint was ASAS 40 response at 12 weeks. Across all the participants, the mean age was 42 years old, 84.5% were male, 89.1% of patients were HLA-B27 positive, and 11.2% of patients had been previously treated with a TNF inhibitor.

In 2023, the results of the BE MOBILE 1 (nr-AxSpA) and BE MOBILE 2 (r-axSpA)[52] trials were published. In these trials, patients were randomly allocated (1:1) to either BKZ 160 mg q4w or placebo. The trials lasted for 52 weeks and included 254 patients with nr-axSpA and 332 patients with r-axSpA. From week 16, in the open-label phase, all patients received BKZ. The primary endpoint was ASAS 40 response at week 16. In the BE MOBILE 1 study, 128 patients with nr-axSpA received BKZ and 126 placebo. In the BKZ and placebo groups respectively, the mean age was 40 and 39 years, while 57% and 51.6% of the patients were male, 80.5% and 74.6% were HLA-B27 positive, and 7.8% and 13.5% had been previously treated with TNF inhibitors. In the BE MOBILE 2, 221 patients with r-axSpA received BKZ and 111 placebo. In the BKZ and placebo groups respectively, the mean age was 41 and 39 years, while 72.4% and 72.1% of patients were male, 86.4% and 83.8% were HLA-B27 positive, and 16.7% and 15.3% had received previous treatment with TNF inhibitors.

Regarding the risk-benefit balance, the evidence identified shows that outcomes with BKZ differed significantly from those with placebo in terms of reducing key clinical disease scores. Further, these studies did not raise any concerns in relation to adverse effects.

Other considerations: The ASAS-EULAR recommendations for the management of patients with axSpA were also taken into account[47].

Based on the group's experience, the GDG considers that BKZ may be used in patients with axSpA who have an inadequate response and/or intolerance to NSAIDs.

JAK inhibitors

Tofacitinib vs. placebo

Two studies were identified assessing the efficacy and safety of tofacitinib (TOFA, 5 mg/12 h) compared to placebo.

The first RCT[53] lasted for 12 weeks and included 207 patients with axSpA who were randomised to TOFA at a dose of 2 mg, 5 mg or 10 mg, twice daily, or placebo. In the TOFA and placebo groups, respectively, the mean age was 41 and 42 years while 63% and 75% of patients were male.

The second RCT[54] included 269 patients with active axSpA who were randomly allocated to receive TOFA (5 mg/12 h) or placebo for 16 weeks. In the TOFA and placebo groups, respectively, the mean age was 42 and 40 years old while 87% and 79% of patients were male.

The overall quality of the evidence was rated as high.

Regarding the risk-benefit balance, the evidence identified shows that results with TOFA differ significantly from those with placebo in terms of reducing key clinical disease scores. Further, these studies do not raise any concerns in relation to adverse effects.

Other considerations: The ASAS-EULAR recommendations for the management of patients with axSpA were also taken into account[47].

Based on the group's experience, the GDG considers that TOFA may be used in patients with radiographic axSpA who have an inadequate response and/or intolerance to NSAIDs.

Upadacitinib vs. placebo

The SR by Ortolan[55] included a single study on upadacitinib (UPA), namely, the SELECT-AXIS 1[56] trial, which included 189 patients with active r-axSpA who had not previously received biological therapy. Patients were randomly allocated to receive UPA 15 mg/d (n=93) or placebo (n=94) for 14 weeks. The primary endpoint was ASAS 40 response at week 14. In the UPA and placebo groups, respectively, the mean age was 47 and 44 years, 68% and 73% of patients were male, and 75% and 78% were HLA-B27 positive.

Subsequently, other articles not included in the aforementioned SR have been published on the use of UPA in axSpA. The SELECT-AXIS 2 trial consisted of two separate studies: substudy 1 was a 14-week RCT in patients with r-axSpA with an open-label extension study of 90 weeks[57], and substudy 2 was a 52-week RTC in patients with nr-axSpA with an open-label extension study

lasting another 52 weeks[58]. Substudy 1[57] included 420 patients with active r-axSpA randomly allocated to receive UPA 15 mg/d (n=211) or placebo (n=209) The primary endpoint was ASAS 40 at week 14. in the UPA and placebo groups, respectively, the mean age was 43 and 42 years, 73% and 76% of patients were male, and 85% and 81% were HLA-B27 positive. This study was open to patients who had previously received biological therapy. In the UPA group, 73% of patients had received a TNF inhibitor and 14% an IL-17 inhibitor vs. 76% and 11% respectively in the placebo group.

Other considerations: The ASAS-EULAR recommendations for the management of patients with axSpA were also taken into account[47].

Based on the group's experience, the GDG considers that UPA may be used in patients with axSpA who have an inadequate response and/or intolerance to NSAIDs.

Equity, acceptance and feasibility of implementation

The GDG considers that, in our setting, there are no marked inequities in access to IL-17 and JAK inhibitors.

The group also considers it likely that all those involved in the use of these drugs (health authorities, specialists, and patients) will find their use in clinical practice acceptable, given the good efficacy of these drugs and their low adverse effect rates, as well as the experience accumulated over the years in the use of advanced therapies.

On the other hand, antirheumatic therapies, including tsDMARDs and bDMARDs, are commonly used in our setting. The experience accumulated over the years by rheumatologists facilitates the introduction and use of drugs for new therapeutic targets.

Outcome assessment by patients

In the GDG's judgement, it is unlikely that there is variability in how patients rate the main outcomes.

Resource use

Searches were not conducted for information on the costs of the drugs assessed, given that this topic is usually deemed to be beyond the scope of CPG recommendations; therefore, the GDG considers that it has insufficient data to make any recommendations on resource use.

Clinical question 2 (Updated)

In axSpA, does pharmacological treatment with bDMARDs or JAK inhibitors slow the progression of structural damage?

Recommendations

Recommendation 2: The GDG considers that there is insufficient good-quality evidence available to make a definitive recommendation on the use of bDMARDs or JAK inhibitors for slowing the progression of structural damage in patients with axSpA; however, the group does suggest assessing predictors of the progression of structural damage when considering prescribing these drugs (Good clinical practice recommendation)[U].

[U] Recommendation related to an updated question

Quality of the evidence

Regarding radiographic progression, the presence of baseline radiographic damage (syndesmophytes on spinal X-rays) is the most important predictor[59, 60]. Other factors that have been associated with faster progression of radiographic damage are being male, smoking, and most notably, the persistence of disease activity (assessed clinically by measuring blood CRP levels and/or indicated by bone marrow oedema on MRI)[60, 61]. Further, a 12-year follow-up study of the patients of the OASIS cohort[62] found that a greater disease activity (as measured by the Axial Spondyloarthritis Disease Activity Score, ASDAS) is longitudinally associated with faster radiographic progression (low quality of evidence).

Biological therapies have been shown to reduce inflammation in the sacroiliac joints and spine, as assessed by MRI, observed as early as 6 weeks after the start of treatment. This effect is superior to that achieved with NSAIDs or SSZ[63-66] (moderate quality of evidence). For this reason, there may be a "therapeutic window" in the early stages of the disease (nr-axSpA), in which biological therapies are particularly effective at inhibiting the development of foci bone of inflammation in the sacroiliac joint and spine[67]. Reduction in bone marrow oedema after biological therapies is associated with good control of disease activity and low CRP levels, especially in nr-axSpA. Nonetheless, in the first studies, the resolution of bone marrow oedema after 2 years of TNF inhibitor therapy, especially in patients at more advanced stages of the disease, did not seem to slow the appearance of foci of fatty degeneration (FD) or the progression of structural damage (syndesmophytes)[68-70].

In relation to this, there is evidence that the development of FD together with inflammation and FD without prior inflammation are both significantly associated with syndesmophyte formation after 5 years of infliximab (IFX) therapy[71]. On the other hand, other data suggest that administration of TNF inhibitors for more than 4 years is associated with significantly less progression of spinal damage, as assessed by plain radiography (modified Stoke Ankylosing Spondylitis Spine Score, mSASSS)[72, 73]. The earlier and the longer the treatment, the better, less progression of damage being observed when TNF inhibitor therapy was initiated earlier, especially when started within 5 years of disease onset, and when the duration of TNF inhibitor use was longer[73].

Results from the main clinical trials on SEC seem to indicate that reductions in structural damage are associated with no development of new fatty lesions and slower progression of structural damage in the spine after 2 years (overall change in mSASSS: 0.3, SD: -2.52), with progression also being slow (change in mSASSS: 0.38-0.52) in patients with predictors of progression, such as syndesmophytes or high CRP levels at baseline[74].

Only preliminary data are available concerning radiographic progression and combination therapy with biologics and NSAIDs. A single study with 40 patients with ankylosing spondylitis observed less radiographic progression after 2 years as assessed by mSASSS in the group treated with TNF inhibitors plus NSAIDs than in the group treated with TNF inhibitors alone[75].

2023 update

To date, there are no robust data to affirm the existence of a therapeutic window in axSpA, as it is unclear whether treatment in the early stages of the disease leads to better long-term outcomes. A recent SR did not find differences in treatment response as a function of disease duration or radiographic damage, and concluded that the evidence regarding this issue is very limited[76].

Similar to TNF and IL-17 inhibitors, JAK inhibitors have been shown to be effective in reducing inflammation as measured by the Spondyloarthritis Research Consortium of Canada (SPARCC) score, both in the sacroiliac joint and spine, although it should be recognised that the evidence to date is mainly from pivotal clinical trials[57, 77].

TNF inhibitors have been shown to slow spinal progression in patients with r-axSpA. Similarly, both SEC and IXE (IL-17 inhibitors) have been associated with a low rate of radiographic progression at 2 years of follow-up. Regarding JAK inhibitors, the only data available on radiographic progression are from clinical trials. Specifically, UPA was reported to achieve a mean change in mSASSS of 0.7 (95% CI 0.3 to 1.1) after 2 years of follow-up[77].

To date, only one head-to-head clinical trial (the SURPASS trial) has been specifically designed to assess radiographic progression at 2 years in patients treated with a TNF inhibitor (ADA) vs. an IL-17-A inhibitor (SEC). This study showed low rates of spinal progression at 2 years of follow-up, and between-group differences did not reach significance. Therefore, it can be concluded that these drugs have similar efficacy in terms of slowing the progression of structural damage[78].

Regarding combination therapy with bDMARDs and NSAIDs, there are new studies demonstrating that the efficacy of combination therapy with TNF inhibitors and NSAIDs is superior to that of NSAIDs alone. Specifically, it was found that, after 28 weeks of treatment, patients with r-axSpA who received IFX plus naproxen were more likely to achieve partial ASAS remission than those who received placebo plus naproxen[79]. A subanalysis of this study showed that there were between-group differences not only in measures of clinical response, but also in imaging findings, specifically in the reduction of inflammation in the sacroiliac joints and spine[80]. However, no data were provided on structural progression. Similarly, an open-label clinical trial assessing patients with r-axSpA treated with celecoxib plus etanercept (ETN) vs celecoxib alone showed a better response at 52 weeks in the combination therapy group, in terms of ASAS 20 response rate, as well as greater reduction of inflammation in the spine[81].

Finally, the CONSUL trial has been the only study specifically designed to assess the effect of combination therapy on radiographic spinal progression, although this study compared a bDMARD in combination with an NSAID (GOL plus celecoxib) with the bDMARD alone (GOL). Over 2 years, the combination therapy did not show superiority over the monotherapy in slowing the progression of structural damage in patients with r-axSpA, although a non-significant numerical difference was observed in favour of combination therapy. These data do not clarify whether adding an NSAID to a TNF inhibitor can help to further slow radiographic progression[82].

To conclude, the biological therapy and JAK inhibitors are effective in reducing inflammation in the sacroiliac joints and spine. Further, recent data suggest that both biologics and JAK inhibitors are effective in slowing radiographic progression. It should be noted, however, that the data available to date on the effect of JAK inhibitors on radiographic progression is from pivotal clinical trials of UPA.

Predictors of structural damage include greater baseline radiographic damage, more inflammatory activity (as measured by MRI and CRP levels), being male and smoking.

Clinical question 3 (New)

In axSpA, what are the predictors of response to IL-17 and JAK inhibitors?

Context/Background

Axial spondyloarthritis (both radiographic and non-radiographic) is a chronic inflammatory disease characterised by inflammation in the sacroiliac joints and spine. Both bDMARDs and tsDMARDs tend to be used in patients who have had an inadequate response to NSAIDs. Biological therapies, specifically IL-17 (IL-17A and IL-17A/F) inhibitors, and JAK inhibitors (TOFA and UPA) have been shown to be effective for controlling the signs and symptoms associated with the disease and improving patient quality of life. Nonetheless, a relatively high percentage of patients do not respond to these drugs; and therefore, it would be useful to identify predictors of response to these therapies to improve patient management.

Recommendations

Recommendation 3: In patients with active axSpA starting treatment with TNF, IL-17A, or IL-17A/F inhibitors, assess predictors of good response, such as being male, and elevated CRP. (Weak recommendation in favour)[N].

Recommendation 4: In patients with active axSpA starting treatment with IL-17A, or IL-17A/F inhibitors, assess predictors of radiographic progression, such as being male, older age, smoking, elevated CRP, HLA-B27 positivity and spinal bone marrow oedema on MRI. (Weak recommendation in favour)[N].

[N] Recommendation related to a new question

Important clinical considerations:

- Monitoring and assessment
  - Based on the literature reviewed, it may be useful to measure CRP at each follow-up visit, to identify axSpA patients at a higher risk of structural damage progression. Further, in these patients, smoking should be assessed regularly and smoking cessation encouraged.
  - To date, no studies have provided evidence of the value of predictors of response to JAK inhibitors.

Rationale

These recommendations have been made based on the results of double-blind placebo-controlled RCTs of IL-17A and IL-17A/F and prospective observational studies in which the

variables studied were primary or secondary endpoints. The GDG has decided that it is important to assess predictors of response and radiographic progression in each patient, but this recommendation has been classified as a weak recommendation in favour given that the literature review includes retrospective observational studies with a risk of bias.

The latest ASAS-EULAR recommendations for the management of patients with axSpA are based on two systematic reviews assessing the therapeutic efficacy of pharmacological and non-pharmacological interventions. On the other hand, these recommendations do not include information on predictors of clinical response or long-term poor prognosis[42, 47, 55].

Detailed rationale

IL-17A inhibitors (SEC and IXE) are indicated for patients with r-axSpA or nr-axSpA who have an inadequate response or contraindications to NSAIDs. There is a new recently approved IL-17A/F inhibitor (BKZ) for treating this condition. To date, however, no studies have assessed what factors predict response to this drug.

Although the clinical question included the identification of predictors of response to JAK inhibitors, to date, no studies have addressed this research question, given that these drugs have been recently approved for treating axSpA. Therefore, the results have focused on studies assessing the efficacy of IL-17 inhibition.

Sex:

Men vs. women

Five studies have been identified assessing the influence of sex as a predictor of response to axSpA treatment. The first is an extension study of the MEASURE 1 trial that included 187 patients with active axSpA who received SEC 75/150 mg[83]. The dose could be up-titrated from 75 mg to 150 mg SEC during the follow-up period at the investigators' discretion. The study included both biologic-naïve patients and non-responders to TNF inhibitors. The mean age was 41.6 years old; 71.3% of participants were male, 76.3% were HLA-B27-positive and the mean time since disease onset was 7.7 years.

The second study was a *post hoc* analysis of the COAST-V, W and X trials[84]. It included 574 patients with r-axSpA or nr-axSpA who received sc IXE 80 mg q2w or q4w or placebo. In COAST-V, there was a comparison arm using sc ADA 40 mg q2w. At week 16, patients in the placebo arm were assessed and reassigned to the IXE arm depending on their response, as rated by the researcher. This study included both biologic-naïve patients and non-responders to TNF inhibitors. The mean age was 42.8 years old, 69.2% of patients were men, 81.0% were HLA-B27-positive, and the time since symptom onset was 14.1 years.

The third study was a *post hoc* analysis of the COAST-Y extension study and included 230 patients with r-axSpA from the COAST-V and W studies who received sc IXE 80 mg q2w or q4w[85]. It included patients who remained continuously on IXE with no interruptions (from the pivotal COAST-V and COAST-W studies through to the completion of the COAST-Y extension study) and those who were re-randomised to IXE, including both biologic-naïve patients and non-responders to one or two TNF inhibitors. The mean age was 43.0 years, 81.7% of patients were males, 87.4% were HLA-B27-positive and the mean symptom duration was 15.9 years.

The fourth study was a real-life multicentre observational study on axSpA, which included 249 patients (both biologic-naïve patients and those who were non-responders or intolerant to one or more bDMARDs), who initiated SEC therapy and were followed up for 2 years[86]. The median age was 51 years old, 47.8% of patients were male, 40.9% were HLA-B27-positive and the median disease duration was 9 years.

The last of the five studies was a real-life multicentre observational study on PsA and axSpA, which included 130 patients (both biologic-naïve patients and those who were non-responders or intolerant to one or more bDMARDs) with PsA (62 had axial involvement) and 39 patients with axSpA, who initiated SEC therapy and were followed up for at least 1 year[87]. The mean age was 52.8% years, 48.5% were male, 10.7% were HLA-B27-positive, and the mean time since symptom onset was 12.5 years.

For most of the studies, the overall quality of the evidence for the critical outcomes was rated as moderate, downgraded by one level due to imprecision (95% CIs being wide and crossing the clinical decision threshold) or because they were high-quality open-label extension studies of randomised trials in which groups were maintained although they were no longer blinded. Nonetheless, the quality was rated as poor for important outcomes, given that it was from studies with very small sample sizes and wide CIs around the effect estimates.

The evidence suggests that being male could favour treatment response in certain clinical disease scores, ASAS 40 and ASDAS-LDA, in patients with r-axSpA and nr-axSpA. Additionally, there may be more spinal radiographic progression, as measured by mSASSS, in men than women.

Other considerations: Being male has been identified in previous studies as a predictor of radiographic progression. That is, these results are in line with previous research findings[88].

Based on its own experience and available evidence, the GDG has made a recommendation underlining the importance of paying special attention to female patients, given their lower likelihood of responding to treatment.

Age:

Age > 40 years old vs. < 40 years

Two of the aforementioned studies also assessed age as a predictor of treatment response in axSpA[85, 86].

The quality of the evidence was rated as moderate to low, given that it was from high-quality open-label extension studies of randomised trials in which groups were maintained although they were no longer blinded, or studies with very small sample sizes and wide CIs around the effect estimates.

The available evidence suggests that age does not have a clear influence on therapeutic response. On the other hand, results suggest faster radiographic progression as measured by mSASSS in patients over 40 years of age.

Other considerations: It should be noted that, in this case, age refers to the age at the time of study inclusion and not the age at symptom onset.

Smoking status:

Smokers vs. non-smokers

Three of the aforementioned studies also assessed smoking status as a predictor of treatment response in axSpA[83, 85-87].

The overall quality of the evidence was rated as low, given that it was from studies with very small sample sizes and wide CIs around the effect estimates.

Regarding the risk-benefit balance, the evidence does not show a clear association between smoking and the rate of treatment response. On the other hand, being a smoker may increase the risk of radiographic progression in the spine, as measured using mSASSS.

Based on the group's experience, the GDG considers that smoking may increase the risk of spinal radiographic progression, as measured by mSASSS, in line with scientific literature.

CRP:

Four studies were identified assessing CRP as a predictor of treatment response in axSpA. Three of them have been described previously[83, 85, 86].

The fourth study was a *post hoc* analysis of the MEASURE 1 and 2 trials including 392 patients (both biologic-naïve patients and non-responders to TNF inhibitors) with active axSpA who had received sc SEC 150 mg or placebo and had baseline data on CRP[89]. The mean age of patients was 42.4 years old, 68.9% were male, 74.2% were HLA-B27 positive, and the mean time since the diagnosis of axSpA was 7.1 years.

The quality of the evidence was rated as moderate to low, given that it was from high-quality open-label extension studies of randomised trials in which groups were maintained although they were no longer blinded, or studies with very small sample sizes and wide CIs around the effect estimates.

Regarding the risk-benefit balance, the evidence identified shows that elevated CPR at baseline may increase the likelihood of a good therapeutic response, as measured by ASAS 20. Additionally, an elevated CRP may be associated with faster radiographic progression in the spine.

Other considerations: The 2022 ASAS-EULAR recommendations for the management of patients with axSpA suggest assessing CPR before using any type of biologic or tsDMARD[47]. In relation to this, the recommendation is to consider a biological drug in patients with high disease activity and objective signs of inflammation, such as elevated CRP and positive sacroiliac joint MRI findings or radiographic sacroiliitis.

HLA-B27:

Two of the aforementioned studies also assessed HLA-B27 status as a predictor of treatment response in axSpA[85, 86].

The quality of the evidence was rated as moderate to low, given that it was from high-quality open-label extension studies of randomised trials in which groups were maintained although they were no longer blinded, or studies with very small sample sizes and wide CIs around the effect estimates.

The evidence indicates that treatment response is not associated with HLA-B27 positivity. Nonetheless, HLA-B27-positive patients may have a higher risk of radiographic progression.

Inflammation on MRI:

Two of the aforementioned studies also assessed MRI findings as a predictor of treatment response in axSpA[85, 86].

The quality of the evidence was rated as moderate to low, given that it was from high-quality open-label extension studies of randomised trials in which groups were maintained although they were no longer blinded, or studies with very small sample sizes and wide CIs around the effect estimates.

Regarding the risk-benefit balance, the evidence identified shows that clinical response is not associated with inflammation on MRI. On the other hand, patients with this finding may have a higher risk of spinal radiographic progression, as measured by mSASSS.

Equity, acceptability, and feasibility of implementation

In the GDG's judgement, the influence of predictors probably does not have an impact on equity in relation to response to treatment with these types of drugs, or on the acceptability or feasibility of the implementation of the treatment.

Outcome assessment by patients

In the GDG's judgement, it is unlikely that there is variability in how patients rate the main outcomes.

Resource use

Searches were not conducted for information on the costs of the drugs assessed, given that this topic is usually deemed to be beyond the scope of CPG recommendations; therefore, the GDG considers that it has insufficient data to make any recommendations on resource use.

Clinical question 4 (Updated)

In patients with axSpA who have an inadequate response to a first TNF inhibitor, what is the efficacy of a different TNF inhibitor or targeted therapy?

Recommendations

Recommendation 5: After an inadequate response to a first TNF inhibitor in patients with axSpA, use another TNF inhibitor, an IL-17A or IL-17A/F inhibitor or a JAK inhibitor (Strong recommendation in favour)[A].

[U] Recommendation related to an updated question

Important clinical considerations:

- Subgroups to be considered:
- *Patients ≥65 years old:* Prioritise options other than JAK inhibitors in ≥65-year-olds, patients who are active smokers (or have a history of heavy smoking), and those who have an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible dose.

Quality of the evidence

Treatment with a second TNF inhibitor or a JAK inhibitor in patients with axSpA who have an inadequate response to a first TNF inhibitor is effective in a high percentage of patients, although the experience with SEC is still limited. On the other hand, the clinical response observed is lower than that in patients receiving a first biologic[90-96] (very low quality of evidence). There is no evidence of differences in efficacy or drug survival after a switch in TNF inhibitor or therapeutic target (SEC). The efficacy decreases with successive biologics, but response to a third biologic has also been reported[90-96] (very low quality of evidence). Some data suggest a better response in patients when switching to a second TNF inhibitor due to secondary failure or toxicity of a first therapy than in patients with primary failure of a TNF inhibitor.

Drug survival was lower after successive switches to different TNF inhibitors[90, 91, 93,95], although the differences did not reach significance, possibly due to small sample sizes. Nonetheless, there do seem to be differences in drug survival in favour of patients who switch due to secondary failure or toxicity rather than primary failure[97] (very low quality of evidence). In cases of primary failure of a TNF inhibitor, consider changing the therapeutic target and using SEC.

2023 update

In patients with axSpA in whom a first TNF inhibitor has failed, whether due to loss in efficacy or adverse effects, it is beneficial to use the same therapeutic target or switch to IL-17 or JAK inhibitors[43, 44, 98-103], no significant differences being observed between TNF inhibitors, IL-17A inhibitors or JAK inhibitors in efficacy or drug rentention[98-102].

The benefit of using another TNF inhibitor when a first one has failed was confirmed in a non-systematic review of the literature[98]. This review identified predictors of drug survival, including being male and peripheral arthritis, as well as typical characteristics of patients who switched TNF inhibitor, including being female, advanced age, more active disease, greater symptom burden, enthesitis, more ankylosis and a higher erythrocyte sedimentation rate.

Some recent publications have focused on the efficacy and survival of second-line biologics. These include two retrospective cohort studies in Korean[102] and Swiss[100] populations, using an alternative TNF inhibitor vs. SEC as the next line of treatment. Both studies found no significant differences, at 1 year, in efficacy (as measured by an improvement of at least 50% in the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI 50]) or drug discontinuation between the two therapeutic targets. Similarly, another non-systematic review on the efficacy of different targets after treatment failure with a TNF inhibitor in rheumatoid arthritis, PsA and axSpA, found no significant differences between the therapeutic targets used after failure of a first TNF inhibitor, though there was a paucity of evidence[99].

SEC tends to be used in later lines of treatment than TNF inhibitors[113. 102]. JAK inhibitors (TOFA and UPA) and IL-17A/F inhibitors (BKZ) have become part of the therapeutic arsenal for axSpA. They have shown to be effective in patients with r-axSpA in whom treatment with a TNF or IL-17A inhibitor was discontinued due to inefficacy or safety concerns [51, 52, 54, 57, 58, 101, 104].

The RCTs carried out with these alternative agents include subpopulations in which efficacy is assessed after failure of TNF inhibitors [43-46, 49, 51, 52, 54, 57, 58, 103-105], and some studies have focused on later lines of treatment[98-102]. There is a notable lack of robust scientific evidence on lines of treatment after failure of TNF inhibitors; however, there is even less evidence on the efficacy of TNF inhibitors after using other therapies such as IL-17 or JAK inhibitors, or in patients with nr-axSpA. Possibly, the recommendation should have been formulated by changing the term “first TNF inhibitor” to “first advanced therapy drug (including bDMARDs and tsDMARDs)”, but when the previous ESPOGUÍA was published, there was no evidence on failure of IL-17A or JAK inhibitors and subsequent use of TNF inhibitors. Despite this, the GDG considers it reasonable

to use TNF inhibitors after an inadequate response to IL-17A inhibitors and assumes that the response of patients with nr-axSpA would not differ from that of patients with r-axSpA. To date, the accumulated clinical experience with biological therapies suggests that drugs with different therapeutic targets may be used in the most appropriate sequence for a given case, and in the event of failure or intolerance, patients may be switched to alternative drugs with different therapeutic targets.

There is no evidence regarding the efficacy of other bDMARDs (such as rituximab or abatacept [ABA]) after failure with TNF inhibitors.

Recently approved drugs, such as IXE, UPA, TOFA and BKZ, have been shown to be effective in pivotal clinical trials in patients with failure to TNF and IL-17A inhibitors [43-46, 49, 51, 52, 54, 57, 58, 103-105], but these findings still need to be confirmed in the real world.

Clinical question 5 (New)

In axSpA, can bDMARD therapy be tapered or withdrawn?

Context/Background

Axial spondyloarthritis is a chronic disease that tends to affect young working-age people. It has an impact on personal, work, and social activities, as well as causing pain, limiting functional capacity and worsening quality of life, and can lead to irreversible sequelae. The treatment of axSpA is based on a first-line treatment with NSAIDs and physical therapy, and if these fail, biological therapy (TNF, IL-17A, or IL-17A/F inhibitors) and/or tsDMARDs (JAK inhibitors) are indicated. The development of biological therapies has been a turning point in the treatment and outcomes of this disease. The results with these new treatment options have had a positive impact on disease outcomes, even achieving sustained disease remission in some cases. Nonetheless, these drugs are not free from potential adverse effects and are relatively expensive. Despite this, the risk-benefit ratio is good provided that there is active disease or risk of reactivation. On the other hand, when there is a low disease activity or the patient is in remission, it remains unclear which strategy is the most appropriate regarding the dose or duration of biological therapy. Given all this, it is logical to consider changing the treatment regimen in patients who have achieved the desired response, seeking to reduce the risk of toxicity and costs. In relation to this, the recommendations of the Spanish Society of Rheumatology, and the recent ASA-EULAR and SPARTAN updates suggest that in patients with sustained low disease activity or in remission, treatments can be tapered, while advising against withdrawing the treatment. For the development of this guideline, it was assessed whether the evidence supports the withdrawal or tapering with bDMARDs in patients with AxSpA[47, 106-112].

Recommendations

Recommendation 6: In patients with axSpA who have achieved low disease activity or sustained remission (for at least 6 months), assess the possibility of tapering bDMARD therapy, once the patient has agreed and under clinical monitoring (Strong recommendation in favour)[N].

Recommendation 7: In patients with axSpA who have achieved low disease activity or sustained remission, bDMARD therapy should not be withdrawn systematically due to the increased risk of disease reactivation (Strong recommendation in favour)[N].

[N] Recommendation related to a new question

Important clinical considerations:

- Implementation-related factors to consider when reducing the total dose administered:
  - In the case of intravenous bDMARDs (IFX being the most widely used), the dose given in the day hospital can be reduced based on the patient's weight
  - In the case of bDMARDs administered subcutaneously using a pre-filled pen or syringe, the dosing interval can be increased.

Rationale

These recommendations are based on RCTs and open-label clinical trials assessing tapering or withdrawal of biological therapy in patients with either r-axSpA or nr-axSpA. The primary endpoints used in the various trials are sustained remission or low disease activity, or alternatively, the occurrence of flares, after drug withdrawal or tapering. Currently, three therapeutic targets have been approved for axSpA in the event of treatment failure with NSAIDs (TNF, IL-17A or A/F, and JAK). Nonetheless, the evidence is mostly from studies on TNF inhibitors, with one study on one IL-17A inhibitor and none on JAK inhibitors.

Detailed rationale

Treatment interruption or withdrawal

One RCT was identified evaluating the impact of treatment withdrawal on the maintenance of sustained remission in patients with axSpA who had been in remission for more than 6 months[113]. Specifically, the study assessed treatment withdrawal in 305 patients with nr-axSpA who had achieved inactive disease (ASDAS<1.3) for at least 6 months before inclusion. Treatment withdrawal was compared to continuation of ADA at the standard dose of 40 mg every 14 days at 10 months of follow-up.

Three more RCTs were identified investigating the impact of treatment withdrawal on the maintenance of sustained remission in patients with axSpA who had been in remission for less than 6 months.

The first trial included 313 patients with axSpA with a disease duration of less than 5 years, who achieved sustained remission during the induction period (ASDAS<1.3 at months 4 and 7)[114]. The study compared treatment withdrawal to continuation of CZP at the standard dosing interval with a follow-up of 12 months.

The second study included 155 patients with axSpA who achieved sustained remission during the lead-in period (ASDAS<1.3 at month 4 or 5 and ASDAS<2.1 at both visits)[115]. The study

compared withdrawal to continuation of IXE at the standard dosing interval with a follow-up of 10 months.

The third study included 188 patients with nr-axSpA with a disease duration of less than 5 years and inactive disease (ASDAS<1.3) at 7 and 10 months after treatment initiation[116]. Treatment withdrawal was compared to continuation of GOL at the standard dosing interval with a follow-up of 12 months.

The overall quality of the evidence was rated as moderate: in some cases, it was downgraded because the randomisation sequence generation was unclear or the sample size was small, while in others, the magnitude of the effect observed was sufficiently high to upgrade the quality.

The RCTs found that patients in whom treatment was withdrawn had more disease flares during the follow-up, or were significantly more likely to lose their low disease activity or remission status than patients in whom treatment was continued at the dose specified in the summary of product characteristics (SmPC). These results were observed in both radiographic and non-radiographic forms of the disease, and with both TNF and IL-17A inhibitors, regardless of how long patients had been in a state of remission or low disease activity.

The different RCTs included patients with r-axSpA and nr-axSpA who had been in remission or had low disease activity for a variable period. The treatment was continued as per the SmPC in one arm, while in the other, treatment was withdrawn. Patients were followed-up for a variable time of between 10 and 12 months and it was assessed whether they remained in remission or a state of low disease activity. Most of the trials considered TNF inhibitors, only one focusing on IXE (an IL-17A inhibitor). There is no evidence for IL-17A/F or JAK inhibitors. The time for which patients were required to remain in remission or with low disease activity also varied.

Regarding the risk-benefit balance, the evidence identified shows that bDMARD withdrawal may jeopardise the maintenance of flare-free remission and inactive disease in patients with axSpA, regardless of how long they have been in remission or had low disease activity. These patients would also have a higher risk of flares.

Based on the evidence, the group's experience, and the recommendations of scientific societies such as the SER[106], ASAS-EULAR[47] and SPARTAN[107], the GDG recommends against systematic treatment withdrawal in patients with axSpA on biological therapy, due to an increase in flares and recurrence of disease activity.

Tapering

Three RCTs were identified assessing the effect of increasing the dosing interval on the maintenance of remission in patients with axSpA who had been in sustained remission for at least 6 months.

The first study included 120 patients with axSpA with no evidence of active disease (BASDAI score < 2) for at least 6 months before study inclusion[117]. Increasing the dosing interval of TNF inhibitors was compared to using the standard dosing interval at 12 months of follow-up.

The second study included 58 patients with axSpA with low disease activity (ASDAS < 2.1) for at least 6 months before inclusion[118]. It compared a progressive increase in dosing interval and subsequent withdrawal of TNF inhibitors to standard dosing at 12 months of follow-up.

The third study included 40 patients with axSpA with low disease activity (ASDAS < 2.1) for at least 6 months before inclusion[119]. It compared increasing the dosing interval to standard dosing of ETN at 6 months.

Two of the studies cited above (in relation to treatment withdrawal) also assessed increasing the dosing interval in patients with axSpA who had sustained remission for at least 6 months[114, 116].

Finally, an RCT was identified assessing remission in 43 patients with axSpA in remission (defined as BASDAI<4 with normal CRP levels) at inclusion, without specifying the duration of the remission[120]. Increasing the dosing interval was compared to continuation of ETN at the standard dosing interval at 24 months.

The overall quality of the evidence was rated as low in the studies that considered patients with sustained remission for more than 6 months, due to an unclear risk of selective reporting bias and the small sample sizes and subsequent lack of statistical power in some cases. For the studies considering sustained remission for less than 6 months, the quality of the evidence was rated as moderate for most of the outcome variables; but low in some cases, because the randomisation process was unclear and the sample size was small. For the studies that presented data on remission at inclusion, the quality of the evidence was rated as low due to a lack of information on the randomisation process and an unclear risk of bias regarding outcome measures and selective reporting of results, as well as the small sample size with the resulting lack of statistical power.

The evidence shows that the strategy of increasing dosing intervals allows patients to remain with the same level of disease activity as before the intervention, without significant differences compared to those in the treatment arm on doses as per the SmPC. The effect is observed in

radiographic and non-radiographic forms of the disease. The time patients were required to be in remission or have low disease activity varies between studies: although most use a cut-off of 6 months, some authors set a minimum of 12 weeks[108], and Yates et al. [109] did not take into account disease activity before starting to taper and it should be highlighted that they did not demonstrate non-inferiority of dose reduction, that is, a tapered dose was not as effective as the standard dose. The authors that applied a criterion of 6 months in remission or with low disease activity did so arbitrarily, though it is true that this cut-off was selected by most studies, and is supported by the recommendations of several scientific societies.

In the opinion of the GDG, regarding the hypothesis that increasing the dosing interval in bDMARD therapy is not worse than this therapy with dosing as per the SmPC for maintaining remission or low disease activity in patients with axSpA, it is difficult to draw a general conclusion across the studies. The dosing intervals, time in remission or with low disease activity before tapering, length of follow-up and disease score used to assess disease activity (BASDAI, ASDAS) differed between the studies. All the studies focused on TNF inhibitors; none considering IL-17 or JAK inhibitors. In general, the preferred strategy is to increase the dosing interval rather than reduce the dose. This is probably related to technical issues concerning these drugs. One of the drugs has an intravenous route of administration and the dose is prepared by the hospital pharmacy (adjusting for body weight) but all the others are administered using a prefilled syringe or pen, with no manipulation of the drug or the device.

Regarding the risk-benefit balance, the evidence identified shows that increasing the dosing interval of a DMARD in patients with axSpA with sustained remission or low disease activity is comparable to standard dosing, with no significant differences between these treatment strategies.

Other considerations: It should be noted that response to resuming the standard dose of the biological therapy, as per the SmPC, in the event of a flare was set as a secondary objective in some of the trials assessed[112-114, 116]. They showed that most, but not all, patients respond to resuming the standard dose.

The SPARTAN group[107] suggests the following are negative predictors of successful tapering: being female, HLA-B27 negativity, high physician global assessment score and elevated CRP.

Finally, it is interesting to assess the safety considerations related to drug tapering. Vinson et al. published a meta-analysis including 13 studies (9 on rheumatoid arthritis and 4 on axSpA) that assessed tapering of bDMARDs and safety measured in terms of serious infections,

malignancies and cardiovascular events[110]. They conclude that, though there is a paucity of evidence, it has so far been observed that the rate of serious infections decreases with dose tapering, while differences in malignancies, cardiovascular events and death do not reach significance.

Dose tapering can be performed in two different ways. The first strategy involves reducing the dose (the amount of drug given at one time); this would be used in the case of IFX, as it is administered at hospital and is adjusted for body weight. The second strategy is to reduce the dosing frequency (that is, increase the dosing interval) and this would also apply to drugs administered using a prefilled syringe or pen.

In brief, only one bDMARD (IFX) is administered intravenously and doses are prepared in the hospital pharmacy department (adjusting for patient weight), while all the other drugs are administered using a prefilled syringe or pen, with no manipulation of the drug or the device. Given that both strategies reduce the total dosage used, the term tapering is used interchangeably, regardless of the strategy employed to achieve it.

Based on the group's experience and evidence reviewed, the GDG considers that tapering of biological therapies may be considered in axSpA patients in remission or with low disease activity for a certain time, arbitrarily setting the criterion at 6 months. The decision should be made jointly with the patient and regular follow-up should be continued.

Equity

In the GDG's judgement, there is no significant inequity regarding treatment tapering.

Acceptability

To date, no studies have been found on patient satisfaction with these different strategies. Some trials included quality of life as a secondary objective but found no significant differences between treatment arms[111, 114, 118].

On the other hand, the relevant scientific societies recommend involving patients in decision-making to ensure that decisions are made jointly by agreement[47, 106, 107].

Patient assessment of outcomes

In the GDG's judgement, it is unlikely that there are differences in how patients assess the main outcomes

Monitoring and assessment

Clinical monitoring and check-ups when starting to taper a biologic should be similar to those performed in usual practice, that is, clinical assessment and tests every 12-16 weeks.

Research priorities

Studies with longer follow-up periods are required to be able to assess other variables, such as the progression of structural damage and the safety of tapering strategies in the long term.

Further, more studies are needed on reducing doses and increasing dosing intervals focusing on different treatment targets.

Additionally, further research is warranted to find biomarkers that could help identify individuals who would be good candidates for strategies involving treatment tapering or withdrawal among patients with axSpA who are in sustained remission.

Clinical question 6 (New)

In axSpA, what is the efficacy of bDMARDs and tsDMARDs in treating extra-musculoskeletal manifestations (uveitis, psoriasis and IBD)?

Context/Background

Axial spondyloarthritis is a chronic inflammatory musculoskeletal disease mainly involving the axial and peripheral skeleton (arthritis, enthesitis and dactylitis) but which also has extra-musculoskeletal manifestations; the latter include acute anterior uveitis, IBD and psoriasis.

The presentation of axSpA can influence the disease prognosis and guide the use of specific bDMARDs. Uveitis is the most common extra-musculoskeletal manifestation in spondyloarthritis; in most cases, it is treated locally, but its intensity and severity sometimes warrant treatment with csDMARDs and/or bDMARDs. Regarding IBD, its potential seriousness requires an intensive workup by a gastroenterologist, and new drugs are available for this condition. With respect to psoriasis, there is a large therapeutic arsenal and many of the drugs are the same as those used for axSpA.

Recommendations

Recommendation 8: In patients with axSpA and uveitis, use monoclonal TNF inhibitors and CZP for preventing anterior uveitis episodes (Strong recommendation in favour)[N].

> ***Recommendation 8.1:*** TNF inhibitors, especially ADA, are also recommended for treating refractory or recurrent anterior uveitis when conventional therapies have failed (Good clinical practice recommendation)[N].
>
> ***Recommendation 8.2:*** In axSpA, do not use ETN for the prevention or treatment of anterior uveitis (Good clinical practice recommendation)[N].

Recommendation 9: In axSpA, the GDG considers that there is no evidence for recommending the use of IL-17 or JAK inhibitors for the prevention or treatment of anterior uveitis. (Good clinical practice recommendation)[N].

Recommendation 10: In patients with axSpA and active IBD, use monoclonal TNF inhibitors* or JAK inhibitors** for the management of IBD (Strong recommendation in favour)[N].

*Approved: IFX and ADA for ulcerative colitis and Crohn's disease; GOL only for ulcerative colitis.

**Approved: UPA for ulcerative colitis and Crohn's disease; TOFA only for ulcerative colitis.

Recommendation 11: In patients with axSpA and IBD, do not use IL-17 inhibitors (Strong recommendation against)[N].

Recommendation 12: Given the lower incidence of psoriasis in axSpA, there is less evidence of the efficacy of the different treatments for psoriasis in this context; therefore, the GDG suggests following the recommendations for PsA (Good clinical practice recommendation)[N].

[N] Recommendation related to a new question

Important clinical considerations:

- Subgroups to be considered:
  - *Patients ≥65 years old:* Prioritise options other than JAK inhibitors in ≥65-year-olds, patients who are active smokers (or have a history of heavy smoking), and those who have an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible dose, especially in patients with IBD, a condition in which the doses given are higher than those used in axSpA
- Implementation-related factors to consider:
  - The majority of bDMARDs indicated for treating axSpA (TNF and IL-17 inhibitors) are also indicated for treating moderate-to-severe psoriasis. In the case of JAK inhibitors (UPA and TOFA), no indication in plaque psoriasis is mentioned in their SmPC, and therefore, their use in patients with axSpA and moderate-to-severe plaque psoriasis should be assessed jointly with dermatologists.

Rationale

These recommendations have been made based on the results of double-blind RCTs of IL-17, IL-23, JAK inhibitors and apremilast in which the variables studied were primary or secondary endpoints. After a review of the literature, it was concluded that in terms of efficacy/effectiveness of bDMARDs and tsDMARDs in the treatment of extra-musculoskeletal manifestations of axSpA, monoclonal TNF inhibitors are preferred for the management of uveitis and IBD (ADA and IFX being indicated for Crohn´s disease and ulcerative colitis, and GOL only for colitis), and for psoriasis, either TNF or IL-17 inhibitors may be used, although the latter are more effective. Regarding JAK inhibitors, they seem to have a similar performance to TNF inhibitors in IBD and the results are modest compared to TNF and IL-17 inhibitors in psoriasis, while to date they have no proven efficacy in uveitis.

Detailed rationale

UVEITIS

BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Monoclonal TNF inhibitors vs placebo

One SR was identified assessing the effect of several monoclonal TNF inhibitors on the onset of anterior uveitis in patients with axSpA[121]. The objective was to assess the incidence of anterior uveitis in patients with r-axSpA or nr-axSpA treated with monoclonal TNF inhibitors (IFX, ADA, GOL or CZP) compared to placebo. The review included 17 studies on patients with axSpA treated with TNF inhibitors (n=2101 patients received monoclonal TNF inhibitors; 2497 received placebo). In relation to treatment duration, the mean and median length of follow-up was 22.7 weeks (SD 18.5) and 16 weeks (range: 6-104) respectively.

The evidence identified shows that the incidence of anterior uveitis was significantly lower in patients treated with monoclonal TNF inhibitors than those given placebo.

Etanercept

The aforementioned SR also assessed the effect of ETN on the incidence of anterior uveitis compared to placebo, based on ten studies (n=3196)[121].

The relation between treatment with this drug and the incidence of anterior uveitis in patients with axSpA is a matter of debate in the medical literature. Some studies suggest that the use of ETN may be associated with a higher incidence, while other studies have found no clear association.

The evidence identified shows negligible differences in the incidence of anterior uveitis using ETN compared to placebo, although the impression from clinical practice is that the use of ETN is not associated with improvements in uveitis compared to monoclonal TNF inhibitors. Likely, ETN does not trigger anterior uveitis flares, and what may be occurring is that it does not help prevent new episodes.

The overall quality of the evidence was rated as moderate due to heterogeneity in the studies included and their methodology or the risk of bias from having missed relevant studies.

Regarding the risk-benefit balance, the evidence identified shows the safety and utility of TNF inhibitors in the management of uveitis. Special mention should made of ETN, which has yielded mixed results. This drug does not seem to be as effective as monoclonal TNF inhibitors:

specifically, it is not associated with a higher rate of uveitis flares than placebo, but does not prevent episodes as effectively as monoclonal TNF inhibitors.

Other considerations

The latest ASAS-EULAR recommendations for the management of patients with axSpA conclude that when there is a history of recurrent uveitis, preference should be given to anti-TNF monoclonal antibodies[47].

Based on the group's experience and the aforementioned data, the GDG considers that TNF inhibitors may be used for preventing anterior uveitis flares in patients with axSpA, with a preference for monoclonal TNF inhibitors and CZP in particular. In line with this, the group considers that ETN should not be recommended for preventing or treating anterior uveitis flares. Additionally, TNF inhibitors, especially ADA, may also be used for treating refractory or recurrent anterior uveitis when conventional therapies have failed.

Regarding the treatment of other forms of non-infectious non-anterior uveitis, with a risk of visual impairment in patients with axSpA, the SER Research Unit has recently drafted recommendations for treating non-anterior non-infectious non-neoplastic uveitis not associated with demyelinating diseases[122].

Its conclusions in this regard are:

> In cases of non-anterior non-infectious non-neoplastic refractory uveitis not associated with demyelinating diseases, "systemic corticosteroids are recommended to control acute inflammation, notably when there is a risk of vision loss and in cases of bilateral involvement" (Strong recommendation, in favour).
>
> In moderate or severe cases of this type of uveitis with a chronic course, "the use of conventional synthetic immunomodulators is recommended for long-term control of inflammation and/or as a corticosteroid-sparing agent" (Strong recommendation, in favour).
>
> In serious or refractory cases of this condition, "the use of anti-TNF-α monoclonal antibodies is recommended, especially adalimumab" (Strong recommendation in favour).

For further information, consult extracts of this report in Appendix 3 and the full report on the SER website.

Interleukin-17 inhibitors

IL-17 inhibitors vs. placebo

A systematic review, cited above, also considered the effect of IL-17 inhibitors (SEC and IXE) on uveitis in patients with axSpA[121]. It assessed the effect of these drugs on the incidence of anterior uveitis, based on eight studies (n=4241).

Brodalumab (IL-17 receptor A) vs. placebo

A multicentre study was identified that was conducted at 48 sites across 3 countries. It assessed the efficacy and safety of brodalumab (BRD, 210 mg sc) (at weeks 0, 1, and 2, and then every other week) compared to placebo for 16 weeks in patients with active r- or nr-axSpA (n=159)[123], recording the number of patients who developed uveitis.

Bimekizumab (IL-17A/F) vs. placebo

The review identified one multicentre study conducted at 83 sites across 14 countries. It assessed the efficacy and safety of BKZ (160 mg sc), compared to placebo over 24 weeks in patients with active r- or nr-axSpA (n=586) [52], recording the number of patients who developed uveitis.

The evidence identified shows that the incidence of anterior uveitis flares does not increase with the use of IL-17A inhibitors (SEC and IXE) compared to placebo, although these drugs have not been found more effective than monoclonal TNF inhibitors in clinical practice.

The evidence found does not indicate that more patients with axSpA develop uveitis among groups treated with BRD or BKZ than among those receiving placebo. BRD has not yet been approved in Spain. Regarding BKZ, which has recently been approved for axSpA, there are indirect data based on *post hoc* analysis of trials in axSpA suggesting that it may reduce the rate of anterior uveitis flares. Nonetheless, further research is needed to confirm this protective effect.

In studies assessing TNF and IL-17A inhibitors in axSpA, incident uveitis is a rare event. Nonetheless, evidence indicates that monoclonal TNF inhibitors are associated with a lower incidence of uveitis than IL-17A inhibitors or placebo.

The overall quality of the evidence was rated as moderate in the case of the SR, given the heterogeneity in the studies included and their methodology as well as the indirectness of the evidence, in that they included patients with r- and/or nr-axSpA and/or peripheral (rather than

axial) spondyloarthritis. In the case of the RCTs, the quality was rated as low due to a risk of bias because the outcome variables of interest were not the primary objectives of the studies, rather the relevant data were recorded to assess potential adverse events, the small sample sizes or the study duration being short for detecting adverse events.

Regarding the risk-benefit balance, the evidence identified shows that IL-17 inhibitor therapy gives mixed results regarding the occurrence of uveitis and although the differences compared to placebo are negligible, the overall and real-world data indicate that monoclonal TNF inhibitors have higher levels of efficacy and safety in the treatment of uveitis. Data from pivotal studies on BKZ and BRD point to similar rates of anterior uveitis flares to those observed with placebo.

Based on the group's experience and the aforementioned data, the GDG considers that IL-17 inhibitors cannot currently be recommended for the management of uveitis.

Targeted synthetic disease-modifying antirheumatic drugs

JAK inhibitors

Upadacitinib vs. placebo

Two multicentre parallel-group trials were identified assessing the efficacy and safety of UPA (15 mg once daily) compared to placebo in patients with axSpA, including patients with no or an inadequate response to bDMARDs. These were the SELECT-AXIS 2[57, 58] trials (the first carried out at 114 sites across 83 countries, n=313; and the second at 119 sites across 22 countries, n=421). These trials reported cases of uveitis up to 14 weeks or 30 days after the last dose of the study drug.

Additional considerations: A recent study has provided data after 52 weeks of follow-up[124].

Tofacitinib vs. placebo

A multicentre study was identified assessing the efficacy and safety of TOFA (5 mg, twice daily) compared to placebo for 16 weeks (n=269)[54]. Any cases of uveitis were recorded.

The overall quality of the evidence was rated as low due to a risk of bias, given that the outcome variables of interest were not the primary objectives of the studies, rather the relevant data were recorded to assess potential adverse events, the small sample sizes or the study period being short for detecting adverse events.

Regarding the risk-benefit balance, the evidence identified shows that JAK inhibitor therapy offers some subtle benefits over other drugs for the management of uveitis.

Concerning UPA, indirect data from *post hoc* analysis of trials in axSpA suggest that it may reduce the rate of anterior uveitis flares, but further studies are required to confirm this protective effect.

Based on the group's experience and the aforementioned data, the GDG considers that JAK inhibitors cannot currently be recommended for the management of uveitis.

INFLAMMATORY BOWEL DISEASE

BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

TNF inhibitors vs placebo

One SR was identified assessing the effect of TNF inhibitors in IBD in patients with axSpA[125]. Its objective was to compare new onset and flares of IBD, in patients with spondyloarthritis treated with TNF inhibitors (IFX, ETN, ADA, CZP or GOL) compared to placebo. These IBD events were analysed independently in psoriasis, PsA and SpA. The SR included 28 studies of patients with axSpA treated with TNF inhibitors (n=2559 treated patients and n=1697 controls). The median duration of treatment was 16 weeks.

Etanercept

Etanercept vs. placebo

One SR was identified assessing the effect of ETN on reducing IBD recurrence compared to placebo[126]. Its objective was to determine, in ≥17-year-olds with r-axSpA or nr-axSpA, whether the risk of IBD varied between patients receiving biological therapy and those receiving other therapies. The TNF inhibitors analysed were ETN, IFX, ADA, CZP and GOL. The review included 22 RCTs with control groups that received placebo or other bDMARDs (n=3845 patients exposed to bDMARDs with a follow-up of 1240.7 patient-years compared to n=1895 patients exposed to placebo with a follow-up of 582.6 patient-years). The duration of the treatment ranged from 6 to 28 weeks. Studies in which it was uncertain whether cases recorded were new-onset IBD or flares of existing IBD were excluded from the primary analysis. Eight studies (n=2751) were included for the comparison of ETN vs placebo.

Etanercept vs. monoclonal TNF inhibitors

One of the aforementioned SRs also compared ETN with monoclonal TNF inhibitors in terms of reduction in IBD recurrence, based on seven studies (n=1961)[121].

Based on the data from the review, and the group's experience in clinical practice, the GDG considers that there is negligible additional risk of IBD recurrence with bDMARDs compared to placebo. Indeed, TNF inhibitors are widely used by gastroenterologists for the management of IBD.

The evidence confirms that the differences between TNF inhibitors and placebo are negligible in terms of the development of new-onset IBD or flares in patients already diagnosed with this disease, and this is in line with routine clinical practice.

Regarding ETN, the results suggest a higher incidence of IBD recurrence with ETN than with placebo.

The RCTs and their extensions suggest a small absolute -but non-significant- increase in recurrence with ETN compared to other monoclonal TNF inhibitors.

The impression from clinical practice is that the use of ETN does not trigger new-onset IBD or flares of existing disease, but it does not act on the inflammatory process at the gut level, while the use of other drugs (monoclonal TNF inhibitors) is associated with a lower incidence of IBD.

The quality of the evidence was rated as moderate due to either the heterogeneity in the studies included and their methodology or the indirectness of the evidence, in that they included patients with r- and/or nr-axSpA and/or peripheral spondyloarthritis.

Regarding the risk-benefit balance, the evidence identified shows the safety and utility of TNF inhibitors in the management of IBD. Special mention should made of ETN, which has yielded mixed results. This drug does not seem to be as effective as monoclonal TNF inhibitors: specifically, it is not associated with a higher rate of IBD flares than placebo, but does not prevent episodes as effectively as monoclonal TNF inhibitors.

<u>Other considerations</u>

The latest ASAS-EULAR recommendations for the management of axSpA in patients with IBD point to the efficacy of monoclonal TNF inhibitors and a lack of efficacy of ETN[47]. Nonetheless, according to the British Society for Rheumatology Biologics Register for Ankylosing Spondylitis (BSRBR-AS), it does not seem that the excess incidence of IBD is associated with exposure to ETN compared to monoclonal TNF inhibitors.

Based on the group's experience and the aforementioned data, the GDG considers that monoclonal TNF inhibitors can be recommended for the management of IBD. It should be taken

into account that in the case of concomitant IBD, IFX and ADA are indicated for ulcerative colitis and Crohn's disease, while GOL is only approved for colitis.

Interleukin-17 inhibitors

IL-17A inhibitors vs. placebo

One of the aforementioned SRs also evaluated the effect of IL-17 inhibitors, SEC and IXE compared to placebo, in relation to the risk of IBD recurrence, based on seven studies (n=1762) [125].

IL-17A inhibitors vs. monoclonal TNF inhibitors

Another of the aforementioned SRs also evaluated the effects of IL-17A inhibitors compared to monoclonal TNF inhibitors in terms of reduction in IBD recurrence rate, based on seven studies (n=2989)[126].

Brodalumab (anti-IL-17 receptor A) vs. placebo

A previously cited RCT recorded the number of patients who developed IBD (ulcerative colitis or Crohn's disease) among a sample with active r- or nr-axSpA treated with sc BRD (210 mg at weeks 0, 1, and 2 and then every other week) compared to placebo for 16 weeks (n=159)[123].

Bimekizumab (IL-17A/F) vs. placebo

Another aforementioned study recorded the number of patients who developed ulcerative colitis or Crohn's disease among a sample with active r- or nr-axSpA treated with sc BKZ (160 mg) compared to placebo over 24 months (n=586)[52].

Regarding IL-17A inhibitors, the evidence identified shows that the IBD-related events are rare, with rates similar to those in the placebo groups. No statistically significant differences were found in the risk of new or recurrent IBD between IL-17 inhibitor and control treatments, probably due to the fact that, in general, there were few IBD-related events. Nonetheless, the GDG is aware that, in clinical practice data and as stated in the SmPC, the use of IL-17 inhibitors has been associated with the development of IBD events (with reports of new cases or exacerbations of IBD in patients known to have the disease), and hence, recommends against using this type of DMARD in patients with known IBD.

Regarding the use of BRD and BKZ in active axSpA, the evidence found does not indicate that more patients with axSpA develop IBD (ulcerative colitis or Crohn's disease) among groups receiving these therapies than among those receiving placebo. Given that BRD has not yet been

approved in Spain, and that BKZ has only been recently approved for axSpA, clinical practice has yet to provide substantial data on IBD.

Although the evidence shows a negligible effect size, for the difference in development of IBD with treatment with IL-17A versus monoclonal TNF inhibitors (other than ETN), in clinical practice, monoclonal TNF inhibitors have shown to be superior in terms of efficacy, these being widely used for the management of both axSpA and IBD.

The overall quality of the evidence was rated as moderate in the case of the SR due to heterogeneity in the studies included and their methodology and also the indirectness of the evidence, in that they included patients with r- and/or nr-axSpA and/or peripheral spondyloarthritis. In the case of the RCTs, the quality was rated as low due to a risk of bias because the outcome variables of interest were not the primary objectives of the studies, rather the relevant data were recorded to assess potential adverse events, the small sample sizes or the study duration being short for detecting adverse events.

Regarding the risk-benefit balance, the evidence identified shows that results with IL-17 inhibitor therapy are mixed in terms of the development of IBD and although the differences compared to placebo are negligible, overall and real-world data indicate greater efficacy and safety of monoclonal TNF inhibitors in IBD. Data from pivotal studies on BKZ and BRD show similar rates of development of IBD with these drugs and placebo.

Other considerations

Recent ASAS-EULAR recommendations for the management of axSpA conclude that in patients with a history of active IBD, preference should be given to the use of anti-TNF monoclonal antibodies (IFX and ADA, indicated for Crohn's disease and ulcerative colitis, and GOL only for colitis)[47].

Based on the group´s experience and the aforementioned data, the GDG considers that IL-17 inhibitors are not indicated and therefore cannot currently be recommended for the management of IBD.

Targeted synthetic disease-modifying antirheumatic drugs

JAK inhibitors

Upadacitinib vs. placebo

Two aforementioned studies recorded the number of patients who presented with IBD among a sample treated with UPA (15 mg once daily) compared to placebo at 14 weeks and 30 days after the last dose[57, 58].

Tofacitinib vs. placebo

Another study mentioned above recorded the number of patients who developed IBD among a sample treated with oral TOFA (5 mg twice daily) compared to placebo over 16 weeks (n=269) [54].

Regarding UPA, the differences compared to placebo are negligible in terms of the development of IBD. These data are important and in line with clinical experience, real-world data and clinical trials, in which UPA has shown to be effective for IBD (approved in the SmPC for ulcerative colitis and Crohn´s disease).

As with UPA, negligible differences were observed in rates of IBD between TOFA therapy and placebo. These data are valuable and in line with data from the real world and clinical trials, in which it has shown to be effective for IBD (approved in the SmPC for ulcerative colitis).

The overall quality of the evidence was rated as low due to a risk of bias, given that the outcome variables of interest were not the primary objectives of the studies, rather the relevant data were recorded to assess potential adverse events, the small sample sizes or the study period being short for detecting adverse events.

Regarding the risk-benefit balance, the evidence identified shows that JAK inhibitors are safe in axSpA, particularly UPA and TOFA in relation to the development of IBD, both these drugs being approved for various indications (UPA for ulcerative colitis and Crohn's disease and TOFA for ulcerative colitis).

Based on the group´s experience and the aforementioned data, the GDG considers that JAK inhibitors can be recommended for the management of IBD.

PSORIASIS

Targeted synthetic disease-modifying antirheumatic drugs

JAK inhibitors

Upadacitinib vs. placebo

Two of the aforementioned studies recorded the number of patients who developed psoriasis among a group of patients treated with UPA (15 gm, once daily) compared to placebo at 14 weeks and 30 days after the last dose[58, 77].

Tofacitinib vs. placebo

Another study also recorded the number of patients who developed psoriasis among a group of patients treated with oral TOFA (5 mg twice daily) compared to placebo over 16 weeks (n=269)[54].

Regarding UPA and TOFA, the differences compared to placebo were negligible in terms of the development of psoriasis. These data are important and in line with clinical experience, real-world data and clinical trials, in which these drugs have shown to be effective for psoriasis (though there are fewer data than for bDMARDs, and they are not currently indicated in the SmPC).

The overall quality of the evidence was rated as low due to a risk of bias, given that the outcome variables of interest were not the primary objectives of the studies, rather the relevant data were recorded to assess potential adverse events, the small sample sizes or the study period being short for detecting adverse events.

Regarding the risk-benefit balance, the evidence identified shows that JAK inhibitors, particularly UPA and TOFA, are safe in axSpA concerning the development of psoriasis.
Based on the group´s experience and the aforementioned data, the GDG considers that JAK inhibitors can be considered in patients with axSpA and concomitant psoriasis, although decisions should be made jointly with dermatologists, especially in patients with moderate-to-severe psoriasis, given that JAK inhibitors are not formally indicated for psoriasis, as per the SmPC.

Equity, acceptance and feasibility of implementation

The GDG considers that, in our setting, there are no marked inequities in access to these bDMARDs.
The group also considers it likely that all those involved in the use of these drugs (health authorities, specialists, and patients) will find their use in clinical practice acceptable, given the

good efficacy of all these drugs, and their low adverse effect rates, as well as the experience accumulated over the years in the use of advanced therapies.

On the other hand, antirheumatic therapies, including tsDMARDs and bDMARDs, are commonly used in our setting. The experience accumulated over the years by rheumatologists facilitates the introduction and use of drugs for new therapeutic targets.

Outcome assessment by patients

In the GDG's judgement, it is unlikely that there is variability in how patients rate the main outcomes.

Resource use

Searches were not conducted for information on the costs of the drugs assessed, given that this topic is usually deemed to be beyond the scope of CPG recommendations; therefore, the GDG considers that it has insufficient data to make any recommendations on resource use.

Clinical question 7 (Updated)

In axSpA, what type of exercise programme is most effective in improving clinical and functional outcomes?

Recommendations

Recommendation 13: In adult patients with axSpA, exercise programmes should be used to improve symptoms, quality of life and health-related physical fitness as part of the treatment of the disease (Weak recommendation in favour)[A].

Recommendation 14: The programmes should include aerobic exercises and be performed in a group under the supervision of a physiotherapist* (Weak recommendation in favour)[A]

[U] Recommendation related to an updated question

*Appendix 5 provides more detailed information to guide patients concerning this type of exercise.

Exercise and education are considered the cornerstone of non-pharmacological treatment for patients with axSpA[127, 128]. There are no high-quality studies on the role of exercise in patients with few mobility and other functional limitations, but to ensure that it is safe and effective, it seems reasonable to apply the *American College of Sports Medicine*'s guidelines on exercise and physical activity in patients with chronic conditions[129]. Most studies on exercise programmes specifically exclude patients at the ankylosing stage and focus on those at intermediate-to-advanced stages of the disease. In these patients, who are moderately affected by the disease, a wide range of exercise programmes have been used, with an emphasis on traditional stretching exercises that is unwarranted given insufficient data to demonstrate the superiority of one type of exercise over another[130].

Quality of the evidence

One SR in adults with axSpA assessed the effects of exercise on various domains of the disease (pain, stiffness, quality of life, physical function, disease activity, and health-related physical fitness) and cardiovascular risk factors[131]. It included patients with moderate-to-advanced disease and at least one of the study groups received an exercise intervention. The exercise programmes differed in duration, frequency, type, place where the exercise was performed, and level of supervision. The general conclusion was that exercise therapy in patients with spondyloarthritis is more beneficial than no intervention and exercise should be performed regularly. The specific results were as follows:

- There is moderate evidence supporting the use of exercise-based interventions to improve physical function (Bath Ankylosing Spondylitis Functional Index [BASFI]), disease activity (BASDAI) and chest expansion compared to controls.

- There is weak evidence of a positive effect of the interventions on pain, stiffness, axial mobility and cardiorespiratory function.

- Adding aerobic training to flexibility exercises does not reduce cardiovascular risk but does improve cardiorespiratory outcomes.

- Supervised group exercise has a greater effect than home-based exercise in terms of quality of life, but not other outcomes.

It remains unclear which exercise protocol is best for improving clinical and functional outcomes in axSpA.

This review also compared exercise programmes with other treatment modalities (inpatient rehabilitation, balneotherapy, respiratory kinesiotherapy using incentive spirometry, spa-exercise therapy, etc.) No significant improvement was observed in measures of disease activity or functional capacity[131] (low-to-moderate quality of evidence).

An SR of patients with ankylosing spondylitis who were clinically stable on bDMARDs analysed the potential synergic role between exercise therapy and these drugs. In 10 out of the 15 studies included, the rehabilitation protocol with exercises was associated with significant improvements in functional capacity (BASFI) and axial mobility (BASMI); 6 studies found significant improvements in quality of life (36-Item Short Form Survey [SF-36], Health Assessment Questionnaire [HAQ] and Ankylosing Spondylitis Quality of Life Questionnaire [ASQoL]), and 9 reported significant decreases in the BASDAI score. Positive effects were also observed on psychological well-being and fatigue, factors that also help to improve quality of life. One of the studies showed that certain types of exercise such as Pilates were associated with significant improvements in BASDAI, BASFI and BASMI scores. The authors concluded that the positive effect of TNF inhibitor therapy does not mean that patients should stop participating in exercise programmes, given their synergic effect[132] (low-to-moderate quality of evidence).

2023 update

A meta-analysis assessing the efficacy of different types of exercise programmes in ankylosing spondylitis found that such programmes have a moderate effect on disease activity, function and mobility, regardless of the type of exercise[133]. They concluded that exercise programmes

combining flexibility and muscle strength training can have a great effect, especially on mobility. The programmes that included aerobic exercise showed significant efficacy in improving function. Another meta-analysis, along similar lines, also supports the potential of exercise programmes for these outcomes[134]. Additionally, an SR showed the efficacy of exercise interventions in managing pain, function and disease activity in patients with ankylosing spondylitis[55].

A meta-analysis assessed the effect of exercise training programmes with aerobic components on CRP, erythrocyte sedimentation rate, and self-reported disease activity, compared to non-aerobic rehabilitation[135]. The exercise training programmes reduced the levels of acute phase reactants and improved self-reported disease activity, though the study did not clarify the mechanisms by which these benefits are achieved. A similar SR found that aerobic exercise did not have beneficial effects on disease activity, physical function or biological parameters compared to control conditions in patients with ankylosing spondylitis[136].

Another SR that compared exercise programmes with an inactive control (no intervention, waiting list) or usual care concluded that such programmes may reduce pain, and probably slightly improve function and slightly reduce the patient global assessment of disease activity, compared to no intervention[137].

An SR that assessed the role of global postural re-education (GPR) in ankylosing spondylitis indicated that it is beneficial, but not more so than other conventional treatments, except in its effect on spinal mobility, where GPR was found to be superior[138].

Other studies have evaluated the efficacy of exercise supervised by a physiotherapist compared to home-based exercise in ankylosing spondylitis. Both programmes had a positive effect, regardless of disease activity and physical function[55]. Although both may be effective for reducing BASMI, BASDAI, BASFI and depression scores in patients with ankylosing spondylitis, supervised programmes may be more effective for reducing disease activity[139]. Further, supervised physiotherapy was more effective than usual care in improving disease activity, functional capacity and pain in patients with this disease[140].

A meta-analysis evaluated the efficacy of water therapy in improving disease activity (BASDAI), functional capacity (BASFI), spinal mobility (BASMI) and pain (visual analogue scale) in patients with ankylosing spondylitis, and observed a beneficial effect[141].

Another meta-analysis compared the outcomes of two strategies for treating ankylosing spondylitis, namely, training with specific exercises (intervention group) versus physical therapy

(control group). It was concluded that Pilates, GPR, aerobic and aquatic exercise may help to reduce impairment and activity limitations[142].

Finally, another SR assessed the effect of specific exercises on pulmonary function, and aerobic and functional capacity in patients with ankylosing spondylitis[143], and found positive results.

Although the course of the disease can be highly variable, exercise programmes have shown efficacy in improving numerous clinical and functional outcomes at intermediate-to-advanced stages of ankylosing spondylitis. Nonetheless, there is a paucity of evidence in patients at early stages of the disease (a short time after the onset of signs and symptoms) or at the ankylosing stage. A prospective study with ankylosing spondylitis patients followed up over 4.5 years suggests that at early stages, the ideal approach is recreational aerobic exercise, at the same intensity and for the same amount of time as in the healthy population. Back-specific exercises should be reserved for intermediate-to-advanced stages[144].

Experts also indicate that as well as the traditional programmes (spinal and chest flexibility, posture and breathing exercises), there are data from more novel approaches (strength and aerobic training, Pilates, aquatic exercises, GPR, and personalised training programmes, among others) that have shown efficacy in these patients, not only in reducing disease activity and improving physical function and mobility but also for reducing the levels of acute-phase reactants. Aerobic exercise programmes improve cardiovascular health. Ideally, exercise programmes should be tailored, supervised, and followed up over time to assess the long-term outcomes. Patient associations could play a key role in this aspect of treatment[145].

Only one in three patients with ankylosing spondylitis does exercise at the minimum recommended frequency, usually attributing this to fatigue or lack of time [146]. The GDG considers that physical activity should be prescribed to complement drug treatment from the moment the disease is diagnosed.

Clinical question 8 (New)

In axSpA, do obesity and/or smoking increase disease activity, accelerate radiographic progression of structural damage and impair treatment response?

Context/Background

Since the previous ESPOGUÍA, new studies have been conducted into the potential influence of obesity and smoking on disease activity, radiographic progression, and treatment response in axSpA. It is important to develop recommendations that address the role these modifiable health-related factors play in the activity and progression of axSpA.

Recommendations

Recommendation 15: In axSpA, encourage smoking cessation and recommend maintaining a BMI between 18.5 and 25 kg/m^2 to improve disease control **(Strong recommendation in favour)^N.**

^{N} Recommendation related to a new question

Important clinical considerations:

- Subgroups to be considered:
  - *Patients who smoke*: these patients should be offered referral to smoking cessation services or their general practitioner, to receive information about such services.
  - *Patients with overweight/obesity:* these patients should be offered referral to weight management services, when available in the health service, or their general practitioner, to receive information about such services.

Rationale

Smoking and overweight (or obesity) have been associated with greater disease activity and poorer treatment response in patients with axSpA, and smoking has also been associated with faster radiographic progression. Nonetheless, no direct data from any studies demonstrate a beneficial effect of smoking cessation or weight loss in axSpA. All data are from observational studies, providing a low quality of evidence. Despite this, the GDG considers that clinical experience and evidence are sufficient to recommend smoking cessation and maintaining a BMI<25 kg/m^2 to improve disease control and outcomes.

Detailed rationale

Smoking:

Never smokers vs. former smokers

Three studies have been identified assessing the influence of smoking in patients with axSpA by comparing never smokers to former smokers.

One of the studies included a retrospective cohort (SPACE) of 194 never smokers compared to 78 former smokers[147]. Among other factors, it assessed the effect of smoking on disease activity in patients with axSpA over 12 months. This study conducted multivariable analysis adjusted for potential confounding factors: age, sex, level of education, and treatment with NSAIDs, csDMARDs or bDMARDs.

Another study included patients from the BSRBR-AS and compared 234 never smokers to 187 former smokers[148]. It analysed the impact of smoking on the response to TNF inhibitors in patients with axSpA. The analysis was adjusted for the following potential confounders: age, sex, time since symptom onset, level of education, baseline CRP, New York Classification criteria, HLA-B27 status, BMI, alcohol use and comorbidities. Assessments were conducted at 3 and 6 months.

The third study was also based on the BSRBR-AS (Dec 2012-June 2017). It included patients starting TNF inhibitor therapy, and compared 224 never smokers to 177 former smokers[149]. It assessed the effect of smoking on TNF inhibitor discontinuation in axSpA. Similarly, the analysis was adjusted for the following potential confounders: age, sex, time since symptom onset, educational attainment, baseline CRP, New York classification criteria, HLA-B27 status, BMI, alcohol use and comorbidities.

Non-smokers vs smokers

Seven studies were identified assessing the influence of smoking on axSpA by comparing current non-smokers (never smokers or ex-smokers) with smokers. Two of them have been described previously[147, 148].

Another SR evaluated the association of smoking with clinical parameters and structural damage in axSpA. It included nine studies that provided data for this comparison and the majority adjusted their analysis for confounding factors. The authors conducted a descriptive analysis of the results due to the great heterogeneity in the studies[150].

The fourth SR assessed the relationship of smoking and alcohol use with disease-specific outcomes in several rheumatic diseases, including axSpA[151]. It included three studies that

provided data for this comparison and the majority adjusted for confounding factors. They did not conduct a meta-analysis given the heterogeneity of the studies included.

The fifth SR evaluated the relationship between smoking and cumulative radiographic structural damage based on cross-sectional studies of patients with axSpA[152]. It combined descriptive results with meta-analysis only for the cross-sectional studies. Three studies that provided data for this comparison were included and the majority adjusted for potential confounders.

Finally, another study included patients from a prospective cohort (DESIR), and compared 234 non-smokers with 206 smokers[153]. It assessed the relationship between smoking and imaging findings in patients with axSpA. Patients were assessed at 3, 6 and 12 months.

The quality of the evidence was rated as very low to low for both critical and important outcomes, due to the observational nature of the studies as well as their small sample sizes, and lack of information regarding the follow-up period and the time since smoking cessation.

Regarding the risk-benefit balance, the evidence identified shows that smoking may increase disease activity and accelerate radiographic progression of structural damage, as well as impair treatment response.

Other considerations

Various organisations and documents support these results as reflected in the 2022 ASAS-EULAR Recommendations for the Management of axSpA, which state that patients should be provided with education concerning axSpA, and encouraged to do regular exercise and stop smoking [47].

Based on the group's experience, the GDG considers that smoking may increase disease activity and impair treatment response, as well as accelerate the progression of structural damage in patients with axSpA.

Weight Categories (Body Mass Index)

Overweight vs. Normal weight

Three studies were identified assessing the influence of overweight compared to normal weight in patients with axSpA.

One SR assessed the effect of weight/BMI on response to bDMARD and tsDMARD therapy. The rationale for not performing a meta-analysis was the heterogeneity of the studies included. It included four studies that provided data for this comparison and the majority of them adjusted for potential confounders[154].

Another SR evaluated whether overweight and obesity are associated with greater disease activity in adults with axSpA[155]. Despite the clinical heterogeneity between the studies included (in terms of disease duration, prevalence of HLA-B27 or sex ratio), the authors conducted a meta-analysis using a random effects model. The I^2 statistic resulting from the meta-analysis was very low, although the 95% CI was wide. This was probably due to the homogeneity in terms of exposure. This review included six studies providing data for this comparison and most of them did not adjust for potential confounders.

Another study included 1074 patients with axSpA from a Chinese prospective cohort (CASPIC). Given that this was an Asian population, the BMI categories are different to those used in Western populations: normal weight (BMI 18.5-24 kg/m^2), overweight (BMI 24-28 kg/m^2) and obesity (BMI >28 kg/m^2)[156]. This study evaluated the effect of overweight and obesity on disease activity, functional capacity and response to bDMARDs.

The quality of the evidence was rated as very low to low both for critical and important outcomes, due to the observational nature of the studies included, the variable risk of bias, differences in BMI categories (in Asian vs Western populations), the inclusion of studies with great clinical heterogeneity, the pooled analysis of cross-sectional and observational studies, and the lack of adjustment for potential confounders.

Regarding the risk-benefit balance, the evidence identified shows that overweight may increase disease activity and impair treatment response.

<u>Other considerations</u>

These results are also supported by the EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases, which note that patient-specific factors, including body weight, that influence pharmacokinetics should be taken into account when interpreting blood concentrations of biological drugs[157].

Based on the group's experience and the evidence gathered, the GDG considers that overweight may increase disease activity and impair treatment response in patients with axSpA.

Obesity vs. Normal weight

All three studies considered for the previous comparison also evaluated the influence of obesity compared to normal weight in patients with axSpA[154-156]. Some of them included studies that did not adjust for potential confounding factors, having only performed univariate analysis.

The quality of the evidence was rated as very low to low for both critical and important outcomes, due to the observational nature of the studies, the variable risk of bias, differences in BMI categories (in Asian vs Western populations), the inclusion of studies with great clinical heterogeneity, the pooled analysis of cross-sectional and observational studies, and the lack of adjustment for potential confounders.

The evidence identified shows that obesity may increase disease activity and impair treatment response.

Other considerations

These results are also supported by the EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases, which note that patient-specific factors, including body weight, that influence pharmacokinetics should be taken into account when interpreting blood concentrations of biological drugs[157].

Based on the group's experience and the evidence gathered, the GDG considers that obesity may increase disease activity and impair treatment response in patients with axSpA.

Overweight/obesity vs. normal weight

Three studies evaluated the influence of overweight and obesity compared to normal weight in patients with axSpA. One of the aforementioned SRs included five studies making this comparison[155]. Another of the aforementioned SRs included only one study with results for this comparison and did not adjust for potential confounding factors, having only performed univariate analysis[154].

Finally, another study used the mSASSS as the outcome measure of interest (defining radiographic progression as a score of 1 or more) and performed sagittal plane radiographs of the cervical and lumbar spine rated by a single evaluator[158]. For this analysis, the authors included 30 patients treated with TNF inhibitors who had data on mSASSS recorded and a 5-year follow-up. They performed a univariate regression analysis.

The quality of the evidence was rated as very low both for critical and important outcomes, due to the observational nature of the studies included, the variable risk of bias, the inclusion of studies with great clinical heterogeneity, the pooled analysis of cross-sectional and observational studies, the lack of adjusting for potential confounders and the imprecision associated with CIs crossing the line of no effect.

The evidence identified shows that overweight and obesity may increase disease activity and impair treatment response.

Other considerations

These results are also supported by the EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases, which note that patient-specific factors, including body weight, that influence pharmacokinetics should be taken into account when interpreting blood concentrations of biological drugs[157].

Based on the group´s experience and the evidence gathered, the GDG considers that overweight and obesity may increase disease activity and impair treatment response in patients with axSpA.

Obesity vs. Non-obesity

One of the aforementioned SRs is the only study identified evaluating the influence of obesity compared to non-obesity in patients with axSpA[154]. It included five studies for this comparison in patients with r-axSpA treated with SEC.

The quality of the evidence was rated as very low to low both for critical and important outcomes, due to the observational nature of the studies included, the variable risk of bias, the inclusion of studies with great clinical heterogeneity, the pooled analysis of cross-sectional and observational data, and the imprecision associated with CIs crossing the line of no effect.

Regarding the risk-benefit balance, the evidence identified shows that obesity may increase disease activity and impair treatment response.

Other considerations

These results are also supported by the EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases,

which note that patient-specific factors, including body weight, that influence pharmacokinetics should be taken into account when interpreting blood concentrations of biological drugs[157].

Based on the group´s experience and the evidence gathered, the GDG considers that obesity may increase disease activity and impair treatment response in patients with axSpA.

7.2 Treatment of psoriatic arthritis (PsA)

Clinical question 9 (Updated)

In PsA, does early detection and pharmacological treatment improve functional capacity, slow structural damage and enhance quality of life?

Recommendations

Recommendation 16: In patients with peripheral PsA and predictors of poor prognosis*, start pharmacological treatment as soon as possible with csDMARDS and/or bDMARDs, to improve signs and symptoms, functional capacity and quality of life, by suppressing inflammation (Weak recommendation in favour)[A].

*Polyarthritis, structural damage, elevated CRP, dactylitis or nail disease

[U] Recommendation related to an updated question

PsA is a chronic inflammatory disease of the musculoskeletal system, skin and skin appendages that can lead to joint destruction, impairing functional capacity and quality of life. It is important to identify predictors of poor prognosis in the first visits, since these may influence decisions concerning treatment. In cohorts of patients with a short history of the disease (≤ 2 years), joint erosions have been identified in nearly 50% of cases. Bone erosion and other signs of joint damage are closely associated with reductions in functional capacity and poor overall prognosis[159,160]. Early pharmacological intervention may prevent structural damage, thereby maintaining functional capacity and quality of life in patients with PsA.

Quality of the evidence

In a prospective study of 1077 patients with PsA followed-up for 32 years, patients were divided into two groups depending on when they were seen at a specialist clinic: a) within the first 2 years after diagnosis (early PsA, n=436); or b) more than 2 years after diagnosis (established PsA, n=641). The group with established PsA showed greater radiographic progression and were less likely to have received DMARD therapy including biologics[161] (very low quality of evidence).

A *post hoc* analysis of a double-blind RCT with ETN (50 mg/week, n=372) stratified patients depending on disease duration: a) ≤ 2 years (early PsA) or b) > 2 years (established PsA). At 24 weeks, the early PsA group showed greater improvements in patient-reported outcome measures (PROMs)[162, 163] (very low quality of evidence).

An open-label study in 35 patients with early oligoarticular/enthesitis-related PsA (disease duration < 2 years) compared treatment with full-dose NSAIDs for 3 months, followed by the addition of MTX, versus combination treatment with NSAIDs and MTX from the start. Although patients in the combination treatment group showed significantly greater improvements in swollen joint count (SJC) and tender joint count (TJC) at 3 months ($p < 0.05$), no such differences were observed at 6 months. The authors suggest that, in patients with early oligoarticular PsA, a 3-month delay in the start of MTX treatment does not lead to differences in clinical efficacy[164] (very low quality of evidence).

A 24-week multicentre longitudinal observational study assessed the efficacy and safety of TNF inhibitors in 29 patients with early PsA (disease duration < 12 months), with an inadequate response to conventional treatment based on NSAIDs and DMARDs. At week 24, 82% of patients achieved a EULAR good response (improvement in DAS 28 >1.2) and 13.8% a moderate response, while 3.5% were non-responders. All the variables assessed improved from baseline ($p<0.001$). Given these results, the authors suggest that TNF inhibitor therapy is effective in patients with early peripheral PsA[165] (very low quality of evidence).

A prospective study involved a 5-year follow-up of 197 patients with early PsA (<2 years since symptom onset), to gather information on predictors of treatment response. The most striking finding of the study was that a short delay between symptom onset and diagnosis was the main predictor of favourable outcome[166] (very low quality of evidence).

A cross-sectional study of a cohort of 283 patients assessed the effect of a delay in the first visit to a rheumatologist on various functional and structural outcomes. The mean delay to the first visit for a rheumatology assessment was 1 year (IQR 0.5-2.9). Multiple regression analysis revealed that being seen later by a specialist was significantly associated with developing peripheral joint erosions and lower HAQ scores (OR 4.25, p= 0.0019 and OR 2.2, p= 0.004, respectively). A diagnostic delay > 1 year was associated with developing arthritis mutilans, a lower likelihood of achieving c,drug-free remission and poorer functional capacity. A diagnostic delay > 2 years was more likely in patients with low educational attainment and low BMI and was also related to more peripheral joint erosions and lower HAQ scores. The authors concluded that a diagnostic delay from symptom onset until the first assessment by a rheumatologist is

linked to the development of peripheral joint erosions and more functional impairment in the long term[167] (very low quality of evidence).

Lastly, the TICOPA trial evaluated the benefits of early intervention and tight clinical control (group 1: q4w) compared to usual clinical practice (group 2: every 12 weeks) in 206 patients with early PsA (symptom duration <24 months). It observed higher ACR 20, ACR 50 and ACR 70 response rates at 48 weeks in group 1 than in group 2. Additionally, benefits were observed in group 1 patients in terms of control of their psoriasis and improvements in functional capacity and quality of life scores. In contrast, no differences were observed in radiographic progression at the end of the follow-up[168] (very low quality of evidence).

2023 update:

More recent studies have compared the effect of biological therapy with MTX in treatment-naïve patients, but the population selected did not have early PsA. Specifically, in treatment-naïve PsA, an RCT evaluated whether the combination of GOL plus MTX was superior to MTX alone, in achieving remission[169]. Regarding efficacy, the primary endpoint was reached by 81% of patients given TNF inhibitor plus MTX and 42% of those given MTX alone (p = 0.004). There was also a significant difference in favour of the TNF inhibitor plus MTX arm at week 22 in PROMs, such as HAQ and SF-36 scores.

Similarly, another RCT evaluated the efficacy of two strategies for dactylitis treatment: GOL plus MTX vs placebo plus MTX in treatment-naïve PsA[170]. High-performance MRI was performed at baseline and 24 weeks. At 24 weeks, 31.0% (9/29) of all patients had no dactylitis-related inflammatory lesions: 53.8% (7/13) of those treated with GOL plus MTX compared to 12.5% (2/16) of those treated with placebo plus MTX. The GOL plus MTX group had greater reductions in inflammation scores on the Outcome Measures in Rheumatology PsA MRI Scoring System between baseline and week 24. No significant between-timepoint differences were observed in bone erosion or proliferation. A study based on data from the TICOPA trial also did not observe any significant between-group differences at 48 weeks of follow-up in the subgroup of patients that underwent joint ultrasound and MRI at baseline and week 48[171].

A recent study conducted in The Netherlands in more than 700 patients with early PsA reported that a > 12-month delay between symptom onset and the diagnosis of PsA by a doctor was associated with a lower likelihood of achieving minimal disease activity (MDA) or remission as measured by the Disease Activity index in Psoriatic Arthritis (DAPSA) score, at 3 years of follow-up. Female sex, disease onset with back pain or enthesitis, and normal CRP levels were associated with a longer diagnostic delay[172].

In developing the recommendations, the GDG has been aware of the scarcity of evidence on the efficacy of early pharmacological intervention and certain issues related to the quality of the studies included. In particular, it recognises that: a) while *post hoc* analyses are considered inadequate and should be interpreted with caution, they may sometimes be justified to make use of the data gathered in a clinical trial, but in any case, if considered, they should be purely exploratory; b) open-label non-randomised studies are typically susceptible to certain types of bias; and c) if a study does not include a radiographic assessment and only includes patients with oligoarticular or enthesitis-related PsA, the results cannot be extrapolated to other peripheral forms of PsA.

Overall, the results of the studies identified point in a similar direction in terms of the efficacy of early pharmacological intervention, namely, they suggest that the shorter the time from symptom onset to treatment, the better the treatment response. It has also been reported that delays in the first visit to the rheumatologist are associated with more structural damage, poorer response to DMARD therapy, and poorer functional capacity. From this, despite a lack of robust evidence, it can be inferred that early pharmacological intervention may result in better outcomes from a clinical perspective, as well as in terms of physical function, PROMs and quality of life. Further, bDMARDs may be superior to conventional therapies or treatment with MTX alone as a pharmacological treatment in patients with established treatment-naïve disease.

The GDG considers that -although the evidence found does not come from RCTs- early pharmacological intervention, and possibly also tight control with treat-to-target strategies, may improve clinical prognosis in patients with PsA. On the other hand, aggressive tight control strategies may be associated with a higher incidence of adverse events.

Clinical question 10 (Updated)

In PsA, what is the efficacy of csDMARDs in treating axial and peripheral disease, enthesitis and dactylitis?

Recommendations

Recommendation 17: In patients with active peripheral PsA, use csDMARDs (MTX, LFN and SSZ) as the first-line treatment (Strong recommendation in favour)[A].

> ***Recommendation 17.1:*** Among csDMARDs, MTX is considered the treatment of choice, given its effects on arthritis and psoriasis (Weak recommendation in favour)[A].
>
> ***Recommendation 17.2:*** Do not use csDMARDs for treating axial disease (Weak recommendation in favour)[A].

[U] Recommendation related to an updated question

Quality of the evidence

An RCT comparing MTX and placebo did not find significant differences in the majority of the activity scores proposed, benefits only being observed in skin involvement and physician and patient global assessment scores. On the other hand, the major methodological limitations of this study should be taken into account (patients with low disease activity were included, the recruitment period was extremely long, the mean doses of MTX were below usual doses and a large number of patients were lost to follow-up), as they call into question the validity of the study[173, 174] (low quality of evidence).

One retrospective study compared the course of peripheral arthritis in a new cohort with that in a cohort from a previous study by the same authors, patients in the more recent cohort receiving higher doses of MTX. At 24 months, 68% of the patients in the new cohort showed a ≥40% reduction in joint counts, and there was a trend to greater improvement compared to that observed in the old cohort[175] (very low quality of evidence).

A previously cited RCT evaluated the efficacy of MTX compared to an NSAID for 3 or 6 months. The group with continuous MTX therapy showed significant improvements in SJC and TJC[164] (low quality of evidence).

In the TICOPA study (assessing a treat-to-target strategy) in patients with early PsA, 22% of patients who received MTX alone achieved MDA[168].

Several studies were identified evaluating the efficacy of leflunomide (LFN). In a prospective observational study, the majority of patients (86.4%) achieved a Psoriatic Arthritis Response Criteria (PsARC) response, with significant reductions in mean SJC and TJC. Further, over half of the patients with dactylitis (51.2%) experienced significant improvement [176] (very low quality of evidence).

Other studies assessing the efficacy of LFN alone, compared to MTX or in combination with MTX, found no significant differences between the interventions[177,178] (low/very low quality of evidence).

Regarding the efficacy of SSZ, one SR was identified, which did not provide detailed data on the results of the studies but drew the following overall conclusions: it was effective for treating peripheral arthritis; two studies reported data on dactylitis and did not find significant differences between SSZ and placebo; one study did not find a significant benefit over placebo in enthesis; and in a small case-control study (20 patients), SSZ had no effect on radiographic progression[179].

2023 Update

Since the previous ESPOGUÍA, no new studies have been published on the efficacy of LFN and SSZ; nor have there been studies whose primary objective was to assess the efficacy of MTX in PsA. Hence, the evidence for updating the response to this clinical question is scarce and of uneven quality. The GDG has considered it useful to include certain studies that may help sustain the validity of the recommendations, even though they did not meet the inclusion criteria, because the comparison was not between MTX and placebo.

Regarding peripheral arthritis, one RCT identified (the SEAM-PsA trial) compared three treatment arms: MTX, ETN and ETN plus MTX. In the absence of a control group, MTX monotherapy showed greater efficacy in measures assessing peripheral arthritis (50.7%, 30.6%, and 13.8% for ACR 20, 50, and 70 responses, respectively) and improvement in physical function (-0.41) at 24 weeks. The fact that the maximum dose was 20 mg/week may have underestimated the potential impact of MTX[180]. Another RCT identified (the COMPLETE-PsA trial, comparing MTX plus LFN vs MTX plus placebo), showed that treatment with MTX plus placebo reduced disease activity, as measured by the Psoriatic Arthritis Disease Activity Score (PASDAS), but the reduction was significantly smaller than that observed with the combination of MTX and LFN. However, no differences were found between the combination therapy and MTX monotherapy in the reduction of DAPSA score at week 16[181].

Insufficient evidence has been found regarding the role of MTX in the prevention of structural damage or radiographic progression. In the SEAM-PsA trial, the rate of radiographic progression in the MTX arm was very low, with a mean change of 0.08 from baseline to week 48. A total of 89.4% of patients showed no progression. On the other hand, these patients had little radiographic damage at baseline, and this may have contributed to the low rate of radiographic progression observed[180].

There is also limited evidence regarding the efficacy of MTX in the treatment of patients with predominantly enthesitis-based disease. The SEAM-PsA trial reported resolution rates of enthesitis of 43.1% and 51% at 24 and 48 weeks, respectively, in the group treated with MTX monotherapy, with differences compared to ETN monotherapy being nonsignificant at 24 weeks (52.6%, p=0.11), but reaching significance at 48 weeks (66.3%, p=0.01)[180].

Regarding PsA with dactylitis, in the SEAM-PsA trial, the dactylitis resolution rate in the group treated with MTX monotherapy was 65.2% at 24 weeks, with no differences compared to ETN monotherapy (76.4%, p=0.12) or combination therapy with ETN and MTX (79.3%, p=0.05) [180].

Another RCT was identified (the GO-DACT trial) (n=44 patients) with two arms: GOL plus MTX and MTX plus placebo, using the maximum MTX doses of 25 mg/week. The primary endpoint was the change in the Dactylitis Severity Score from baseline to 24 weeks. The secondary endpoints were: the change in the Leeds Dactylitis Index and dactylitis remission at the end of the study. Results showed greater efficacy in the GOL plus MTX group. The changes in the Leeds Dactylitis Index were greater in this group. The rate of dactylitis remission was low and similar in both groups (30% and 18.1%, respectively, p=0.47) [170]. Another RCT identified (n=51 patients with early PsA) did not show differences in the results related to dactylitis between a GOL plus MTX group and a group treated with MTX monotherapy (p=0.31) [169].

No new evidence was identified concerning the use of csDMARDs for treating axial manifestations of PsA.

The GDG considers, despite the low level of evidence found, that csDMARDs have a high cost-effectiveness ratio as the first-line treatment for peripheral arthritis. Given the recommendations of other bodies such as EULAR and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), this is a strong recommendation. A weak recommendation has been made to use MTX as the first choice.

Regarding the treatment of enthesitis and dactylitis, several studies have been published assessing the effect of MTX on these manifestations as a secondary objective. None of these

studies made comparisons with placebo, and this affects the conclusions regarding its efficacy. Nonetheless, the high percentage of responders may support the use of MTX for enthesitis in PsA. Given these results, in the 2021 update of the GRAPPA recommendations, MTX was conditionally recommended for the initial treatment of enthesitis and dactylitis[182]. One of the circumstances in which it may be used is in patients with associated peripheral arthritis. If a good response is not observed, despite the aforementioned treatment, the use of bDMARDs or tsDMARDs would be an appropriate option.

The use of csDMARDs in axial PsA is not warranted. The GDG has made a weak recommendation against their use, due to the scarce evidence and the fact that future research is unlikely to address this issue.

Clinical question 11 (New)

In PsA, what is the efficacy of IL-23 and IL-17 inhibitors and targeted synthetic drugs (JAK inhibitors and apremilast) in treating axial and peripheral disease, enthesitis and dactylitis?

Context/Background

PsA is a chronic inflammatory disease that may affect as many as a third of patients with psoriasis[183]. This condition may cause joint destruction and chronic disability in a high percentage of patients, and hence, an intensive approach to treating the disease is crucial to avoid long-term sequelae[184]. Among the therapeutic approaches available, biological therapies and tsDMARDs have been found to be effective for controlling the signs and symptoms associated with the disease and improving quality of life, as well as minimising long-term sequelae. Among biological therapies, TNF inhibitors were the first available and are the biologics for which most experience has been accumulated over the past 25 years. Over the last decade, however, new bDMARDs as well as tsDMARDs have been approved. It is essential to establish their efficacy in treating the different musculoskeletal domains of this psoriatic disease to design care protocols for routine clinical practice.

Recommendations

Recommendation 18: In patients with active PsA, after an inadequate response and/or intolerance to a csDMARD or a bDMARD (TNF inhibitor), use IL-17A, IL-17A/F or JAK inhibitors for treating axial or peripheral disease, enthesitis and dactylitis* (Strong recommendation in favour)[N].

*Appendix 2 contains the recommendations in the previous guidelines as complementary information.

Recommendation 19: In patients with active PsA, after an inadequate response and/or intolerance to a csDMARD or bDMARD (TNF inhibitor), use IL-23 inhibitors for treating peripheral disease, enthesitis and dactylitis* (Strong recommendation in favour)[N].

*Appendix 2 contains the recommendations in the previous guidelines as complementary information.

Recommendation 20: In patients with active PsA, after an inadequate response and/or intolerance to a csDMARD or a bDMARD (TNF inhibitor), use IL-17A, IL-17A/F, IL-12/23 or IL-23 or JAK inhibitors for controlling structural damage* (Strong recommendation in favour)[N].

*Appendix 2 contains the recommendations in the previous guidelines as complementary information.

Recommendation 21: In patients with active PsA who have an inadequate response and/or intolerance to a csDMARD, consider using apremilast for treating peripheral disease, enthesitis and dactylitis (Weak recommendation in favour)[N].

[N] Recommendation related to a new question

Important clinical considerations:

- Subgroups to be considered:
  - *Patients ≥65 years old:* Prioritise options other than JAK inhibitors in ≥65-year-olds, patients who are active smokers (or have a history of heavy smoking), and those who have an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible dose.
  - *Patients with axPsA:* the only agent shown to be effective for treating axPsA in an RCT is SEC, an IL-17A inhibitor. Indirect evidence suggests that TNF inhibitors or other IL-17A and IL-17A/F inhibitors, as well as JAK inhibitors, may be good treatment options for the axial domain of PsA.
  - *Drug groups:* Although there are some differences between different IL-17 inhibitors (A and A/F) and different JAK inhibitors, the GDG believes that recommendations should be made by drug group, as it is not currently possible to demonstrate that small differences in the mechanism of action between drugs in the same group lead to significant differences in efficacy or safety profile (given a lack of head-to-head clinical trials of different drugs in the same group for treating PsA).
  - There are, however, two types of IL-17 inhibitors with different mechanisms of action: 1) inhibition of IL-17A (SEC and IXE), and 2) inhibition of both IL-17A and IL-17F (BKZ). Therefore, for the purposes of ESPOGUÍA, all of them are grouped as IL-17 inhibitors.
  - tsDMARDs: 1) PDE4 inhibitors (apremilast), and 2) JAK inhibitors (TOFA and UPA).

Rationale

These recommendations have been made based on the results of double-blind placebo-controlled RCTs of IL-17, IL-23, or JAK inhibitors or apremilast in which the variables of interest were the primary or secondary endpoints, and the results have shown statistically significant differences compared to placebo, in treatment-naïve patients and as well as those with an inadequate response and/or intolerance to biologics. Although some outcomes, such as the slowing of structural damage, have not been demonstrated in all the treatment arms of the clinical trials with IL-23 inhibitors, the GDG considers that these drugs have a clinically significant effect on this domain, and that the limited sample sizes in these trials, together with the good

results in the placebo group, have hindered achieving this goal. The GDG considers that this should not limit the strength of the recommendations concerning the use of IL-23 inhibitors for slowing structural damage.

To date, no consensus has been reached on the definition of axPsA, and hence, studies assessing the axial domain of PsA are heterogeneous as well as scarce. The only clinical trial designed to assess the efficacy of a drug in treating this domain is the MAXIMISE study for SEC that, using a clinical definition of axial involvement, demonstrated the greater efficacy of sc SEC 150 mg or 300 mg compared to placebo[185]. Although no specific clinical trials investigating this domain have been conducted for other IL-17 inhibitors or JAK inhibitors, their approval for axSpA suggests they may have efficacy in axPsA.

On the other hand, there is even less evidence regarding IL-23 inhibitors in this domain. Although the STAR trial is underway, and *post hoc* analyses have already been published suggesting the efficacy of IL-23 inhibitors in axPsA[186], the current lack of RCT data, together with the negative results concerning the efficacy of these drugs in axSpA[187], lead the GDG to defer making any recommendations on the use of IL-23 inhibitors in axPsA until more evidence is available.

Detailed rationale

Interleukin 17 inhibitors

IL-17A inhibitors

A total of 11 RCTs were identified assessing the efficacy and safety of IL-17A inhibitors over 12 to 24 weeks.

The SPIRIT-P1[188] (including patients who were naïve to bDMARDs but allowing previously treatment with csDMARDs) and SPIRIT-P2[189] (patients previously treated with bDMARDs, with an inadequate response and/or intolerance to a TNF inhibitor) included 679 patients with active PsA treated with sc IXE (80 mg) q2w or q4w or placebo over 24 weeks.

The FUTURE 1[190], 2[191], 3[192], 4[193] and 5[194], MAXIMISE[195], ACHILLES[196], ULTIMATE[197] and CHOICE[198] trials included a total of 3880 patients treated with SEC (300/150/75 mg) compared to placebo over 12 to 24 weeks. The FUTURE and CHOICE trials considered peripheral involvement as the primary endpoint and included patients with active PsA who were treatment-naïve or who had an inadequate response to csDMARDs or TNF inhibitors, the MAXIMISE trial assessed axial manifestations, the ACHILLES study explored the resolution of Achilles enthesitis and the reduction in enthesitis-related disease burden, and the ULTIMATE trial assessed the inhibition of synovitis, as detected by Doppler ultrasound.

The AMVISION 1 and AMVISION 2[199] trials included 962 patients treated with sc BRD 140/210 mg (on day 1, at week 1 and 2 and then every other week) compared to placebo over 24 weeks. The AMVISION 1 trial included patients with an inadequate response or intolerance to csDMARDs; while AMVISION 2 did not apply this criterion.

The overall quality of the evidence was rated as moderate because, in several of the clinical trials, it was unclear whether there was allocation concealment and/or blinding of the endpoint.

Overall, the evidence shows that IL-17A inhibitors have significantly different effects compared to placebo in reducing peripheral symptoms and structural damage, and achieving the resolution of the enthesitis and dactylitis, as well as improving axial manifestations. In terms of adverse effects, all the drugs in this group have a low-risk profile, upper respiratory tract infections being the most common complication. Fungal infections, especially by *Candida albicans*, are a type of adverse effect that seems to be associated with this group of drugs, and this is attributable to IL-17 playing a role in host defence against fungi on mucocutaneous surfaces. Nonetheless, most cases of these infections are isolated incidents, respond well to treatment, and rarely lead to treatment discontinuation.

Other considerations: Based on the group´s experience, the GDG considers that IL-17A inhibitors may be used for treating arthritis, enthesitis, and dactylitis, as well as the axial domain of PsA. They have all been evaluated as primary or secondary endpoints in phase 3 clinical trials conducted for the purpose, and have shown statistically significant superiority over placebo. Open-label follow-up studies of these patients confirm the results.

IL-17A and IL-17F inhibitors

Two RCTs (BE OPTIMAL[200] and BE COMPLETE[201]) were identified assessing the efficacy and safety of BKZ (160 mg) compared to placebo over 24 weeks in a total of 1112 patients. The BE OPTIMAL trial assessed the efficacy and safety of BKZ in biologic-naïve patients with active PsA. Of 1163 patients recruited, 852 met selection criteria and were randomly allocated to the BKZ arm (n=431), ADA 40 mg as the active comparator group (n=140) or placebo (n=281). A related publication analysed the patients who completed week 52 of the BE OPTIMAL trial[202].
The BE COMPLETE trial evaluated the efficacy and safety of BKZ in patients with active PsA who had an inadequate response or intolerance to TNF inhibitors. It included 556 patients (267 in the BKZ 160 mg arm and 133 in the placebo group).

The results concerning the resolution of enthesitis and dactylitis were reported pooling data from the BE COMPLETE and BE OPTIMAL RCTs.

The overall quality of the evidence was rated as high.

Regarding the risk-benefit balance, the evidence identified shows that results with BKZ differ significantly from those with placebo in relation to the reduction of peripheral symptoms and structural damage, and resolution of enthesitis and dactylitis, with a similar safety profile to that of other IL-17A inhibitors.
Based on the group´s experience and the evidence gathered, the GDG considers that IL-17A/F inhibitors may be used for treating arthritis, enthesitis, and dactylitis, as well as the axial domain of PsA. They have all been evaluated as primary or secondary endpoints in phase 3 clinical trials conducted for the purpose and have shown statistically significant superiority over placebo, except concerning the axial domain, which was not directly assessed in clinical trials with BKZ. Nonetheless, the efficacy of other IL-17 inhibitors in treating this domain and the demonstrated efficacy of BKZ in axSpA[51] leads the GDG to recommend this drug for the axial domain of PsA.

Interleukin 23 inhibitors

Five studies were identified evaluating the efficacy and safety of IL-23 inhibitors over 24 weeks. The KEEPsAKE-1 and 2 trials[203, 204] evaluated the efficacy and safety of RIS 150 mg compared to placebo in patients who were naïve and had an inadequate response or intolerance to biologics, respectively.
The DISCOVER-1/2[205, 206] and COSMOS[207] trials evaluated the efficacy and safety of guselkumab (GUS) 100 mg compared to placebo in patients who were naïve or resistant to biologics.

The overall quality of the evidence was rated as moderate because, in several clinical trials, it was unclear whether allocation concealment was performed or the generation of the randomisation sequence was not described.

Regarding the risk-benefit balance, the results from these clinical trials confirm the efficacy of IL-23 inhibitors in treating arthritis, enthesitis and dactylitis, as well as slowing structural damage, although differences did not reach significance in some subgroups. The adverse effects were mostly mild, with good risk-benefit and safety profiles.

The axial domain has only been assessed in *post hoc* analyses, these indicating positive results. Nonetheless, the fact that IL-23 inhibitors are not indicated for axSpA and the lack of direct evidence from clinical trials in PsA (axial disease not being the primary or secondary endpoint in any of the trials) lead the GDG to recommend against the use of this group of drugs for the axial domain of PsA, until more evidence is available.

Targeted synthetic disease-modifying antirheumatic drugs

JAK inhibitors

Four studies were identified evaluating the efficacy and safety of JAK inhibitors. The OPAL-BEYOND[208] and OPAL-BROADEN[209] trials evaluated the efficacy and safety of TOFA 5 or 10 mg compared to placebo in patients who were naïve or resistant to biologics.
The SELECT PsA-1[210] and SELECT PsA-2[211] trials evaluated the efficacy and safety of UPA 15 mg or 30 mg compared to placebo in biologic-naïve or -resistant patients.

The overall quality of the evidence was rated as moderate because, in some studies, the random sequence generation and allocation concealment were not clear, and there was a high risk of incomplete data.
Regarding the risk-benefit balance, the results from these clinical trials confirm the efficacy of JAK inhibitors in treating arthritis, enthesitis and dactylitis, as well as for slowing progression of structural damage. Although the safety profile of JAK inhibitors based on data from clinical trials in PsA does not differ from that of other drugs, such as TNF and IL-17 inhibitors, the recent results of a phase 4 clinical trial in rheumatoid arthritis have restricted the use of these drugs to certain clinical contexts. Although the ORAL SURVEILLANCE[212] trial only evaluated >50-year-old patients with rheumatoid arthritis and cardiovascular risk factors who initiated treatment with TOFA or TNF inhibitors (ETN or ADA, depending on the region), international regulators have extrapolated the study findings to all JAK inhibitors and their indications[213].

During a median follow-up of 4 years, the incidence of major adverse cardiovascular events (MACE) and cancer was higher with combined TOFA doses (3.4%; 98 patients and 4.2%; 122 patients, respectively) than with a TNF inhibitor (2.5%; 37 patients and 2.9%; 42 patients). The hazard ratios were 1.33 (95% CI: 0.91 to 1.94) for MACE and 1.48 (95% CI: 1.04 to 2.09) for cancer; therefore, the non-inferiority of TOFA was not demonstrated. The incidence rates of opportunistic infections (including herpes zoster and tuberculosis), all herpes zoster (serious and non-serious), and nonmelanoma skin cancer were higher with TOFA than with a TNF inhibitor[212].

The GDG has taken into account that, given these results, the EMA recommends that all JAK inhibitors should only be used in in the following groups of patients if no other suitable treatment options are available: people over 65 years of age, smokers or former smokers, people with a history of atherosclerotic heart disease or other cardiovascular risk factors, and those with other risk factors for cancer. It also recommends that these drugs should be used with caution in patients with known risk factors for venous thromboembolism other than those listed above. These recommendations apply regardless of the indication for use of the drug.

Apremilast

Five RCTs were identified evaluating the efficacy of apremilast (20/30 mg) compared to placebo. These were the ACTIVE[214] and PALACE 1[215], 2[216], 3[217] and 4[218] trials. In a meta-analysis of data from these five studies, ACR 20 response rates were 30.8% in patients treated with apremilast compared to 16.7% in those given placebo (RR 1.87; 95% CI 1.57 to 2.23).

The quality of the evidence was rated as moderate because, in some of the trials, the random sequence generation and allocation concealment were unclear. The safety profile was good, and in the trials, the rates of adverse effects with the study drug were similar to or in some cases lower than with placebo.

Regarding the risk-benefit balance, the results from these clinical trials confirm the efficacy of apremilast in treating arthritis, enthesitis and dactylitis, although its effect is moderate, especially for the most demanding endpoints, such as ACR 70 response. Further, apremilast has not been shown to slow the progression of structural damage. The adverse effects were mostly mild, confirming good risk-benefit and safety profiles.

Based on the group´s experience and the evidence gathered, the GDG considers that apremilast may be used to treat peripheral arthritis, enthesitis and dactylitis in patients with moderate disease activity and a low risk of structural damage progression.

Equity, acceptability, and feasibility of implementation

In the GDG's judgement, in our setting, there are no marked inequities in access to these bDMARDs or tsDMARDs as a function of geographical location, socioeconomic status, race or ethnic group.

The group also considers it likely that all those involved in the use of these drugs (health authorities, specialists, and patients) will find their use in clinical practice acceptable, given the good efficacy of all these drugs, and their low adverse effect rates, as well as the experience accumulated over the years in the use of advanced therapies in patients with chronic arthritis.

On the other hand, antirheumatic therapies, including tsDMARDs and bDMARDs, are commonly used in our setting. The experience accumulated over the years by rheumatologists facilitates the introduction and use of drugs for new therapeutic targets.

Outcome assessment by patients

In the GDG's judgement, it is unlikely that there is variability in how patients rate the main outcomes.

Resource use

Searches were not conducted for information on the costs of the drugs assessed, given that this topic is usually deemed to be beyond the scope of CPG recommendations; therefore, the GDG considers that it has insufficient data to make any recommendations on resource use.

Monitoring and assessment

Clinical monitoring and check-ups for patients on these therapies should be similar to those performed in usual practice, that is, a first assessment and tests at 6-8 weeks after starting on the drug, and subsequently, check-ups every 3-6 months depending on disease activity. All these drugs are generally fast-acting, and hence, their efficacy can be assessed after 12 to 24 weeks of therapy.

Research priorities

Direct head-to-head comparison studies are needed to compare the different treatments approved for PsA. This will allow for better positioning of each drug within the therapeutic arsenal for PsA.

There is a need for an agreed definition of axPsA with the goal of obtaining homogeneous samples of patients for conducting epidemiological studies and clinical trials.

Further research should be performed in which variables such as enthesitis and dactylitis are the primary endpoint, rather than secondary objectives as they have been to date. This would provide better evidence on the efficacy of various treatments in these domains.

Biomarker studies are needed to allow treatments to be tailored for patients with PsA.

Clinical question 12 (New)

In PsA, what is the efficacy, effectiveness and safety of IL-17, IL-23, IL- 12/23 and JAK inhibitors compared to TNF inhibitors?

Context/Background

The number of treatment options for PsA has grown substantially over the last decade. Based on emerging evidence with different agents, several widely used consensus recommendations have been published to guide the treatment of this condition. Although treatment options other than TNF inhibitors (IL-17A, IL-17A/F, IL-12/23, IL-23, JAK and PDE4 inhibitors) have been shown to be superior to placebo in RCTs, less is known about the performance of these new options in the real world. On the other hand, the hierarchy or sequence for using these drugs is practically unknown. Moreover, the choice of therapeutic target requires striking a careful balance between efficacy, effectiveness and safety. For this reason, clinicians need high-quality data on the use of the various therapeutic targets in the context of routine clinical practice [182, 219, 220].

Recommendations

Recommendation 22: In patients with active PsA, use any bDMARD (TNF, IL-17A or 17A/F, IL-23, or IL-12/23 inhibitors) or a JAK inhibitor, given that there is no evidence that there is a significant difference between them in terms of efficacy, effectiveness or safety, apart from a difference in efficacy in treating extra-musculoskeletal manifestations (Strong recommendation in favour)[N].

[N] Recommendation related to a new question

Important clinical considerations:

- Subgroups to be considered
  - *Patients ≥65 years old:* Prioritise options other than JAK inhibitors in ≥65-year-olds, patients who are active smokers (or have a history of heavy smoking), and those who have an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible dose.
  - *Patients with axPsA:* the only agent shown to be effective for treating axPsA in an RCT is SEC, an IL-17A inhibitor. Indirect evidence suggests that TNF inhibitors or other IL-17A and IL-17A/F inhibitors as well as JAK inhibitors may be good treatment options for the axial domain of PsA.

Rationale

These recommendations are based on the results of studies on TNF, IL-17, IL-23, IL-12/23 or JAK inhibitors. The conclusions show that the efficacy/effectiveness of the various biological therapies in PsA is similar, without robust evidence of the superiority of any one target over another. Therapies targeting IL-17 and IL-23 only appear to be superior to TNF inhibitors for treating skin disease in PsA, obtaining similar results for the musculoskeletal domain (arthritis, enthesitis, and dactylitis). JAK inhibitors perform similarly to drugs with other targets, but the safety issues with these drugs, which affect certain subgroups described above, suggest their use after biological therapies. These recommendations are in line with the recent 2023 EULAR guidelines for the management of PsA[221].

Detailed rationale

Interleukin 17A inhibitors

Secukinumab vs. Adalimumab

One RCT has been identified (the EXCEED[222] trial) evaluating the efficacy and safety of SEC compared to ADA in 853 biologic-naïve patients with active PsA (49% women; mean age 49±12.4 years). A dose of sc SEC 300 mg was administered at baseline, at weeks 1, 2, 3, and 4, and subsequently q4w until week 48, while ADA 40 mg was administered q2w from baseline until week 50.

The safety profiles of SEC and ADA were consistent with data from previously published studies. Adverse events were observed in 330 (77%) of the 426 patients in the SEC group and 338 (79%) of the 427 patients in the ADA group. There were two reported cases of IBD in the SEC group, both cases corresponding to flares in patients with a history of IBD.

Other considerations: In a *post hoc* analysis focused on enthesitis, at baseline, 498 cases were identified in 851 (58.5%) patients based on the Leeds Enthesitis Index (LEI) and 632 cases in 853 patients (74.1%) based on the SPARCC enthesitis index[223]. Patients with enthesitis at baseline generally had greater disease activity. The rates of resolution were similar in the SEC and ADA groups at week 24 (49.6%/45.8% and 43.6%/43.5% as measured by LEI/SPARCC index with SEC and ADA respectively) and week 52 (60.7%/53.2% and 55.3%/51.4% as measured by LEI/SPARCC index with SEC and ADA respectively), and times until enthesitis resolution were also similar. Similar levels of improvement were observed with both drugs at individual enthesitis sites. In both groups, enthesitis resolution was associated with improvements in quality of life at week 52.

Additionally, two matching-adjusted indirect comparisons have been identified. One compared SEC and IFX, concluding that there were no differences in the ACR 20/50/70 responses between SEC (300 mg) and IFX at weeks 6/8 and 14/16 (both adjusted for placebo) and at week 24 (not adjusted for placebo)[224]. At weeks 54/52, the non-placebo-adjusted ACR 20/50 responses were greater with SEC 300 g than with IFX (OR 2.72; 95% CI: 1.33 to 5.57; p = 0.006 and 2.69; 95% CI: 1.41 to 5.11; p = 0.003), respectively. These observations were unchanged with the use of different imputation methods. The other study compared SEC and ETN, concluding that the ACR 20/50/70 response rates at week 24 were significantly greater in patients treated with SEC than with ETN (ACR 20: OR 3.28; 95% CI 1.69 to 6.38; p<0.001; ACR 50: OR 1.90; 95% CI 1.04 to 3.50; p=0.038, and ACR 70: OR 3.56; 95% CI 1.51 to 8.40; p=0.004)[225].

The quality of the evidence was rated as moderate due to imprecision, the 95% CIs crossing the line of no effect.

Regarding the risk-benefit balance, the evidence identified shows no significant differences between SEC and ADA in relation to reducing signs/symptoms of peripheral arthritis and the progression of structural damage or achieving the resolution of enthesitis and dactylitis.

Ixekizumab vs. Adalimumab

A relevant pivotal trial was identified, namely, SPIRIT-H2H, a phase 3b/4 multicentre open-label RCT together with its extension study[227]. This research evaluated the efficacy and safety of IXE compared to ADA in a total of 566 biologic-naïve patients (44.8% women) with active PsA who had an inadequate response to csDMARDs.

The overall quality of the evidence was rated as low due to the lack of blinding and the imprecision, CIs crossing the line of no effect or the clinical decision threshold.

In patients treated with IXE, the rate of adverse events was lower (4.2% vs 12.4% in the group treated with ADA) as was the rate of treatment discontinuation (4.2% vs 7.4%); RR: 0.34 95% CI: 0.18 to 0.65. Patients in the IXE group also experienced fewer infections (1.8% vs 2.8% with ADA); RR: 0.34 (95% CI 0.18 to 0.65), but had a higher rate of Candida infections (2.5% vs 1.1%). Two cases of IBD were reported in the IXE group between weeks 0 and 24 (one case of Crohn´s disease and one of ulcerative colitis); no cases were observed from weeks 24 to 52. No cases were reported in the ADA group.

Other considerations: In the SPIRIT H2H trial, the entire population included had no prior exposure to bDMARDs, and hence, it is not known how drugs with the targets considered would perform in other scenarios. On the other hand, comparing patients who experienced a complete

response (ACR 50 + Psoriasis Area Severity Index [PASI] 100) to those who experienced a response only for articular disease (ACR 50) or only for skin disease (PASI 100), significantly higher percentages ($p<0.05$) of the group with a complete response reached stringent endpoints such as MDA and very low disease activity at weeks 24 and 52. Complete responders were also significantly more likely than those with response for skin disease or no response at all to achieve DAPSA low activity or remission, enthesitis and dactylitis resolution and improvement in HAQ disability index score at weeks 24 and 52 ($p<0.001$).

A similar response was observed with IXE alone or combined with csDMARDs, while the response to ADA was influenced by the use of a csDMARD (MTX). Specifically, the following response rates were observed: simultaneous achievement of ACR 50 and PASI 100 using monotherapy, 37.8% with IXE vs. 19.0% with ADA ($p=0.007$), and using combination therapy, 39.9% with IXE vs. 29.1% with ADA ($p=0.026$); achievement of ACR 50 using monotherapy, 51.1% with IXE vs 41.7% with ADA ($p=0.227$), and using combination therapy, 49.2% with IXE vs 53.3% with ADA ($p=0.479$); and achievement of PASI 100 using monotherapy, 65.6% with IXE vs 34.5% with ADA ($p\leq0.001$), and using combination therapy, 63.7% with IXE vs 44.2% with ADA ($p\leq0.001$). These data support the use of IXE monotherapy, while they suggest that combination therapy with ADA plus MTX performs better than ADA monotherapy.

The quality of the evidence was rated as low due to imprecision, either because the 95% CIs crossed the line of no effect or clinical decision threshold, or in some cases, patients knew which treatment they were receiving and may have told researchers while being assessed.

Regarding the risk-benefit balance, the evidence identified shows no significant differences between IXE and ADA in relation to reducing signs/symptoms of peripheral arthritis and the progression of structural damage or achieving the resolution of enthesitis and dactylitis.

Interleukin 17A/F inhibitors

Bimekizumab vs. Adalimumab

One study was identified evaluating the efficacy and safety of BKZ compared to ADA (BE OPTIMAL)[200]. This was a phase 3 multicentre placebo-controlled double-blind RCT lasting 52 weeks, with an active comparator (ADA). Participants were randomly assigned through an interactive voice response system (3:2:1, stratified by region and number of bone erosions at baseline) to BKZ 160 mg q4w, placebo q2w, or the comparator (ADA 40 mg q2w), all administered subcutaneously. At week 16, patients who had been randomly assigned to placebo switched to BKZ (160 mg) q4w. At the start of the study, 496 (58%) of the 852 patients were receiving MTX, and 425 (50%) had psoriasis affecting at least 3% of their body surface area (BSA),

this subgroup having a mean PASI score of 8.1 (SD 6.6). Further, 717 patients (84%) had ≥1 bone erosion or a high-sensitivity CRP level of at least 6 mg/l (or both).

The quality of the evidence was rated as moderate using the GRADE system.

At week 16, the percentage of patients who achieved MDA was higher among those treated with BKZ than those receiving placebo (194/431 [45%] vs. 37/281 [13%]; and 63/140 [45%] of those receiving ADA; RR: <0.01, 95% CI: -0.23 to -0.19). At week 24, 209 (48%) of the 431 patients who received BKZ achieved MDA. Patients who switched from placebo to BKZ at week 16 showed improvements at week 24 (MDA: 106/281 [38%]) while 67 (48%) out of 140 patients in the ADA group achieved MDA at week 24 (RR: 1.01; 95% CI: 0.83 to 1.24). Using the GRADE system, the quality of the evidence was rated as high at week 16 and moderate at week 24.

The adverse effects reported were typical of an IL-17 inhibitor, with no new safety concerns.

Other considerations

The BE OPTIMAL study is not a true head-to-head study. It had an active comparator arm in which patients received ADA, but no power calculations were performed to assess the superiority or non-inferiority of the two drugs. In this context, it should be noted that a similar percentage of patients who received BKZ and ADA achieved ACR 50 at week 16 (the primary endpoint; 44% and 46% respectively). On the other hand, a higher percentage of patients who received BKZ achieved improvement in both ACR 50 and PASI 100 at week 16, suggesting that, in bDMARD-naïve patients with PsA and psoriasis affecting ≥ 3% BSA, BKZ may have a similar effect to ADA on the musculoskeletal component and perform better in relation to the skin disease.

The quality of the evidence was rated as moderate due to imprecision, the 95% CIs crossing the line of no effect.

Regarding the risk-benefit balance, evidence shows no significant differences between BKZ and ADA in relation to reducing signs/symptoms of peripheral arthritis and the progression of structural damage or achieving the resolution of enthesitis and dactylitis.

To conclude, regarding the risk-benefit balance, the evidence identified shows that IL-17 inhibitors, except for performing better in relation to skin disease, are associated with similar outcomes to ADA in terms of efficacy/effectiveness and safety.

Based on the group´s experience and the aforementioned data, the GDG considers that IL-17 inhibitors may be used for treating all musculoskeletal domains of PsA (arthritis, enthesitis, and dactylitis) with similar effectiveness to TNF inhibitors, and that they have been shown to be

clearly superior to TNF inhibitors in the treatment of skin disease. These drug groups have a similar safety profile, except for some class effect with IL-17 inhibitors (higher risk of Candida infection and IBD reactivation).

Interleukin 23 or interleukin 12/23 inhibitors

Ustekinumab vs. TNF inhibitors

One prospective RCT was identified (the ECLIPSA trial) assessing ustekinumab (UST) compared to TNF inhibitors (block randomisation, allocation ratio of 1:1) in patients with PsA and active enthesitis defined as at least one tender entheseal site included in the SPARCC enthesitis index who are non-responders to MTX therapy at the maximum tolerated dose (up to a maximum of 25 mg/week) for at least 3 months[228]. Patients were followed up for 24 weeks with visits from baseline and at weeks 12 and 24. Of the 47 patients included, 23 were treated with UST and 24 with TNF inhibitors (ADA, n=10; CZP, n=6; ETN, N=5; and IFX, n=3).

The primary endpoint of the study —resolution of enthesitis as measured by the SPARCC enthesitis index (score of 0) at 24 weeks— was achieved in 73.9% of patients receiving UST and 41.7% of those receiving TNF inhibitors (p = 0.018). The quality of this study is very low, and in this case, it was not possible to calculate the RR. No safety data were provided.

Other considerations: Additionally, the literature search identified the PsABio study which sought to assess the effectiveness of UST at 6 months compared to TNF inhibitors analysing LDA/remission[229]. This is a prospective observational cohort study of patients with PsA who received first- to third-line UST or a TNF inhibitor at 92 sites across 8 European countries. In the final analysis of the 868 participants with follow-up data at 6 months (UST, n=426; TNF inhibitors, n=442), who had long-standing disease and a high mean clinical DAPSA score (31.0 vs. 29.8, respectively), 45.7% of patients treated with UST and 50.7% of those treated with TNF inhibitors achieved clinical DAPSA LDA at 6 months, while 14.9% in the UST group compared to 19.2% in the TNF inhibitor group achieved clinical DAPSA remission. MDA was achieved in 26.4% of patients receiving UST compared to 30.8% of those receiving TNF inhibitors.

Safety data were similar in the two groups. Specifically, 17.9% of patients in the UST group and 20.9% of patients in the TNF inhibitor group experienced at least one adverse event, 3.5% and 1.6% respectively experiencing at least one serious adverse event. The authors concluded that UST and TNF inhibitors showed similar efficacy.

Guselkumab vs. TNF inhibitors

A network meta-analysis was identified, aiming to compare GUS with other biologics used for PsA in terms of safety and joint and skin efficacy[230]. Regarding ACR 20 response, GUS every 8 weeks (q8w) was comparable to IL-17 inhibitors and sc TNF inhibitors, but superior to UST (45 mg), ABA and apremilast, while intravenous GOL achieved a better ACR 20 response than GUS q8w. Similar results were observed for ACR 50 and ACR 70 responses. GUS q8w provided poorer results than IV TNF (that is, GOL and IFX). Results were similar for GUS q4w.

In terms of safety, the comparisons that were significantly in favour of GUS were: GUS vs. IXE 80 mg q2w (RR: 0.76; 95% CI: 0.62 to 0.93); GUS vs. iv IFX 5 mg/kg (RR: 0.68; 95% CI: 0.55 to 0.87); GUS vs. ADA (RR: 0.96; 95% CI: 0.78 to 1.16); GUS vs. GOL 50 mg (RR: 0.78; 95% CI: 0.62 to 0.99); GUS vs. CZP 400 mg (RR: 0.77; 95% CI: 0.62 to 0.99); and GUS vs. apremilast 30 mg (RR: 0.82; 95% CI: 0.68 to 0.96).

Other considerations: The most recent update of this meta-analysis has added comparators not considered in the 2021 SR, namely, RIS and UPA[231]. In terms of ACR 20 response, GUS q8w and q4w ranked 14th and 12th respectively, among 23 interventions and was comparable to most of the other active agents, including RIS, JAK inhibitors, sc TNF inhibitors, UST 90 mg, and most IL-17A inhibitors. Intravenous TNFs and SEC 300 mg obtained a better ACR 20 response than GUS q8w, while only GOL IV showed a better ACR 20 response than GUS q4w. Given the use of a multinomial model, all the conclusions for GUS remained the same for ACR 50 and 70.

Regarding the progression of structural damage as measured by the Sharp/van der Heijde score, GUS q8w and q4w ranked 8th and 3rd, respectively, among 18 interventions. In particular, GUS q4w was better than RIS and ABA. Both GUS doses achieved results comparable to those with most of other agents, including UPA, but were associated with poorer outcomes than iv TNF inhibitors (GOL and IFX).

For PASI 90, GUS q8w and q4w ranked 2nd and 1st, respectively, among 23 interventions and were better than most other agents, including all sc TNF and JAK inhibitors, UST 45 mg, apremilast, and ABA. Further, both doses of GUS were comparable to RIS and most IL-17A inhibitors, but point estimates consistently favoured GUS for this level of response (PASI 90). Given the use of a multinomial model, all conclusions for GUS remained the same for PASI 75 and 100.

The majority of agents were comparable in terms of serious adverse events. GUS q8w and q4w ranked 9th and 6th, respectively, among 23 interventions. Both doses of GUS were associated with better outcomes than CZP 400 mg or IFX 5 mg/kg.

The quality of the evidence was rated as very low in the case of UST due to imprecision, either because the 95% CIs crossed the line of no effect or there was a lack of blinding, in some studies, or to small sample sizes, or the design in others. In the case of GUS, the quality was rated as low to moderate due to the heterogeneity of studies in terms of patients included, duration of treatment, unclear blinding or different lengths of follow-up.

Regarding the risk-benefit balance, the evidence identified shows that results with IL-23 or IL-12/23 inhibitors do not differ significantly from those with TNF inhibitors in terms of efficacy/effectiveness and safety, except in that they achieve a better skin response.

Based on the group´s experience and the aforementioned data, the GDG considers that IL-12/23 and IL-23 inhibitors may be used for treating musculoskeletal manifestations of PsA (arthritis, enthesitis and dactylitis) with comparable effectiveness to that of TNF inhibitors. These agents are clearly superior to TNF inhibitors in the treatment of skin disease. The overall safety profile of these agents seems to be better than that of TNF inhibitors.

Janus kinase inhibitors

Tofacitinib 5 mg/10 mg vs. adalimumab

One RCT was found that assessed the efficacy and safety of TOFA in patients with active PsA who have an inadequate response to csDMARDs (OPAL Broaden)[232]. In this 12-month RCT, patients were randomly allocated (2:2:2:1:1) to receive: oral TOFA 5 mg twice daily (n=107), oral TOFA 10 mg twice daily (n=104), ADA 40 mg as a single dose injected subcutaneously every other week (n=106), placebo with a blinded switch to TOFA 5 mg at 3 months (n=52), or placebo with blinded switch to TOFA 10 mg at 3 months (n=53).

During the 12-month study period, serious adverse events were recorded in 7% of the patients receiving continuous TOFA at a dose of 5 mg, 4% of those receiving continuous TOFA at a dose of 10 mg and 8% of the patients receiving ADA, and treatment was discontinued due to adverse events in 6%, 3% and 4% of patients, respectively.

Other considerations: According to data from the aforementioned meta-analysis, there seem to be no differences between ADA and TOFA 5 mg in the likelihood of achieving an ACR 20 response (RR 1.15; 0.92 to 1.37) or a PASI 90 response (RR 1.42; 0.95 to 2.19), or in the risk of treatment discontinuation due to serious adverse events (RR 0.56; 0.13 to 2.0)[231].

Upadacitinib 15 mg/30 mg vs. adalimumab

The literature search identified an RCT (SELECT-PsA 1)[210] and its subsequent update[233] evaluating the efficacy and safety of UPA compared to ADA in patients with an inadequate response to

csDMARDs. Patients were randomly assigned at a 1:1:1:1 ratio to receive: oral UPA (15 mg or 30 mg once daily), placebo or ADA (40 mg every other week). Of the 1705 patients randomised, 1704 patients received at least one dose of the active drug or placebo (429 received the 15 mg dose of UPA, 423 received the 30 mg dose of UPA, 423 received placebo and 429 received ADA). Overall, 1548 patients (90.8%) completed week 24 of the study while on UPA, placebo or ADA. The baseline demographic and clinical characteristics of patients were similar across all groups. Outcomes in terms of radiographic progression and resolution of dactylitis and enthesitis were similar with each of the two UPA doses and ADA.

The rate of serious adverse events was higher with UPA 30 mg (exposure-adjusted event rate [EAER]: 12.0 events per 100 patient-years [E/100 PY]; 9.9 to 14.3) than with UPA 15 mg (9.0 E/100 PY; 7.2 to 11.0) or ADA (8.9 E/100 PY; 6.8 to 11.3). The rate of adverse events that led to discontinuation of the study drug was lower with UPA 15 mg (4.4 E/100 PY; 3.2 to 5.9) than with ADA (6.8 E/100 PY; 5.0 to 9.0) or UPA 30 mg (7.1 E/100 PY; 5.6 to 9.0).

Other considerations: Although UPA was found to be superior to ADA, this was mainly observed with the 30 mg dose. Given that this dose is not indicated in the SmPC of the drug for treating PsA, the position of the GDG is based on comparisons with the 15 mg dose, taking into account that the primary endpoint was ACR 20 response and that is the basis of the non-inferiority test. The results of the aforementioned SR do not indicate substantial differences between the two interventions[231]. In terms of the likelihood of an ACR 20 response, the RR was 1.02 (0.92 to 1.13); the mean difference in the progression of structural damage as measured by the Sharp/van der Heijde score was negligible [-0.03 (-0.19 to 0,13); and the RR for the PASI 90 response also did not indicate differences between the treatments (1.09; 0.81 to 1.47).

The potentially slightly better performance of UPA 15 mg over ADA in terms of ACR response may be outweighed by the adverse event profile. The long-term safety follow-up study of patients with PsA in the UPA clinical trial programme (comparing patients receiving UPA 15 mg once daily [n=907] with patients receiving ADA 40 mg every 2 weeks [n=429]) showed that patients treated with UPA experienced higher rates of serious infections (EAER: 3.9 E/100 PY; 95% CI 3.1 to 4.9 vs 1.4 E/100 PY; 95% CI 0.8 to 2.5), opportunistic infections (0.5 E/100 PY; 95% CI 0.2 to 0.9 vs 0), and shingles (3.6 E/100 PY; 95% CI 2.8 to 4.6 vs 0.4 E/100 PY; 95% CI 0.1 to 1.1). It should be highlighted that 29 of 93 (31.2%) cases of coronavirus disease 2019 (COVID-19) infections occurring in patients treated with UPA were serious compared to 4/37 (10.8%) with ADA, and 6 (6.5%) cases were fatal in patients treated with UPA compared to none in with ADA. No cases of active tuberculosis were reported in any of the groups. Further, during the

aforementioned long-term safety follow-up study, the rates of adjudicated MACE were comparable in the two groups (EAER: 0.3 E/100 PY; 95% CI 0.1 to 0.6 vs. 0.3; 95% CI 0.1 to 1.0), with aspirin use being a significant risk factor for MACE (HR: 6.26; 95% CI 1.01 to 37.5) in patients receiving UPA. In the 2023 SR by Mease et al., UPA 15 mg ranked 19th among 23 interventions, in terms of the RR of serious adverse events (the drug ranked 1st corresponding to the one with the lowest RR for serious adverse events).

The quality of the evidence was rated as moderate due to imprecision, the 95% CIs crossing the line of no effect or the clinical decision threshold.

Regarding the risk-benefit balance, the evidence identified shows that results with TOFA and UPA do not differ significantly from those with ADA in relation to musculoskeletal outcomes; however, the overall safety profile seems to be better for TNF inhibitors.

Based on the group´s experience and the aforementioned data, the GDG considers that JAK inhibitors may be used for treating all domains of PsA (arthritis, enthesitis, dactylitis, and skin involvement) with a similar effectiveness to that of TNF inhibitors. Before using these agents, however, the EMA recommendations should be followed regarding the assessment of cardiovascular and cancer risk[213].

Equity, acceptance and feasibility of implementation

The GDG considers that, in our setting, there are no marked inequities in access to these bDMARDs or JAK inhibitors.

The group also considers it likely that all those involved in the use of these drugs (health authorities, specialists, and patients) will find their use in clinical practice acceptable, given the good efficacy of all these drugs, and their low adverse effect rates, as well as the experience accumulated over the years in the use of advanced therapies.

On the other hand, antirheumatic therapies, including tsDMARDs and biological therapies, are commonly used in our setting. The experience accumulated over the years by rheumatologists facilitates the introduction and use of drugs for new therapeutic targets.

Outcome assessment by patients

In the GDG's judgement, it is unlikely that there is variability in how patients rate the main outcomes.

Resource use

Searches were not conducted for information on the costs of the drugs assessed, given that this topic is usually deemed to be beyond the scope of CPG recommendations; therefore, the GDG considers that it has insufficient data to make any recommendations on resource use.

Clinical question 13 (Updated)

In PsA, is combination therapy with MTX and bDMARDs or tsDMARDs more effective than using bDMARD or tsDMARD monotherapy?

Recommendations

Recommendation 23: Use IL-17A, IL-17A/F, IL-23 or IL-12/23 inhibitors alone to treat all manifestations of peripheral PsA. Monoclonal TNF inhibitors, especially IFX, should be used in combination with MTX (Strong recommendation in favour)[A].

- ***Recommendation 23.1:*** Combination therapy with MTX can increase drug survival of monoclonal TNF inhibitors, especially that of chimeric TNF inhibitors (Weak recommendation in favour)[A].

[U] Recommendation related to an updated question

The recommendation in favour of combination therapy for PsA is based on combination therapy with TNF inhibitors and MTX having been shown to be more effective than TNF inhibitor monotherapy in rheumatoid arthritis. Although MTX is recommended as the first-line DMARD in PsA, neither EULAR nor GRAPPA recommend its use in combination therapy with a bDMARD in the long term. Nonetheless, the combination of MTX with monoclonal TNF inhibitors has been proposed as a strategy to achieve a better response in patients with moderate-to-severe psoriasis[234]. Further, this strategy has been reported to show greater efficacy than monotherapy in one study[235], and associated with less immunogenicity in another[236].

Quality of the evidence

Little evidence was identified for addressing this clinical question. Only one study reviewed directly compares efficacy and safety between combination treatment (MTX with a bDMARD or a tsDMARD) and monotherapy. All the other studies identified assess the effect of different doses of bDMARD or tsDMARD therapy compared to placebo. In the research designed to address the question, included in an SR retrieved, and its secondary subgroup analysis (with no direct comparisons), the percentage of patients receiving MTX was very variable, and this reduces the level of the evidence as rated by the classification used.

The SR retrieved includes various types of studies (RCTs, population registries and cohort studies) assessing the effectiveness of ADA, CZP, ETN, GOL and IFX at different doses, compared

to placebo. The studies provide secondary information (*post hoc* analysis) on biological monotherapy compared to a biologic plus MTX. The combination therapies showed very limited beneficial clinical effect compared to bDMARD monotherapy[237] (low quality of evidence). Some population-based studies included in this SR reported that drug survival of TNF inhibitors (mainly IFX, but also ADA in some cases) seems to be longer when combined with MTX[238-240] (very low-to-low quality of evidence).

An RCT assessing the effectiveness of GOL at doses of 50 mg and 100 mg compared to placebo has been reported in three publications presenting analysis at weeks 52, 104 and 256. The *post hoc* analysis provides secondary information on the effectiveness of the biological monotherapy compared to the biologic plus MTX. The clinical improvement observed with the combination treatment compared to monotherapy was negligible[241-243] (low quality of evidence).

Two studies were found evaluating the effectiveness of UST 45 or 90 mg at 6 and 12 months, compared to placebo. The percentage of patients achieving a clinical response was greater with MTX use in the case of the 45 mg dose (43.4%) but without MTX use in the group given the 90 mg dose (53.4%). The *post hoc* analysis of the data on response rates does not show significant differences in efficacy between UST as monotherapy (at different doses) and in combination with MTX[244,245] (very low quality of evidence).

2023 update:

A multicentre randomised controlled, non-inferiority phase 3b trial (the MUST trial) also evaluated the efficacy and safety of UST (45 mg or 90 mg) at 24 and 52 weeks in combination with MTX or placebo. UST plus placebo was not inferior to UST plus MTX, according to the DAS28 index at weeks 24 and 52[246]. The SPIRIT-P1 (biologic-naïve patients) and SPIRIT-P2 (patients with an inadequate response to a TNF inhibitor) trials evaluated the efficacy and safety of IXE with and without a DMARD at 3 years. A *post hoc* analysis was conducted to assess the efficacy and safety in three subgroups: 1) IXE monotherapy; 2) IXE and MTX; and 3) IXE and any DMARD (including MTX). The efficacy was similar in the three subgroups: 59.1%, 67.0%, and 66.1% respectively of the treated patients achieved an ACR 20 response at week 156. Inhibition of radiographic progression (only evaluated in SPIRIT-P1) was also similar across the three subgroups[247].

The OPAL Balance is an open-label long-term extension study of TOFA in patients with PsA who participated in the phase 3 OPAL Broaden and Opal Beyond studies. A 12-month substudy included patients from the OPAL Balance study who completed ≥24 months of treatment with

TOFA and received MTX (7.5-20 mg/week). Patients were randomised 1:1 to receive open-label TOFA 5 mg twice a day openly together with either placebo (TOFA monotherapy) or continued MTX (TOFA + MTX), patients being masked to these additional treatments. No differences were found between groups at 6 months: the change in PASDAS was 0.23 (0.08) for TOFA monotherapy and 0.14 (0.08) for TOFA + MTX (treatment difference, least squares mean: 0.09; 95% CI -0.13 to 0.31)[248].

Regarding UPA, pooled data were analysed on patients with an inadequate response or intolerance to one or more non-biologic DMARD (SELECT-PsA 1) or one or more biologic (SELECT-PsA 2) who received UPA 15 mg or 30 mg once daily as monotherapy or in combination with a DMARD for 24 weeks, or placebo. In this analysis, UPA as monotherapy or in combination with a non-biologic DMARD were similarly effective in the treatment of the main clinical manifestations of PsA (peripheral arthritis, enthesitis, dactylitis, psoriasis, physical function and pain) [249].

Concerning ABA, there are only data from secondary (*post hoc*) analyses of the ASTRAEA trial. At week 24, ABA monotherapy was associated with significantly higher ACR 20 response rates than placebo, suggesting that ABA without MTX can be successfully used in patients with PsA who have an inadequate response and/or intolerance to MTX[250, 251].

The KEEPsAKE 2 trial evaluated the efficacy and safety of RIS compared to placebo in patients with active PsA who have an inadequate response or intolerance to ≤2 biological therapies and/or ≥1 csDMARD. Patients were stratified by current DMARD use (0 compared to≥1). The response rates were significantly higher with RIS than placebo, regardless of whether patients received the combination treatment with MTX (51.2% compared to 36.7%) or RIS monotherapy (53.0% compared to 16.0%) [204].

In the FUTURE 2 study, a total of 397 patients with PsA were randomised to SEC 300 mg (n=100), 150 mg (n=100), or 75 mg (n=99) or placebo (n=98). The use of MTX at stable doses was permitted (≤25 mg/week). The ACR 20/50/70 response rates were higher with SEC 300 and 150 mg than with placebo, regardless of concomitant MTX use. In the FUTURE 1 study, based on 606 patients with active PsA who were randomised to SEC or placebo, SEC significantly inhibited radiographic progression at week 24, regardless of whether it was combined with MTX[252, 253].

In the COSMOS study, 289 patients with inadequate response to 1 or 2 TNF inhibitors were randomised to GUS (100 mg) q8w or placebo. The primary endpoint (ACR 20 response) was reached by 44.4% of patients treated with GUS compared to 19.8% of patients treated with placebo (p<0.001); the likelihood of reaching an ACR 20 response at 24 weeks was similar regardless of whether patients received MTX[199].

No efficacy data stratified by concomitant DMARD use have been found for apremilast, tildrakizumab, or BRD.

In the aforementioned studies, the safety profile of bDMARD/tsDMARD monotherapy did not generally differ significantly from that for their combination with MTX[204, 237, 241-254]. Exceptions were the OPAL BALANCE study, in which elevation of liver enzymes was more common with TOFA + MTX[248] and the COSMOS study, in which 37% and 28% of patients receiving MTX had elevated ALT and AST, respectively vs. 28% and 24% of patients receiving GUS monotherapy[207]. Therefore, no valid conclusions can be drawn regarding the efficacy or safety of each biologic combined with MTX compared to bDMARD/tsDMARD monotherapy.

In general, the addition of MTX was not associated with a better clinical response than monotherapy[237]. This lack of difference between monotherapy and combination therapy is clearer with the new molecules than with TNF inhibitors. In the SPIRIT H2H trial that directly compared IXE with ADA, IXE showed a similar improvement in the simultaneous achievement of PASI 100 + ACR 50 and other endpoints, such as MDA, regardless of MTX use. In contrast, ADA markedly increased the treatment response in terms of joint and skin symptoms when combined with MTX[255]. Some patient registries suggest that adding MTX may improve drug survival of anti-TNF monoclonal antibodies (TNF inhibitors), especially in the case of IFX[236-239]. Experts conclude that it is necessary to conduct further high-quality studies designed to evaluate the efficacy of the combination treatment with MTX and bDMARDs/tsDMARDs compared to treatment with bDMARD/tsDMARD monotherapy.

The GDG has issued a strong recommendation in favour, despite the paucity of the evidence retrieved. The clinical experience accumulated over the years, together with the results of the secondary analysis of the clinical trials on various different agents, has led the GDG to agree on this recommendation.

Clinical question 14 (New)

In PsA, what is the efficacy of bDMARDs and tsDMARDs in treating extra-musculoskeletal manifestations (IBD, uveitis and psoriasis)?

Context/Background

The PsA is a chronic inflammatory disease that can be associated with other clinical conditions which include IBD and uveitis, as well as psoriasis. Unlike psoriasis, which has a clear association with PsA, IBD and uveitis are not common.

For this reason, there is uneven knowledge about treatment with bDMARDs and tsDMARDs for these manifestations when associated with PsA. To date, TNF inhibitors, in particular, monoclonal TNFs, have been shown to be effective for treating all three of these extra-musculoskeletal manifestations. On the other hand, IL-23 and JAK inhibitors may be used when IBD is concomitant to PsA.

Recommendations

Recommendation 24: Use TNF, IL-17A, IL-17A/F, IL-12/23 and IL-23 inhibitors for treating psoriasis in patients with PsA and active psoriasis (Strong recommendation in favour)[N].

> ***Recommendation 24.1:*** In patients with PsA and moderate-to-severe psoriasis, the treatments of choice are IL-17A, IL-17A/F, IL12/23 or IL-23 inhibitors, rather than TNF inhibitors (Good clinical practice recommendation)[N].

Recommendation 25: In patients with PsA and active psoriasis, the use of JAK inhibitors can be considered. Patients with moderate-to-severe psoriasis should be assessed jointly by rheumatologists and dermatologists (Good clinical practice recommendation)[N].

Recommendation 26: In patients with PsA and active psoriasis, the use of apremilast can be considered, recalling that it has lower efficacy than bDMARDs or JAK inhibitors (Good clinical practice recommendation)[N].

Recommendation 27: In patients with PsA, do not use abatacept for treating psoriasis, as it has not shown efficacy in this clinical domain (Strong recommendation against)[N].

Recommendation 28: In patients with PsA and IBD, use monoclonal TNF* and IL-12/23, IL-23** and JAK*** inhibitors for managing gut inflammation (Strong recommendation in favour)[N].

**Approved: IFX and ADA in ulcerative colitis and Crohn's disease; GOL only for ulcerative colitis*
*** At the time of drafting the CPG, the only IL-23 inhibitor approved for IBD and Crohn's disease is RIS.*
**** Approved: UPA for ulcerative colitis and Crohn's disease; TOFA only for ulcerative colitis.*

Recommendation 29: In patients with PsA and IBD, do not use IL-17 inhibitors (Strong recommendation against)[N].

Recommendation 30: Given the lower incidence of uveitis in PsA, there is less evidence of the efficacy of these drugs in the treatment of uveitis in this context, and therefore, the GDG suggests following the recommendations given for axSpA (Good clinical practice recommendation)[N]

[N] Recommendation related to a new question

Important clinical considerations:

- Subgroups to be considered
  - *Patients ≥65 years old:* Prioritise options other than JAK inhibitors in ≥65-year-olds, patients who are active smokers (or have a history of heavy smoking), and those who have an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible dose.

Rationale

These recommendations have been made based on the results of SRs and meta-analyses on TNF, IL-17, IL-12/23, IL-23, or JAK inhibitors, or apremilast in which the variable of interest (PASI 75) was the primary or secondary endpoint, and the results have shown statistically significant differences compared to placebo.

Although there are some differences between different TNF inhibitors, IL-17 inhibitors and JAK inhibitors, the GDG believes that recommendations should be made by drug group, as it is not currently possible to demonstrate that small differences between them lead to significant differences in efficacy or safety profile (given a lack of head-to-head clinical trials of different drugs in the same group for treating axPsA).

Detailed rationale

PSORIASIS

BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

TNF Inhibitors

TNF inhibitors vs Placebo

Two SRs were identified assessing the effects of TNF inhibitors in psoriasis in patients with PsA. An SR and meta-analysis was conducted for the 2022 Update of the British Society for Rheumatology guideline for the treatment of PsA that included RCTs evaluating adult patients

who showed an inadequate response/inefficacy to csDMARDS (and were bDMARD naïve) compared to an active comparator or placebo, and assessed the impact of treatment on psoriasis and PASI 75 reponse[256]. The TNF inhibitors evaluated were ADA, ETN, IFX and GOL. They included 9 RCTs (n=1542) and assessments at week 24 of treatment.

Another SR and meta-analysis aimed to determine the effects of bDMARDs on quality of life as assessed by the Dermatology Life Quality Index (DLQI) in patients with PsA[257]. The bDMARDs evaluated were ADA, CZP, GOL, UST, SEC and IXE. They included 7 RCTs in which treatments were compared to placebo (n=3132) and considered a duration of treatment of 12 to 24 weeks.

The overall quality of the evidence was rated as moderate due to unexplained heterogeneity in the results.

Regarding the risk-benefit balance, the evidence identified shows that TNF inhibitors improve psoriasis and psoriasis-related quality of life in PsA.

Based on the group's experience and the evidence gathered, the GDG recommends the use of bDMARDs for treating psoriasis in patients with PsA.

Interleukin 17 inhibitors:

IL-17 inhibitors vs. placebo/IL-17A inhibitors vs. adalimumab/IL-17A/F inhibitor (bimekizumab) vs. placebo

Three SRs were identified evaluating the effect of different IL-17 inhibitors on psoriasis in patients with PsA.

One of them, cited earlier, assessed the effects of two IL-17A inhibitors (SEC and IXE) compared to placebo over 12-24 weeks on the domain of psoriasis and PASI 75 response (n=329)[256]. It also evaluated the effects of SEC and IXE compared to ADA, in patients with plaque psoriasis affecting ≥ 3% BSA at baseline and a PASI 75 response (n=766) or PASI 100 response (n=1183), based on three and two studies respectively.

Another of the SRs cited earlier evaluated the effects of SEC and IXE compared to placebo on the DLQI domain (n=1377) over the same treatment period[257].

Finally, a third SR and meta-analysis evaluated the efficacy and safety of BKZ compared to placebo on the psoriasis domain and PASI 75/100 response in patients with PsA, based on three studies (n=703), with a mean treatment duration of 14.67 weeks.

The overall quality of evidence was rated as moderate due to unexplained heterogeneity in the results or the CIs not overlapping or differing between studies, and the risk of bias from having missed relevant studies, particularly those not published in English.

Regarding the risk-benefit balance, the evidence identified shows that IL-17 inhibitors improve psoriasis and psoriasis-related quality of life in patients with PsA.

Based on the group's experience and the results from comparison studies in patients with psoriasis, the GDG recommends using these drugs as the first-line treatment rather than TNF inhibitors in patients with severe psoriasis.

Il1-12/23 inhibitors

IL-12/23 (ustekinumab) vs. placebo/vs. adalimumab

One of the aforementioned SRs also evaluated the effect of UST compared to placebo in patients with psoriasis affecting ≥3% BSA at baseline on the psoriasis domain and PASI 75 response, based on two studies (n=546) [256]. It also evaluated the effect of UST compared to ADA on the psoriasis domain and PASI 100 response, based on one study (n=47). Another SR evaluated the DLQI response to this drug, based on two other studies (n=943)[257].

The overall quality of the evidence was rated as high for comparing UST to placebo, but low for comparing it to ADA, because of small sample sizes and wide CIs.

Regarding the risk-benefit balance, the evidence identified shows that IL-12/23 inhibitors improve psoriasis in patients with SpA.

Based on the group's experience and the evidence gathered, the GDG considers that IL-12/23 inhibitors can be a treatment option for psoriasis, especially in patients with PsA and mild-to-moderate joint involvement.

IL-23 inhibitors

IL-23 inhibitors vs. placebo

One SR was identified evaluating the effects of various IL-23 inhibitors on psoriasis in patients with PsA.

The SR and meta-analysis evaluated the efficacy and safety of IL-23 inhibitors, namely, GUS, RIS and tildrakizumab, in patients with PsA compared to placebo or an active comparator in treating the psoriasis domain and PASI 90 response, based on six studies (n=2826)[259].

The overall quality of the evidence was rated as moderate due to the risk of bias given the likelihood of having missed relevant studies.

Regarding the risk-benefit balance, the evidence identified shows that IL-23 inhibitors improve psoriasis in patients with PsA.

Based on the group's experience and the evidence gathered, the GDG considers that IL-23 inhibitors are a good treatment option for psoriasis. Tildrakizumab was included in the recommendations, given the results observed and the clinical experience of the GDG dermatologist, despite this agent not being formally indicated for PsA.

Other considerations: In addition, the recommendations from various scientific organisations (EULAR, ACR, GRAPPA, and the Pan-American League of Associations for Rheumatology) support the view that treatment with IL-17, IL-12/23, and IL-23 inhibitors should be considered in PsA in the case of patients with moderate-to-severe psoriasis[182, 221, 260, 261].

Abatacept

Abatacept vs. placebo

One of the aforementioned SRs evaluated the effect of ABA compared to placebo on the psoriasis domain and PASI 75 response, based on one study (n=47)[256].

The overall quality of the evidence was rated as low due to a one-level downgrade for being a study with a relatively small sample size and wide CIs that cross the thresholds of clinical and statistical significance.

Regarding the risk-benefit balance, the evidence identified shows that treatment with ABA does not have any effect on psoriasis in patients with PsA.

Based on the group's experience and the evidence gathered, the GDG recommends against the use of ABA for treating psoriasis in patients with PsA.

Target synthetic DMARDs

Janus kinase inhibitors

JAK inhibitors vs. placebo

One SR was identified assessing the effects of TOFA and UPA (JAK inhibitors) on the domain of psoriasis in patients with PsA[262]. It aimed to evaluate the efficacy and safety of TOFA and UPA compared to placebo and/or an active comparator in patients with psoriasis affecting ≥3% BSA at baseline on the psoriasis domain and PASI 75 response over 16 weeks based on four studies (n=3161).

Tofacitinib vs. placebo/ v. adalimumab

One of the aforementioned SRs evaluated the effect of TOFA compared to placebo in patients with psoriasis affecting ≥3% BSA at baseline on the psoriasis domain and PASI 75 response, based on two studies with a follow-up of 12 weeks (n=234)[256]. Another of the SRs also evaluated this

response with TOFA 5 mg twice daily compared to placebo over 16 weeks, based on two studies (n=330)[262]. In addition, it assessed the effect of TOFA compared to ADA on the psoriasis domain and PASI 75 response over 12 weeks, based on one study (n=229)[256].

Upadacitinib vs. placebo

One of the aforementioned SRs evaluated the effect of UPA compared to placebo on the psoriasis domain and PASI 75 over 16 weeks, based on one study (n=686)[262].

The overall quality of the evidence was rated as moderate due to the wide CIs, moderate heterogeneity between studies or a lack of statistical significance due to the CIs including the null value.

Regarding the risk-benefit balance, the evidence identified shows that JAK inhibitors can be useful for treating psoriasis in patients with PsA.

Other considerations

The EMA recommends that all JAK inhibitors should only be used in the following groups of patients if no other suitable treatment options are available: people over 65 years of age, smokers or former smokers, people with a history of atherosclerotic heart disease or other cardiovascular risk factors, and those with other risk factors for cancer. It also recommends that these drugs should be used with caution in patients with known risk factors for venous thromboembolism other than those listed above. These recommendations apply regardless of the indication for which the drug is prescribed[213].

Based on the group's experience and the evidence gathered, the GDG considers that JAK inhibitors may have a similar effect to TNF inhibitors, and hence, should not be used as the first option in patients with severe psoriasis.

Apremilast

Apremilast vs. placebo

One of the aforementioned SRs evaluated the effect of apremilast compared to placebo on the psoriasis domain and PASI 75 response over 24 weeks, based on one study (n=306) [256].

The overall quality of the evidence was rated as low, due to imprecision given that it was from a single study and the CIs crossed the line of no effect or the clinical decision threshold.

Regarding the risk-benefit balance, the evidence identified shows that apremilast may be useful for treating psoriasis in patients with PsA.

Based on the group's experience and the evidence gathered, the GDG considers that apremilast may be used in patients with mild psoriasis.

INFLAMMATORY BOWEL DISEASE

BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Tumour necrosis factor inhibitors

TNF inhibitors vs. placebo

One of the aforementioned SRs evaluated the effect of TNF inhibitors on IBD in patients with PsA[125]. Its aim was to compare new onset and flares of IBD, in patients with spondyloarthritis treated with TNF inhibitors (IFX, ETN, ADA, CZP or GOL) compared to placebo. The IBD events were independently analysed in psoriasis, PsA and spondyloarthritis. The review included 28 papers on patients with axSpA treated with TNF inhibitors (2559 treated patients and 1697 controls) and considered a treatment duration of 16 weeks.

The quality of the evidence was rated as moderate due to the heterogeneity of the studies and the indirectness of the evidence, in that they included patients with r- and/or nr-axSpA and/or peripheral spondyloarthritis.

Regarding the risk-benefit balance, the evidence identified shows that treatment with TNF inhibitors is not associated with the development of IBD and does not increase the flare rate in patients with IBD and PsA.

Interleukin 17 inhibitors

IL-17 inhibitors vs. placebo/IL-17A inhibitors vs. adalimumab

Two SRs were identified evaluating the effects of IL-17 inhibitors on IBD in patients with PsA. One of them, cited earlier, assessed the risk of IBD flares with a median follow-up period of 16 weeks (n=2076)[125].

The other SR aimed to evaluate the effects of various IL-17 inhibitors (SEC, IXE, BKZ and BRD) compared to placebo and/or ADA on IBD risk in patients with PsA, based on five studies (n=3346)[263], reporting treatment over 12-52 weeks during the randomised period.

The overall quality of the evidence was rated as moderate due to the heterogeneity between studies, the indirectness of the evidence, in that they included patients with r- and/or nr-axSpA and/or peripheral spondyloarthritis, or the risk of bias given the likelihood of having missed relevant studies.

Regarding the risk-benefit balance, the GDG has taken into account that although the evidence indicates that treatment with IL-17 inhibitors does not increase the onset of IBD in patients with PsA, flare-ups in patients with known IBD and cases of new-onset IBD have been reported according to the SmPC, and hence, the GDG recommends against their use in patients with a history of IBD.

Regarding uveitis, no studies have been identified, and hence, the GDG suggests following the recommendations given for axSpA.
For more information, consult the recommendations for the treatment of non-infectious non-neoplastic uveitis not associated with demyelinating disease in Appendix 3 or on the SER website[122].

Other considerations: The latest 2023 EULAR recommendations for the management of PsA suggest using TNF inhibitors, preferably ADA, in patients with uveitis[221].

Clinical question 15 (New)

In PsA, do obesity and/or smoking increase disease activity, accelerate radiographic progression of structural damage and impair treatment response?

Context/Background

Obesity and smoking are harmful factors often present in patients with PsA. Regarding obesity, there is a causal link with PsA, while the link is less clear for smoking. In any case, both factors seem to be associated with poorer outcomes and may influence treatment response in PsA. Regardless of the potential link, both obesity and smoking are modifiable factors that should be included in a comprehensive approach to managing this psoriatic disease.

Recommendations

Recommendation 31: In PsA, encourage smoking cessation and recommend maintaining a BMI between 18.5 and 25 kg/m^2 to improve disease control (Strong recommendation in favour)^N**.**

^{N} Recommendation related to a new question

Important clinical considerations:

- Subgroups to be considered:
  - *Patients who smoke*: these patients should be offered referral to smoking cessation services or their general practitioner, to receive information about such services.
  - *Patients with overweight/obesity*: these patients should be offered referral to weight management services, when available in the health service, or their general practitioner, to receive information about such services.

Rationale

Although the evidence retrieved to address the PICO question related to this recommendation is weak, the GDG has also considered the 2021 EULAR recommendations regarding lifestyle behaviours and work participation to prevent progression of rheumatic and musculoskeletal diseases. These conclude that both smoking and obesity may worsen various outcomes in these conditions, including PsA (grade B recommendation).

Detailed rationale

Smoking:

Smokers vs. non-smokers

Three studies were identified assessing the influence of smoking in PsA.

One study involved a *post hoc* analysis of the FUTURE 2 and FUTURE 5[264] phase 3 clinical trials. It included 1465 patients and evaluated treatment response with SEC compared to placebo as a function of smoking status (current smoker: yes/no). Only patients with at least two measurements of structural damage were included.

Another study included a retrospective cohort of 102 patients, of whom 33 were current smokers[265]. Patient data were collected at baseline and after 6 months of treatment with TNF inhibitors (IFX, ADA or ETN).

The third study recruited a prospective cohort of 2301 patients, of whom 373 were current smokers[266]. It evaluated the 5-year survival of various bDMARDs (ADA, ETN, IFX, GOL, UST and SEC).

The overall quality of the evidence was rated as low for critical outcomes, due to the observational nature of the studies, and very low for important outcomes, due to the studies also having small sample sizes and short follow-up times and the imprecision associated with the CIs crossing the line of no effect.

Regarding the risk-benefit balance, the evidence identified comparing current smokers to non-smokers shows that smoking may increase radiographic progression of structural damage. Smoking may also increase the risk of an inadequate response to treatment (in terms of drug survival and/or treatment discontinuation).

<u>Other considerations</u>

The 2021 EULAR recommendations regarding lifestyle behaviours and work participation to prevent progression of rheumatic and musculoskeletal diseases (RMDs) indicate that people with RMDs should be encouraged to stop smoking and be informed that smoking is detrimental to symptoms, function, disease activity, progression of disease and development of comorbidities in all RMDs (Level of evidence 2a, Grade B recommendation). Nonetheless, the recommendation concerning the potential negative impact of smoking on response to DMARDs only applies to rheumatoid arthritis (Level of evidence 2a, Grade B recommendation) [267].

On the other hand, a *post hoc* analysis of data from the Oral Surveillance trial indicates that patients receiving TOFA who were ≥65 years old or had ever smoked had a higher risk of cancer (excluding nonmelanoma skin cancer), serious adverse cardiovascular events, myocardial

infarction, venous thromboembolism and all-cause death. This finding applies to all indications of the drug, including PsA[212].

Based on the group's experience and the data outlined above, the GDG considers that patients with PsA who smoke should be encouraged to quit this harmful habit.

Weight Categories (body mass index)

Overweight vs. normal weight

Three studies were identified evaluating the influence of overweight compared to normal weight in PsA.

One of the SRs identified[154] includes a study evaluating the survival of ADA treatment in a retrospective cohort of 199 patients with PsA, at 9 years of follow-up[268]. The authors compared patients with overweight (BMI 25-30 kg/m^2) to those with normal weight (BMI<25 kg/m^2) and adjusted the analysis for potential confounders.

Another of the studies included a prospective cohort of 774 patients with PsA who started treatment with their first bDMARD/tsDMARD (a TNF inhibitor in 90.6% of cases), to assess drug survival at 12 months[269]. Similarly, the authors compared patients with overweight (BMI 25-30 kg/m^2) to those with normal weight (BMI <25 kg/m^2) and adjusted for potential confounders.

The third study was a *post hoc* analysis of the ASTRAEA clinical trial, evaluating the impact of baseline BMI on treatment response to sc ABA compared to placebo[270]. Again, the authors compared patients with overweight (BMI 25-30 kg/m^2) to those with normal weight (BMI<25 kg/m^2). Hand and foot radiographs were taken at baseline and 24 weeks. Radiographic non-progression was defined as a change in Sharp/van der Heijde score for PsA of ≤0 at week 24. The analysis was adjusted for potential confounding factors.

The overall quality of the evidence was rated as low due to the observational nature of the studies.

Regarding the risk-benefit balance, the evidence identified shows that overweight may increase TJCs/SJCs and radiographic progression of structural damage comparing overweight individuals to those with normal weight. Overweight may also increase the risk of an inadequate response to treatment (in terms of treatment discontinuation).

<u>Other considerations</u>

The 2021 EULAR recommendations regarding lifestyle behaviours and work participation to prevent progression of rheumatic and musculoskeletal diseases indicate that people with these

conditions should aim for a healthy weight (Level of evidence 5, Grade D recommendation). They also suggest that people with RMDs with overweight or obesity should work with appropriate health professionals to achieve controlled and intentional weight loss through a healthy diet and increased physical activity, as this may be beneficial for RMD outcomes (Level of evidence 2a, Grade B recommendation) [267].

Further, as noted above, *post hoc* analysis of Oral Surveillance trial data on TOFA indicates that age (≥65 years) and a history of smoking are associated with a higher risk of cancer (excluding nonmelanoma skin cancer), serious adverse cardiovascular events, myocardial infarction, venous thromboembolism and all-cause death and that this applies to all indications of the drug, including PsA[212].

Obesity vs. normal weight

Five studies were identified evaluating the influence of obesity compared to normal weight in patients with PsA.

One of the studies assessed a cohort of 160 patients with PsA after 12 months of treatment[271] and evaluated the survival of UST (IL-12/23 inhibitor). Nearly half (49%) of the patients received MTX and 49% corticosteroids concomitantly. The authors compared patients with obesity (BMI≥30 kg/m^2) to those with normal weight (BMI<25 kg/m^2) and adjusted for potential confounders.

The second study included a cohort of 2301 patients with PsA and evaluated the 5-year survival of various biological drugs including TNF inhibitors (ADA, ETN, IFX and GOL), IL-12/23 inhibitors (UST) and IL-17 inhibitors (SEC)[266]. The study compared patients with obesity (BMI≥30 kg/m^2) to those with normal weight (BMI 18.5-25 kg/m^2). The analysis was also adjusted for potential confounding factors.

Three other studies, cited previously, are included in this comparison as they also compared patients with obesity (BMI ≥30 kg/m^2) to those with normal weight (BMI<25)[268-270].

The overall quality of the evidence was rated as low for critical outcomes, due to the observational nature of the studies, and very low for some of the important outcomes, in accordance with the quality assessment conducted by the authors of the SR in which they were included.

Regarding the risk-benefit balance, the evidence identified shows that obesity may increase SJCs/TJCs, comparing people with obesity to those with a normal weight. The evidence is not conclusive regarding whether obesity also increases radiographic progression and/or the risk of an inadequate response to treatment (in terms of treatment discontinuation/drug survival).

Other considerations

As noted above, the 2021 EULAR recommendations regarding lifestyle behaviours and work participation to prevent progression of rheumatic and musculoskeletal diseases indicate that people with these conditions should aim for a healthy weight (Level of evidence 5, Grade D recommendation), and suggest that those with overweight or obesity work with appropriate health professionals to achieve controlled and intentional weight loss through healthy diet and increased physical activity, as this may be beneficial for RMD outcomes (Level of evidence 2a, Grade B recommendation) [267].

Further, as noted above, *post hoc* analysis of Oral Surveillance trial data on TOFA indicates that age (≥65 years) and a history of smoking (ever smoker) are associated with a higher risk of cancer (excluding nonmelanoma skin cancer), serious adverse cardiovascular events, myocardial infarction, venous thromboembolism and all-cause death and that this applies to all indications of the drug, including PsA[212].

Obesity vs. non-obesity

Two studies were identified evaluating the influence of obesity compared to non-obesity in patients with PsA.

One of the studies included a cohort of 1271 patients with PsA naïve to TNF inhibitors with a follow-up of 5142 patient-years[272]. Data were recorded for 3-6 months, patients with obesity (BMI≥30 kg/m^2) were compared to those without obesity (BMI <30 kg/m^2) and the analysis was adjusted for potential confounders.

The other study included 58 patients with PsA and evaluated the survival of UST (IL-12/23 inhibitor) at 12 months of follow-up, comparing the rate of treatment discontinuation in patients with obesity (BMI ≥30 kg/m^2) to that in those without obesity (BMI <30 kg/m^2)[273]. The analysis was not adjusted for potential confounding factors.

The overall quality of the evidence was rated as low for critical outcomes, due to the observational nature of the studies, and very low for some of the important outcomes, in accordance with the quality assessment conducted by the authors of the SR in which they were included.

Regarding the risk-benefit balance, the evidence identified shows that obesity may increase the risk of an inadequate response to treatment (in terms of drug survival) comparing people with obesity to those without obesity. The evidence is not conclusive regarding whether obesity also increases SJCs/TJCs.

Other considerations

As noted above, the 2021 EULAR recommendations regarding lifestyle behaviours and work participation to prevent progression of rheumatic and musculoskeletal diseases indicate that people with these conditions should aim for a healthy weight (Level of evidence 5, Grade D recommendation), and suggest that those with overweight or obesity work with appropriate health professionals to achieve controlled and intentional weight loss through healthy diet and increased physical activity, as this may be beneficial for RMD outcomes (Level of evidence 2a, Grade B recommendation) [267].

Further, as noted above, *post hoc* analysis of Oral Surveillance trial data on TOFA indicates that age (≥65 years) and a history of smoking (ever smoker) are associated with a higher risk of cancer (excluding nonmelanoma skin cancer), serious adverse cardiovascular events, myocardial infarction, venous thromboembolism and all-cause death and that this applies to all indications of the drug, including PsA[212].

7.3 Treatment of axial spondyloarthritis or psoriatic arthritis

Clinical question 16

In PsA and axSpA, is nurse-led health education beneficial?

Recommendations

Recommendation 32: Nurse specialists should participate in follow-up consultations for patients with axSpA or PsA, face-to-face or over the phone, as this increases patient satisfaction (Weak recommendation in favour)[A].

Recommendation 33: Patients with axSpA or PsA who smoke may benefit from nurse-led smoking cessation programmes, as these can increase smoking cessation rates (Weak recommendation in favour [A].

Recommendation 34: Nurse-led educational workshops may be offered before starting subcutaneous treatments, as they help improve treatment adherence (Weak recommendation in favour)[A].

Recommendation 35: Nurses should be involved in addressing patient concerns and helping them complete self-report questionnaires; provided that they avoid influencing patients' opinions and preferences (Weak recommendation in favour)[A].

Recommendation 36: Patients with PsA may benefit from educational programmes, preferably in groups, led by clinical nurse specialists. This would improve self-management of the disease and treatment adherence (Weak recommendation in favour [A].

[U] Recommendation related to an updated question

Patients with axSpA or PsA with peripheral and/or axial involvement have chronic inflammatory processes that tend to cause pain and functional disability, which may lead to the development of mood disorders such as anxiety and depression. All this has a negative impact on their family, social and work lives. There is consensus that health professionals should provide comprehensive and multidisciplinary care, in which nurses play a key role in delivering educational programmes for patients and their families. This includes all structured activities that seek to enhance patient knowledge of topics related to their condition at the individual, group and community levels[274]. Specifically, rheumatology nurses can contribute to educational programmes for patients that help them manage their condition and the associated comorbidities. The key components of such patient education programmes are: the provision of

information and training of patients about the diagnostic procedures used for their condition, treatments, exercise, pain management and joint care[275].

Quality of the evidence

The scientific evidence on the benefits of nurse-led health education in patients with axSpA or PsA is scarce and the majority of studies have been conducted in samples of patients grouped under the labels of polyarthritis, inflammatory arthritis or rheumatic diseases.

One RCT evaluated the effect of clinical consultations led by a nurse or a rheumatologist on disease control in patients with inflammatory arthritis. Follow-up was carried out at 3, 9 and 21 months, and over this period, significant improvements in patient satisfaction were observed in the group with nurse-led follow-up. Nonetheless, no significant between-group differences were found in DAS 28[276] (moderate-to-high quality of evidence). Another study evaluated an educational programme for patients who smoked, with verbal and written advice from the rheumatologist and nurse-led follow-up on the importance of quitting smoking. The smoking cessation rates were 11.8%, 14.4% and 15.7% at 3, 6 and 12 months respectively[277] (very low quality of evidence).

Other studies evaluated programmes managed or delivered by nurses. These included programmes focused on: assessing fear or pain during the administration of drugs using various devices, patients reporting that the information provided by nurses was helpful or very helpful[278] (very low quality of evidence); evaluating nurse involvement in the completion of questionnaires by patients[278] (very low quality of evidence); comparing group and individual counselling to usual care without an educational programme, highlighting the superiority of these programmes[279] (moderate-to-high quality of evidence); and exploring the role of group counselling in increasing rates of adherence in patients starting their treatment[280] (low quality of evidence).

Several studies evaluated the impact of waiting times and patient satisfaction with telephone consultations held by trained nurses, showing that 72% of patients were satisfied with this type of care, and the waiting time fell by 2 months[281] (very low quality of evidence). Another study evaluated the efficacy of an educational intervention delivered by nurses to reduce literacy barriers and improve health outcomes by providing information material written in clear language, compared to usual care, concluding that this type of intervention is associated with improvements from baseline in mental health and self-efficacy[282] (moderate-to-high quality of evidence).

2023 Update

One open RCT evaluated the impact of a nurse-led self-care programme (graduated exercises at home) and self-assessment of disease activity in patients with axSpA. At 1 year of follow-up, results confirmed patients' willingness to continue self-assessing, showed greater adherence to the exercise programme, higher rates of smoking cessation, and a significant decrease in BASDAI scores, and found that the percentage of patients achieving a Patient-Acceptable Symptom State was numerically higher in the education group[283]. Another publication reporting on the same trial evaluated the impact of a systematic comorbidity screening programme assessing five domains: cardiovascular disease, osteoporosis, cancer, infections, and peptic ulcers. After the follow-up, no differences were observed in a comorbidity management score, though the number of patients who followed recommendations on vaccinations, cancer screening, osteoporosis testing and starting vitamin D supplementation was significantly higher in the active group[284].

An SR was identified that aimed to identify nurse-led interventions in patients with RMDs treated with biological therapies. Three main interventions, education, patient-centred care and nurse-led data collection/monitoring, were correlated with high rates of satisfaction with the care received and increased self-care capacity/treatment adherence. The authors concluded that, after a baseline assessment, rheumatology nurses can plan and standardise their interventions focusing on patient education and personalised care based on real needs (such as psychological well-being and disease control); that collaboration between nurses and rheumatologists is extremely important; and that nurse training should standardise, as much as possible, the knowledge and skills required to assess disease parameters[285].

One observational retrospective study evaluated whether various therapeutic patient education programmes improved adherence to TNF inhibitors. The type of education was classified into three models that ranged from only information provision to individual sessions and individual plus group sessions. The last of these models was associated with less adherence than the other two groups[286].

The GDG also considers it appropriate to mention other publications concerning the role of nursing in rheumatology services. The activities may be direct, involving patients and their nurse, or serving as link between patients and their rheumatologists, other health professionals, patient associations or official bodies. With training and prior preparation, the range of activities can be very broad: information provision, patient follow-up with systematic clinical assessment and measurement of metrological parameters and/or questionnaires; participation in

monitoring of adherence, self-administration, correct dosing, adverse effects of treatments and special situations (vaccination); and administration and monitoring of bDMARDs, subcutaneously, intravenously or orally (according to the current protocols and/or consensus). These activities benefit patients, by resolving issues related to their illness, and benefit rheumatologists, by helping considerably reduce their clinical workload[286-292]. Nurses are on the front line of patient care in the event of infections or surgery, as well as in counselling concerning healthy dietary habits, specific exercises, control of cardiovascular risk factors, smoking cessation and restriction, and alcohol intake. They can help transform patients from mere recipients of care into active players in their own care by showing them and their families the attitudes and technical skills needed to cope with their condition and improve their quality of life[47, 293]. The results of the SCORE project presented at the SER and EULAR conferences concluded that nurse-led rheumatology consultations help reduce the number of primary care consultations and improve clinical outcomes and quality of life for patients, as well as increase their knowledge about the disease, their treatment adherence and the perceived quality of the healthcare provided[294].

7.4 General recommendations on patient management

The management of patients with axSpA or PsA should take into account individual patient characteristics (Grade D recommendation).
Before the early initiation of treatment for axSpA or PsA, patients should be appropriately informed about the pharmacological properties of the proposed drugs, treatment duration, expected benefits and potential adverse effects, and patient preferences should be taken into account (Grade D recommendation).
When prescribing treatment, health professionals should consider: age, previous treatments, tolerance, adverse effects, risk of pregnancy and cost-effectiveness, as well as patient preferences (Grade D recommendation).
Patients and their families should be trained in joint care and self-administration of any biological therapy (Grade D recommendation).
Health professionals should provide personalised information to patients with axSpA regarding the most suitable type of exercise (Grade D recommendation).
Health professionals should provide patients with axSpA with information about smoking cessation programmes (Grade D recommendation).
Given the involvement of multiple organs and tissues in PsA, rheumatologists should work closely with other medical specialists (dermatologists, ophthalmologists, and gastroenterologists) to achieve appropriate control of the corresponding extra-musculoskeletal manifestations (psoriasis, uveitis, and IBD). Close collaboration with dermatologists is essential to achieve early diagnosis and treatment of PsA. (Good clinical practice recommendation).

8. Clinical questions (not in PICO format)

In patients with psoriasis, does early pharmacological intervention prevent or delay the onset of PsA?

The majority of patients (>70%) with PsA have psoriasis at the time of their diagnosis. On the other hand, approximately a third of patients with psoriasis eventually develop PsA. For this reason, cutaneous psoriasis is the main clinical biomarker for the diagnosis of PsA, dermatologists playing a key role in the early detection of PsA. Nonetheless, on average, patients with psoriasis and at risk of PsA take around 10 years to develop the joint disease, and therefore, there is a need to define as clearly as possible the different stages that patients go through, from the onset of psoriasis to the appearance of the first signs of arthritis[295].

Certain factors such as obesity, nail disease, psoriasis severity and a family history of PsA are considered to be associated with the development of PsA in the medium-to-long term (8-12 years), while joint pain (not explained by another condition) and/or subclinical findings of synovial/entheseal inflammation on imaging (ultrasound and MRI) identify a subgroup of patients with psoriasis at a high risk of developing PsA in the short term (1-3 years)[295]. These findings are laying the foundations for previously unimaginable concepts such as the prevention or interception of PsA[295].

Both csDMARDs (such as MTX), tsDMARDs and bDMARDs, including TNF, IL-17, IL-12/23 and IL-23 inhibitors, have shown efficacy in reducing the signs and symptoms of both psoriasis and PsA. Assuming that they share pathogenic pathways, it is biologically plausible that the treatment of moderate-to-severe psoriasis is associated with a reduction in the incidence of PsA[296]. The findings of the latest studies related to the question posed -Does early pharmacological intervention prevent or delay the onset of PsA?- are summarised below.

One study found that subclinical enthesopathy detected on ultrasound in patients with moderate-to-severe psoriasis (without PsA) was mitigated by the use of UST, an IL-12/23 inhibitor. In particular, the mean ultrasound-based inflammation scores significantly decreased by 42.2% from week 0 to 24 and 47.5% by week 42[297]. A prospective open-label single-arm study (IVEPSA) evaluated the effects of SEC (IL-17A) on inflammatory and structural changes detected on MRI or high-resolution peripheral quantitative computed tomography in peripheral joints of patients with psoriasis and joint pain (but no clinical signs of PsA). In the 20 patients included, joint pain significantly improved after 24 weeks of treatment; further, MRI-based global and synovitis scores significantly improved, while no erosion or enthesophyte progression was

observed[298]. These studies are evidence of the potential utility of interventions in patients with psoriasis at a high risk of PsA in the short term (intervention for disease interception).

What is known about the incidence of PsA in patients with psoriasis treated with systemic therapies?

Several studies addressing this issue have been published recently. One of them reported an annual incidence of PsA of 1.2 cases (95% CI: 0.77 to 1.89) in patients with psoriasis receiving biological therapies compared to 2.17 cases (95% CI: 1.53 to 3.06) per 100 patient-years in those treated with phototherapy. Specifically, treatment with bDMARDs was associated with a lower risk of incident PsA (adjusted HR 0.27; 95% CI 0.11 to 0.66)[299]. Similarly, in a cohort of 1719 patients with psoriasis, it was found that the risk of developing PsA was significantly lower in patients treated with biologics (IRR 0.26; 95% CI 0.03 to 0.94), compared to those only treated with topical medication, though not compared to those treated with csDMARDs (IRR 0.35; 95% CI 0.035 to 1.96; p = 0.1007). In that study, the adjusted Cox proportional hazards regression analysis showed that the use of biologics protected against the development of PsA (adjusted HR 0.19; 95% CI: 0.05 to 0.81)[300]. Another study evaluated 203 patients with psoriasis referred for musculoskeletal symptoms and found that the rate of onset of PsA after starting treatment for psoriasis was lower in patients receiving systemic therapies (12% with biologics and 9.6% in csDMARDs) than in those receiving topical medication or no therapy (37.4%, p < 0.001), suggesting a reduction in the risk of *de novo* PsA in patients receiving systemic therapies. Moreover, none of the patients with biologic-treated PsA developed dactylitis compared to 28.6% of those receiving csDMARDs and 48.6% of those receiving only topical medication or no therapy[301]. Another case-control study compared patients (not diagnosed with PsA) who did and did not receive a biological therapy for psoriasis (n=663 in each group)[302]. The risk of developing PsA was significantly higher in the control group (adjusted HR 1.39; 95% CI: 1.03 to 1.87) than the biologic-treated group over 10 years of follow-up [8].

Nonetheless, not all research on this topic points in the same direction as the aforementioned studies. A retrospective cohort study of more than 190,000 patients with psoriasis but without PsA found that, unlike the aforementioned studies, the use of biologics was associated with the development of PsA in patients with psoriasis[303]. Nonetheless, these findings may be explained by bias, such as confounding by indication or protopathic bias, which occurs when a drug is inadvertently prescribed for an early manifestation of a disease that has not yet been detected but is already present at the time of the prescription.

Finally, one may wonder whether the potential protective effect of biological therapies against the development of PsA differs between the types of biologics used to treat psoriasis. A recent retrospective cohort study of over 15,000 patients with psoriasis receiving different biologics showed that the risk of developing arthritis was significantly lower when treated with IL-12/23 (adjusted HR 0.58) and IL-23 inhibitors (adjusted HR 0.41) than with TNF inhibitors. The reduction in the risk of arthritis did not differ significantly between IL-17 and TNF inhibitors[304].

Conclusions: Although there is some evidence that intervention during the subclinical phase of the disease (interception therapies) and intervention in patients with psoriasis at risk of developing arthritis (prevention therapies) may reduce the incidence of PsA, this evidence is still too limited (mostly from retrospective observational studies) to make a general recommendation. The analysis of the influence of systemic treatments in the transition to or prevention of PsA is complicated by various issues. First, patients need long-term longitudinal follow-up because arthritis generally develops several years after the diagnosis of psoriasis. Further, diagnostic accuracy in PsA is difficult to assess (verification bias) due to the heterogeneity in the presentation of the disease and the lack of specific biomarkers. Further, the various domains of PsA may respond differently to the different therapies. The association between systemic therapy and the development of arthritis can also be distorted by confounding by indication (that is, the reason for receiving one treatment, such as severe psoriasis, is also associated with the result of interest, namely, PsA), together with likely protopathic bias (that is, a drug being inadvertently prescribed for an early manifestation of a disease that has not yet been detected but is already present). Therefore, until more research based on well-designed prospective studies or clinical trials is conducted, it cannot be firmly concluded that early systemic treatment prevents or delays the onset of PsA in patients with psoriasis.

Is axial spondyloarthritis the same as axial psoriatic arthritis?

In recent years, a debate has arisen regarding the concept of axPsA corresponding to a diagnosis of PsA and involvement of the sacroiliac joints and/or spine, which also includes psoriatic spondyloarthritis[305-307]. This debate focuses on the differentiation between axPsA and axSpA, with or without cutaneous psoriasis.

The lack of an agreed terminology and definition of axPsA is a problem for its classification and is an unmet need[308].

The main area of genetic overlap between axSpA and PsA (axial or otherwise) is HLA-B*27, more than 80% of patients with axSpA and around 20-30% of patients with PsA being positive for this antigen. On the other hand, symmetric sacroiliitis, typical of axSpA, is associated with the HLA-B*27:05:02 allele, while asymmetric sacroiliitis, typical of axPsA, is associated with the HLA-B*08:01–HLA-C*07:01 haplotype[309]. It should be highlighted that HLA-Cw6 and IL-23R variants are also implicated in axPsA. Therefore, it seems that axPsA has a closer association with genes other than HLA-B*27, while axSpA is strongly associated with this gene.

Regarding clinical and demographic manifestations, it has been described that patients with axSpA are more likely to be men and HLA-B27 positive and have more severe axial manifestations and milder peripheral arthritis than patients with axPsA[310]. Inflammatory lower back pain is less common in patients with axPsA than those with axSpA, and it can even be asymptomatic despite inflammation of the axial skeleton. Nonetheless, the typical symptoms of axPsA tend to include spinal pain at any level, especially in the neck.

A study based on data from the REGISPONSER registry found that patients with axPsA were more commonly women and had a shorter disease duration and diagnostic delay than patients with axSpA and psoriasis. Inflammatory lower back pain, alternating buttock pain and uveitis were more common in the group with axSpA with psoriasis, while peripheral arthritis and nail disease were more common in patients with axPsA. Therefore, it can be concluded that the clinical expression of axPsA is different from that of axSpA with or without psoriasis[311].

Radiographic findings can also help differentiate between axPsA and axSpA. The latter often shows specific changes on radiographs, such as symmetric sacroiliitis, syndesmophytes and a bamboo-like appearance[308]. Radiographic sacroiliitis is also a common feature of axPsA and occurs in between 25% and 50% of patients with PsA, but in up to 70% of cases, it is assymetric[312]. Moreover, these patients more often show only spinal involvement, with no involvement of sacroiliac joints, as well as a greater involvement of the cervical spine than patients with axSpA[313]. Non-marginal syndesmophytes are also more common in patients with axPsA than in patients with axSpA[307].

NSAIDs, physiotherapy and exercise are recommended to control symptoms and improve function in both conditions. Further, both TNF and IL-17 inhibitors have shown efficacy in the treatment of axSpA and axPsA. On the other hand, IL-23 inhibitors are efficacious in PsA, but not axSpA, suggesting differences in the pathophysiology of these conditions. Although clinical trials with IL-23 inhibitors in patients with PsA have shown improvements in clinical measures of axial disease, such as the BASDAI, it is known that such indices are not specific for axial inflammation and the findings may have been more due to improvement in general PsA symptoms, even if the drug has not been effective in treating inflammation of the axial skeleton[314]. Therefore, these

data do not support the use of IL-23 inhibitors in patients with axPsA, as these drugs have not shown to be effective in axSpA. A specifically-designed clinical trial is currently underway to assess the efficacy of IL-23 inhibition in treating axial disease in PsA; it is expected that its results help to advance this debate[186].

In conclusion, axPsA and axSpA with or without psoriasis are considered different diseases, but they are related and share certain clinical features, which can complicate their diagnosis and treatment. Although axPsA and axSpA with psoriasis are both characterised by inflammation of the axial skeleton and may have overlapping symptoms, they are different entities, with different pathophysiological mechanisms and different associations with related illnesses (IBD, psoriasis, and uveitis).

To better understand axPsA, larger prospective studies are required, in patients with PsA who undergo detailed clinical, genetic and imaging assessments. Such studies are underway under the auspices of the ASAS and GRAPPA. Further, disease-specific clinical trials need to be conducted in patients with axPsA to evaluate the efficacy of different drugs in this group of patients.

Which outcome measures are appropriate for assessing the efficacy of biological therapy in patients with PsA or axSpA?

Psoriatic arthritis

Current recommendations on the management of patients with PsA aim to achieve a reduction in disease activity or remission. The evaluation of therapeutic efficacy in PsA tends to be complex given its clinical heterogeneity, and that a transition may occur between clinical phenotypes during the course of the disease, as well as the diversity of measurement instruments proposed. Over the past decade, questionnaires have been developed to measure quality of life and disease impact, and they are very useful for integrating patients' perspectives into the assessment of health outcomes. Further, composite indices have been developed to capture activity across the multiple clinical domains that characterise the disease (musculoskeletal and skin involvement, pain and function).

The combination of clinical response indices (DAPSA or MDA) and PROMs (such as the Psoriatic Arthritis Impact of Disease [PsAID]) have been proposed to decide whether a given biological therapy should be maintained. Nevertheless, there is no consensus on how to evaluate remission or low disease activity.

The DAPSA score is a feasible validated specific tool for evaluating disease activity in patients with PsA. Its main strength is that it explores many joints that are typically affected in PsA but are not included in the DAS 28. Other variables include: systemic inflammation (CRP), pain and patient global assessment of disease. Although DAPSA does not cover skin involvement, dactylitis or enthesitis, it shows a good correlation with the progression of joint damage and patient functional deterioration.

The MDA score evaluates MDA based on seven criteria of which five or more have to be met (TJC ≤ 1, SJC ≤ 1, enthesitis count ≤ 1, PASI ≤ 1 or BSA score ≤ 3%, patient's global visual analogue scale ≤ 20 mm, patient's pain visual analogue scale ≤ 15 mm and HAQ ≤0.5). This score is a continuous measure of disease activity and is useful to assess whether patients are in an MDA.

A questionnaire that measures the impact of PsA is PsAID. It is the most widely known PROM and has been developed from a patient´s perspective, covering almost all the core domains. It has been validated in clinical trials as well as observational studies. Two versions have been developed: one for use in clinical practice that covers 12 domains (PsAID-12) and a shorter one for clinical trials (PaAID-9). This questionnaire is a discriminative instrument that is both reliable and feasible in patients with PsA, allowing measurement of stable and active disease. Further, the separate components of PsAID have been strongly correlated with other specific PROMs,

such as the assessment of the skin in the DLQI, fatigue, etc., indicating that the PsAID is able to evaluate various domains of the disease.

Nonetheless, as well as using DAPSA, skin activity, dactylitis, and enthesitis should be assessed in parallel.

Axial involvement is less common in patients with PsA but, when it does occur, it is likely to be associated with severe psoriasis, higher TJC and impairment in quality of life and physical function. No specific composite indices are yet available for measuring axial involvement in PsA, and until developed, clinicians may employ instruments for axSpA, such as BASDAI and ASDAS. The BASDAI should be used with caution in axPsA, as five of its six items are not specific to axial involvement.

The ASDAS is a composite score that uses some items of BASDAI, together with objective variables such as CRP level and erythrocyte sedimentation rate. Several studies have suggested that this score could be a valuable tool for measuring disease activity and defining clinical remission in PsA.

The GRAPPA-Outcome Measures in Rheumatology group recommends using ASDAS (plus PsAID) in patients with prevalent axial involvement because it includes both objective and subjective measures. The MERECES group reached a consensus on the use of PsAID to evaluate the effects of biological therapy on health-related quality of life, specifically, MDA plus PsAID for peripheral PsA and ASDAS plus PsAID for axPsA.

Axial spondyloarthritis

The outcome measures related to disease activity, physical function and quality of life which are commonly used in axSpA include:

BASDAI: this index evaluates overall disease activity in axSpA, taking into account parameters such as pain, stiffness, swelling and fatigue.

ASDAS: this score is used to evaluate treatment response in patients with axSpA and can also be used to define an inclusion criterion in clinical trials. In addition, it is used to monitor patients over time and adjust treatment as appropriate.

ASQoL: this questionnaire evaluates the impact of the disease on a patient´s quality of life, addressing factors such as pain, mobility, mood and limitations in activities of daily living.

Assessment of SpondyloArthritis International Society Health Index (ASAS-HI): this 17-item index is used to assess health and health-related quality of life in patients with axSpA. It is complementary to BASDAI and other indices used in the assessment of axSpA.

To summarise, treatment response is currently evaluated using a combination of indices that assess inflammatory activity such as ASDAS with CRP (ASDAS-CRP), and less often BASDAI, and quality-of-life questionnaires such as ASQoL and ASAS-HI.

What was the impact of COVID-19 on the care of patients with PsA and axSpA?

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19, the global spread of which led to a pandemic that resulted in the imposition of lockdowns across the world. COVID-19 presents with varying degrees of severity, ranging from asymptomatic infection to death. The severity of the disease was associated with being male, being older, hypertension and immunosuppression.

The impact of COVID-19 on PsA and axSpA has been evaluated by assessing the prevalence and severity of the infection in patients with these diseases, and their immune response to infection and vaccination, as well as the effects on healthcare management[315-322].

In general, studies on this topic have concluded that inflammatory arthritis does not seem to make individuals more prone to SARS-CoV-2 infection or more severe COVID-19. Further, it has been reported that biological therapies, including TNF, IL-17, IL-12/23 and IL-23 inhibitors do not increase the rate or severity of the infection. In contrast, corticosteroid therapies are associated with greater severity of COVID-19.

Several studies[323-330] have demonstrated a poorer humoral response (production of antibodies) after immunisation by vaccination in patients with rheumatoid arthritis, axSpA and PsA treated with TNF, IL-17, or JAK inhibitors and/or MTX than healthy people after a first dose of the vaccine, but normal concentrations of antibodies after the second dose. All the drugs seem to influence humoral response after vaccination but do not affect cellular immune response. Nonetheless, in these cohorts of patients, antiviral antibodies disappear earlier than in the general population; this warrants administering at least two doses of vaccine in these patients and the recommendation to give booster doses to restore the immune response against the virus.

The safety of the vaccines in patients with these conditions has also been assessed. It has been found that vaccine tolerance (in terms of the rate of reactions) is similar to that in the general population and vaccines do not increase arthritis flare rates[331-333].

Regarding the management of care for these patients during the COVID-19 pandemic, in the first phase, consultations and diagnostic tests were cancelled and treatment and key disease

management decisions were postponed[334]. In this difficult context, patients' associations for rheumatic diseases strengthened their efforts to provide reliable information and support services, preventing or reducing the harmful effects of the lockdown and promoting healthy lifestyles[334]. The REUMAVID consortium[335, 336], an international collaboration led by the Health & Territory research group at the University of Seville, conducted an online survey that collected data on the impact of the COVID-19 pandemic. This study collected a substantial volume of interesting data confirming that patients perceived a reduction in healthcare access, an increase in harmful habits, and a deterioration in well-being and mental health. On the other hand, several telemedicine-based healthcare models were deployed, and these were well accepted and covered, even if only partially, healthcare needs during this complicated period[337-341].

In conclusion, patients with PsA and spondyloarthritis do not have a higher risk of developing SARS-CoV-2 infection or more severe COVID-19, despite their rheumatic condition and the immunosuppressive therapies they receive. Further, vaccination is effective and safe in these patients, although they should be given at least two doses. The critical situation during lockdown did have a substantial impact on the care of patients, leading to a deterioration in their mental health and well-being, especially during the first phase. On the other hand, the implementation of telemedicine and the work of patients' associations made it possible to meet patients' essential needs during this pandemic.

9. Perspective of patients with PsA and axSpA

"The disease, an invisible companion for life"
(Reflection of a patient)

It is important to gather information on how patients perceive and understand their diseases. The perspective of patients with axSpA and PsA has been incorporated in this CPG through the direct participation of two patients in the GDG, reviewing the existing scientific studies on this topic and directly asking patients who have volunteered to share their experiences and concerns.

Systematic review

A review was conducted of scientific evidence available from qualitative and quantitative studies that gathered data on the concerns, worries, and needs of patients (adherence, quality of life, etc.) regarding treatment, or investigated the areas in which patients, their families, and caregivers need more information and support.

Below, we summarise the information gathered by reviewing the studies selected.

The diagnosis	
The period between the onset of symptoms and the definitive diagnosis is long and tedious for patients and is described as distressing and discouraging. There are feelings of frustration due to the pain experienced, sleep problems, and not knowing why. The diagnosis of the disease is life-changing for patients, their caregivers and their families and the difficulties they sometimes face in obtaining the correct diagnosis have a psychological impact on them. This phase involves going through a period with symptoms that have no name, but have consequences for all aspects of their life; because -until they have a diagnosis- they are unable first to understand what they are going through and second explain it to others, as well as know how it is going to affect their future. The diagnosis brings a sense of relief knowing that there is a name for what they have and ending the uncertainty about the type of disease it is. After this, however, there is another stage; characterised by worries and negative expectations about managing the rest of their lives. Patients start to think about whether in a few years they will be less independent and require more help from others in their daily life[342-350]. **Hereditary disease:** In relation to the diagnosis, another issue is the uncertainty felt by patients about whether their disease is hereditary. They are mortified by the thought that another member of the family may have the disease and this thought causes concerns in the family. The thought of being "patients for ever" causes	**4 expert opinion documents** **Q+, Q++**

them anxiety; although some patients get the message that their disease is not inherited. Research underlines the importance of clinicians' role in this regard. Health professionals can address this uncertainty if they know how to explain to patients, in simple words and with empathy, the possible role of genetic background[351, 352].	
Disease symptoms	
General tiredness (fatigue) and weakness (asthenia): Fatigue and asthenia are among the main symptoms. For patients, this implies having unfamiliar bodily sensations that are unpredictable and uncontrollable ("like having another body"). These feelings tend to appear suddenly, without a clear cause related to having made an effort that might explain them. Some things that are well tolerated one day, become unbearable another. For this reason, it is difficult for people around them to understand. Asthenia is described as a lack of energy and persistent general weakness that makes it difficult for individuals to carry out their daily activities, especially their work but also their family roles. Mothers identify their problems and highlight the difficulty of managing the burden of caring for their children. Fathers describe a major change in their family lives, finding it difficult to play with their children, a problem that is added to having a lack of energy to help with household chores. Nonetheless, the majority of patients find ways of coping with these problems. Among them, they highlight resting and sleeping, adjusting their level of activity and avoiding stress, breaking hard tasks down into smaller ones, and asking other family members for help. They also ask for more research into non-pharmacological options for counteracting asthenia and fatigue[343, 345, 353-358]. **Pain:** The main characteristic of this symptom is patients' difficulty describing it. They agree it is something that causes distress, due to the uncertainty about how long it will last, and that scares them because they know it will come back. People's relationship with their body changes when pain becomes chronic, that is, when there is no chance of going back to a state without pain. Daily life with pain becomes routine; it becomes "part of the family". A regular companion that paradoxically makes the body feel more dominant than it should, instead of remaining silent. For patients with PsA, the pain is worse than the skin lesions. Patients are aware that it is a symptom, something that only they feel, as it is invisible. Often patients feel that people around them do not believe they are suffering and that this scepticism is present in family, clinical and social spheres[347, 359]. **External appearance:** Patients, especially those with PsA, perceive a stigma related to the "visibility of the disease". And this visibility has two components: as well as skin patches, joint changes may be visible[360].	**Q+, Q++**

Treatment	
Before starting a prescribed treatment, patients seek information on the drugs, by either asking clinicians themselves, reading the drug's SmPC or searching on the Internet. Patients are scared of so-called new drugs, in particular, biological therapies. Thanks to them, most patients report improvements in their functional capacity and ability to work. But they keep on saying that they find other symptoms of the disease difficult and express the need for occupational therapy. Patients understand that to follow the treatment prescribed (treatment adherence) they need to trust their rheumatologist. The most effective way to strengthen the knowledge and change the perceptions of patients regarding medications is through open communication with the rheumatologist based on trust[361-364].	**Q+, Q++**
Living with the disease	
Living with spondylitis: Patients consider spondylitis to be a fluctuating disease. At some points, it lets them lead a more or less normal life. To achieve this, they have to change some daily habits to enable them to move better and avoid overexertion or opt for less high-impact sports activities. At other points, patients have to slow down their activities because, for example, they feel stiffer and more tired (fatigue) or weak (asthenia). And there are times when they have to take a break from their activities because the pain becomes unmanageable [363, 365]. **Living with psoriatic arthritis:** The manifestations of PsA have a major impact on patients' quality of life[366]. For patients with PsA, a disease flare is much more than joint inflammation. In the early phases, patients learn to identify a pre-flare state. With time, they even learn to manage triggers and pre-flares to prevent progression to a full flare, whether with self-management strategies or medication. Nonetheless, they also recognise that sometimes it is impossible to stop flares[367]. Although both men and women have PsA, sex plays a role, the disease and its various clinical manifestations having a greater impact in women; and this is a factor that should be considered in the management of the disease. Further, misconceptions about the disease cause some people to experience a significant increase in distress and adopt ineffective coping styles (e.g., avoidance/blocking)[368-370]. **Management of the disease:** The disease is managed differently depending on the time since the diagnosis. Patients who have lived with the disease for longer cope better. They know what adjustments they have to make in their day-to-day life to cope the best. More recently diagnosed patients find it harder to make these adjustments.	**3 descriptive studies** **Q+, Q++**

In general, the factors identified as most important are adopting a positive attitude, learning to live with the disease, and not caring so much about what others think, as well as learning to adjust the medication and manage it, until everything becomes part of one's daily routines[359, 371, 372]. **Changes in the perception of the person or the "self":** These diseases bring out feelings of vulnerability in patients. And in relation to this, the issue of difficulties in continuing to play family roles stands out. The pain, asthenia, fatigue, lack of mobility and physical limitations all hinder patients' ability to fulfil the role of parents or grandparents in caring for children and grandchildren. It is a more pronounced trait in men, for whom the satisfying feeling of being superheroes (a superman capable of everything) disappears and this is a significant blow to their masculinity. The disease influences their ability to be the ideal father, as expected of them according to socially established norms. As well as all this, they end up in a situation that regularly reminds them that they are ill, with feelings of guilt and indignation because they are not able to do certain things, not able to continue working or have to stay at home[345, 373]. **Work:** The symptoms of these diseases described above, such as tiredness/weakness, and their invisible, fluctuating, and unpredictable nature are obstacles that create problems for these patients or hinder them from working. Two major factors are highlighted: - The workplace environment: difficulties getting to and from work, and premises not being adapted to meet their needs - The difficulties in interpersonal relationships at work: bosses and colleagues having a poor understanding of their illness. Patients hide (or are reticent to discuss) their health problem or illness from bosses due to fear of losing their job, stigmatisation, or suffering negative reactions from colleagues; "like kind of wearing a mask, to hide the arthritis, pretending everything was fine." Patients understand that continuing to work brings significant emotional changes for them. Feelings of guilt, sadness, and depression arise due to the losses and limitations caused by their illness. But they prefer to work, even though it means giving up other things they also think are important. They also describe some solutions that would help or facilitate the situation: greater flexibility in working hours and conditions or well-designed ergonomic changes under the supervision of a professional therapist) [355]. **Social Relationships:** These diseases have a marked impact on social relationships. Negatively, patients highlight their friends finding it difficult to understand their illness, especially if they do not have visible symptoms. This makes them suffer because, little by little, relationships with long-term friends fade away.	

On the other hand, a positive aspect is the chance to build new relationships with other people who also have the same illness and who therefore understand them[345, 347, 374]. **Sexuality:** This type of illness also has a negative impact on patient´s sex lives. The most limiting factors are tiredness and weakness, closely followed by joint and muscle pain. In addition, particular emphasis is placed on the influence of the high levels of anxiety and depression with which they live[356, 357]. Patients understand that sexual function is an important element of quality of life and that there is an association between sexual problems and poor health quality or status. In turn, tiredness, low levels of energy, poor mental health, and limitations in daily life roles due to physical problems or poor physical functioning may be evidence that poor quality of life is another of the reasons why there are problems during sexual relations[375].	
Relationship with health professionals	
Patients have a positive experience with health professionals, but they also express their needs in this regard. They expect clinicians to see and listen to them and be accessible; and they want there to be mutual trust[376].	**Q+, Q++**
The caregivers' perspective	
Living with people with spondylitis or PsA may sometimes be hard for family members or caregivers. The role of caregivers is crucial because they give patients physical and emotional support. On the other hand, caregivers and family members also need to make major changes in their activities of daily living and leisure. And this has some repercussions: - Psychological issues: emotional burden, feelings of guilt, discouragement - Work-related problems, related to their inability to go to work due to caring duties - Effects on relationships and social networks: reduction in leisure and recreational activities Caregivers understand that the burden grows as patients become less independent. They also highlight the lack of institutional support available to them[342, 377].	**Q+, Q++**
Need for information and education for patients	
The main sources of information about the disease used by patients are: the internet, followed by written information provided by hospitals and then information provided by other health professionals who care for them. Regarding patient profiles, women tend to seek more consultations, while elderly people tend to be happier with the quantity of information provided.	**3 descriptive studies** **Q+, Q++**

Patients consider it important to have information about the prognosis of the disease. They expect it to be presented in an encouraging but realistic manner. And they want to know how they may be able to adapt to life with a chronic condition[145, 345, 346, 378]. They also note the need for education, in particular about self-care, management of their feelings and the process of their illness[379].	
Communication	
Patients consider it really important to improve the quality of communication between them and health professionals. Although a vast majority of patients and clinicians are satisfied with the doctor-patient relationship, some patients sometimes feel that the impact of the disease on them is underestimated by clinicians. The quality of the interaction can improve when clinicians take into account factors that reflect the experience of living with a chronic disease. (PROMs); concepts such as isolation, depression, fatigue and relationships with others[380-382].	**3 descriptive studies**

Qualitative study

To explore the experiences with these diseases in patients in our cultural context, a primary qualitative research study was conducted, involving a focus group and an in-depth interview with patients with axSpA or PsA. The data gathered were analysed and the results were interpreted to identify the key issues for our patients. All of this is used to complement the data collected in the systematic review of the literature.

The main conclusions of the qualitative research are summarised in the following table:

Categories	Analysis
Diagnosis	***The ordeal*** The identification of the disease becomes a real ordeal for patients. It can be described as a pilgrimage from doctor to doctor and seeking treatments with a soothing effect. It all starts with the general practitioner, then a physiotherapist, and sometimes a traumatologist, before a proper diagnosis is made. All this drains patients' emotional and physical energy. *"You go to the general practitioner and they blame it on lower back pain."* *"My general practitioner and the traumatologist said it was just an injury. They gave me injections, which worked for a while … they sent me to a surgeon, who cut it open, cleaned it up a bit and asked if I wanted to have my finger amputated. Until the penny dropped and someone referred me to a rheumatologist."*

	"I have had problems since I was young, even during military service, I had problems because I couldn't keep up with the others … after a check-up in the military hospital, they told me: 'go away, you are just a lazy sod'. I was told it might be sciatic nerve pain, or perhaps a herniated disc; maybe I should have surgery, maybe not." ***Impact and relief*** Getting a diagnosis means being able to give a name to the condition, which in itself is a great relief for patients. *"At last, you know what you have got! ... It is really important that they give it a label. You know then that there is going to be a treatment."* *"I didn't know what ankylosing spondylitis was; it was a challenge to even learn the name. But now, it gives me great comfort to help others by sharing my experience."* Later, the process of taking in that one has a chronic condition and the difficulty of accepting it have a major emotional impact on their lives. *"When they tell you, you don´t know how to ask the right questions, it washes over you like a tidal wave: is this for life?"*
Prognosis **Follow-up**	***A companion for life*** Patients´ concerns revolve around the chronic nature of the illnesses. *"The shock of the diagnosis leaves you bewildered. Then, when they explain to you that you have a degenerative disease, that it's for life, it makes you think. At first, you ask yourself: 'Can I do something, is there anything I can do to make it go away?' They tell you that there is nothing you can do."* *"It is difficult to accept that you are going to have to live with this condition forever."* ***Uncertainty*** Patients repeatedly ask for improvements in the information from health professionals concerning the disease course and their prognosis and how it is provided. The short clinical appointments would be less of an issue if doctors were more sensitive. *"Doctors have appointments that last no more than 10 minutes. You leave with loads of questions you don't even know how to ask. The concerns come when you get home."* *"Leaving aside the illness itself, which they have to tell you about, they could also explain that it will progress in various ways … The [doctor's] attitude makes a huge difference, even if they tell you that you may end up in a wheelchair."* *"You don´t know how your condition is progressing, whether it is going well or badly until some time has passed."*
Clinical manifestations,	***Living with pain and getting used to it*** Although spondylitis and PsA have specific features, they share certain symptoms. In both cases, pain is seen as the main symptom in terms of the negative impact on their quality of life.

Signs and symptoms	*"I had joint pain, … above all, backache which stopped me sleeping… Sometimes my arm hurts so much it's as if it was being torn off."* *"Thanks to the physio and the painkillers the doctor gave me, I got some relief, but it wasn´t enough."* *"I have other health problems, but spondylitis is the most painful. It is a very unpleasant illness that causes a lot of pain."* *"When it hurts, I don´t want to talk to anyone, until it eases. Even my wife goes away and leaves me alone when she sees a certain look on my face. I'd rather be by myself because I can do weird movements and get into positions that calm me down. The good thing is that I realise and I tell myself, this is going to happen."* It is not only the disease that is chronic, the pain is also chronic to the point that patients become accustomed to it and find it difficult to quantify. *"Being in constant pain, every day… how can you tell others how you feel?"* *"You get used to the pain. It's not going to go away."* *"One gets used to the pain. I'm in pain every day, and I've got used to it. You get so used to it that it's very difficult to rate it and with time you just cope with more and more."* ***Tiredness, unending tiredness*** Other consequences that are related to physical limitations and important for patients are tiredness (fatigue) as well as a general weakness and lack of energy (asthenia). These are continuous or recurrent and associated with the additional effort required for performing activities of daily living. *"I have always got very tired … Some days I´m not able to do anything, I feel exhausted, … even my voice, I lose my voice, it becomes just a faint whisper."* *"How are you? Tired… I´m constantly tired."*
Treatment	Regarding treatment, the most notable issue relates to the new drug treatments. There are two standpoints: some patients have doubts about the role and clinical outcomes of these drugs, while others support their use and prefer them to their previous medications. *"Among the patients I know, I must have been the most reluctant to start on biologics. I was a bit wary. I started to take biologics because my doctor said it was my only option. I was terrified of injecting myself."* *"I insisted on being treated with biologics because I asked about them and everyone was doing better."* The process of assessing any adverse effects, which is necessary in all cases, determines the subsequent acceptance or rejection of the treatment. *"You start learning about the treatments, and it's a bit alarming. I kept on looking at page after page of adverse effects; I was warned against reading them. The thing is -as there are not many other options- you tell yourself that you are in good hands."*

	More personalised and continuous follow-up of the treatment guidelines would facilitate treatment adherence. *"Another thing is that they give me the medication, but they don´t check whether you take it or not. This is not an easy treatment; it is not just taking a little pill and that´s it."*
Genetic profile	***The shadow of genetic inheritance*** Patients with children have an underlying fear that the condition may be inheritable. They are particularly sensitive about this subject, and their fear is heightened by the way they interpret any potentially relevant symptoms in their close relatives." *"When I started to see problems in my daughter, I noted it all and the doctor kept saying no, well, I don´t know, … and now I see my grandchild and whenever they say something hurts, well…"* *"It is a lottery; you never know."* *"I have become more relaxed with my children over the years. Since I started with it so young, it's got better with every year that has gone by and I have seen that they don't have symptoms."* *"My son had pain in his lower back and heels, and I got scared."*
Impact on daily life	***Major changes in activities*** The disease implies substantial adjustments in patients' daily lives because it affects emotional, social and professional spheres. For many patients, it involves a dramatic slowing in the pace of their daily routine or completely changing what they do. *"I've hardly ever been able to hold my grandchildren in my arms. It seems silly, but it is not. I´m with my granddaughter and she says, 'grandpa, pick me up'; 'No, sorry, I can´t."* ***Problems in the workplace*** The physical limitations reduce patients' functional capacity and ability to work. The personal situation of each patient influences what type of changes occur. *"I found it increasingly difficult to adopt certain postures at work. There were things that I already sensed weren't normal, but I didn't link them. I went to the doctor because I was in pain and kept getting bruises … I thought I was clumsy. I felt much clumsier and found it very difficult to bend down."* *"Stopping work was traumatic."* *"I´ve always enjoyed my job."* More physically demanding jobs are the ones that lead to earlier applications for incapacity for work assessment. *"Age is a factor (49 years for "total incapacity" and 53 years for "absolute incapacity" for work). It's a very young age to stop working, and it's not easy to go through it. I didn't want to get awarded absolute but rather total incapacity, because being at work helped me to not think about the illness."*

	It is difficult to accept the idea of having to stop working. If this eventually happens, patients explore ways to allow them to feel professionally useful. *"When I stopped working, I told myself that I had to find a new path, to change my life. I have tried to get used to my new life and I'm doing OK. I like people calling me and being able to help out, although some days I can't do anything, I feel awful and there's nothing I can do about it. The advantage of not working is that I do stuff when I can … even just going in for a while and assisting my colleagues a bit helps me a lot. Being active helps me."* ***Obstacles to leisure activities*** The illness also forces patients to give up leisure activities they once enjoyed. This has a negative impact on their mood and is perceived as another loss in terms of quality of life. *"Since I was young, I saw my siblings and other people get less tired than me. I made an effort and got exhausted, and they kept going. That upset me a lot when I was young. I used to play a lot of sport but there comes a time when you can´t, because you just can´t. It has been very traumatic for me not being able to anymore."* ***Negative impact on personal and social relationships*** There is little awareness of these diseases among the general public. Patients feel that their illness is not well understood, and in some cases, not even well accepted by people around them. *"When I wake up tired, when I find it difficult to respond … but then others look at you and you don´t look so bad. People around me know that I have psoriatic arthritis because I tell them, as they don't see you unwell. This condition is an unknown for many people."* *"I reached the factory hunched over, got to my post, started warming up and by 10 I´d be fine. They used to say: you are pretending. It's not understood."* *"The feeling of being misunderstood doesn't go away. If you make an effort to dress up, they say how great you look today and you say you are not well."* *"When I found something that properly explained what this illness was about, the first thing I did was phone my family and tell them: I need you to read this."* ***Emotional level*** Emotional problems can become a major issue in these illnesses. They can easily get out of control. Nonetheless, patients find resources to cope with periods of depressive symptoms. They try to stop their illness from taking over their lives. The role of families and their support are essential for overcoming emotional distress. *"Everything tends to affect you a lot. My father recently died from a tough illness and I had a rough time; because of my disability, I´ve not been able to help him as much as I would have liked to because of my condition."*

	"I quite often feel down, I have to admit. I often wake up at night ... I have not ended up falling into depression, because -thank God- my family gives me a lot of support. I get up at night, start crying, get over it and go back to bed and nobody realises … The family is an essential support. If I'd been alone, I would have got depressed. My personality is affected …" In addition, fostering relationships with other people with the same illness and learning about their experiences can serve as emotional therapy. *"I went to a patient association´s meeting and saw other people in the same situation as me."* *"I try to cheer others up and that cheers me up too."*
Coping	***Keeping active*** Doing some type of exercise becomes a lifeline for many patients. To improve the symptoms of their illness, patients have found that regular exercise can alleviate their symptoms and improve their functioning and quality of life. *"They started giving me painkillers, but I can't spend all my life on them, so I ask: what else can I do? Lots of exercise: Pilates, swimming, do as much exercise as possible. Now, with Pilates, I rarely wake up at night. Before, the rare thing was being able to sleep. Thanks to exercise, I have less pain and I'm more supple. But I can do it because I don´t have to go to work."* *"You have to do something, be involved in something; because if you're dwelling on it, that's when you get down."* ***Adapting to limitations*** Although the physical and emotional effects differ between patients, most develop skills that enable them to cope well with their illness and adapt to the limitations it places on their daily lives. *"As these diseases start when you are young, you learn to live with them. "* *"You get used to the limitations. I know that there are certain things I can't do, but I manage to get things done in some other way."* *"You know there are lots of things you can't do, but you get around your deficiencies (limitations), …put on your shoes, socks, sitting down… you do it your way and have a normal life."* ***Always a positive attitude*** Patients develop a coping mechanism in response to the illness, which could be likened to a survival instinct. It involves adopting positive attitudes to stop their health condition from undermining their lives emotionally. But there is also a common demand concerning their need for psychological support to achieve this. *"Learn how to cope with the illness and how to live with it."* *"I don´t have any problems talking about my illness."* *"The way you handle the illness and your attitude are really important. One thing that you don't get for this illness is the psychological support you ought to receive. When you are 20 years old and are told that you have a condition that is going to get worse and worse… you must have a positive attitude to accept everything that comes your way."*

	"The gene for spondylitis is a positive attitude gene because it makes you overcome challenges and put on a brave face." *"Although the pain runs through me, I try to hide from others."*
Relationship with health professionals	***Good rapport*** Regarding the doctor-patient relationship, there are various factors to consider, including the concept of "good rapport". Notably, most patients report a very good rapport with rheumatologists. Nonetheless, there are outstanding needs in terms of communication with clinicians being two way: more personalised care and training in "knowing how to care" to foster trust in health professionals. *"The interaction could not have been better."* *"It is important that doctors call you by your name. More personalised care (by specialists), like going to a general practitioner."* *"That someone knows your name, smiles at you."*

10. Recommendations for future research

● Studies are needed to compare the pathogenesis of axPsA and axSpA; and develop criteria based on distinguishing and overlapping features for the diagnosis of axSpA and PsA, as well as assessing spinal involvement in PsA to define similarities and differences compared to that in axSpA.

● Strategy and cost-effectiveness studies should be conducted comparing biosimilars (bDMARDs) with MTX as a first-line treatment.

● Clinical and biological markers for identifying the stage before the onset of PsA need to be found to diagnose the disease early.

● Diagnostic criteria need to be defined for very early onset PsA and the role of imaging.

● Studies should be carried out assessing the relationship of gut and skin microbiomes with disease onset and progression.

● Multiomic techniques need to be applied to the analysis of synovial tissue in PsA, to identify cells and molecules that could play an important role in diagnosis and treatment.

● Patients with axSpA or PsA should be studied to identify which individuals can have their therapy tapered or withdrawn with minimal risk of relapse.

● Methodologically sound studies are required to identify nurse-led health education programmes that are applicable in our setting and could benefit specific patients with PsA or axSpA.

● Future research should seek to advance our understanding of the effects of early drug therapy on functional capacity, structural damage and quality of life in axSpA and PsA.

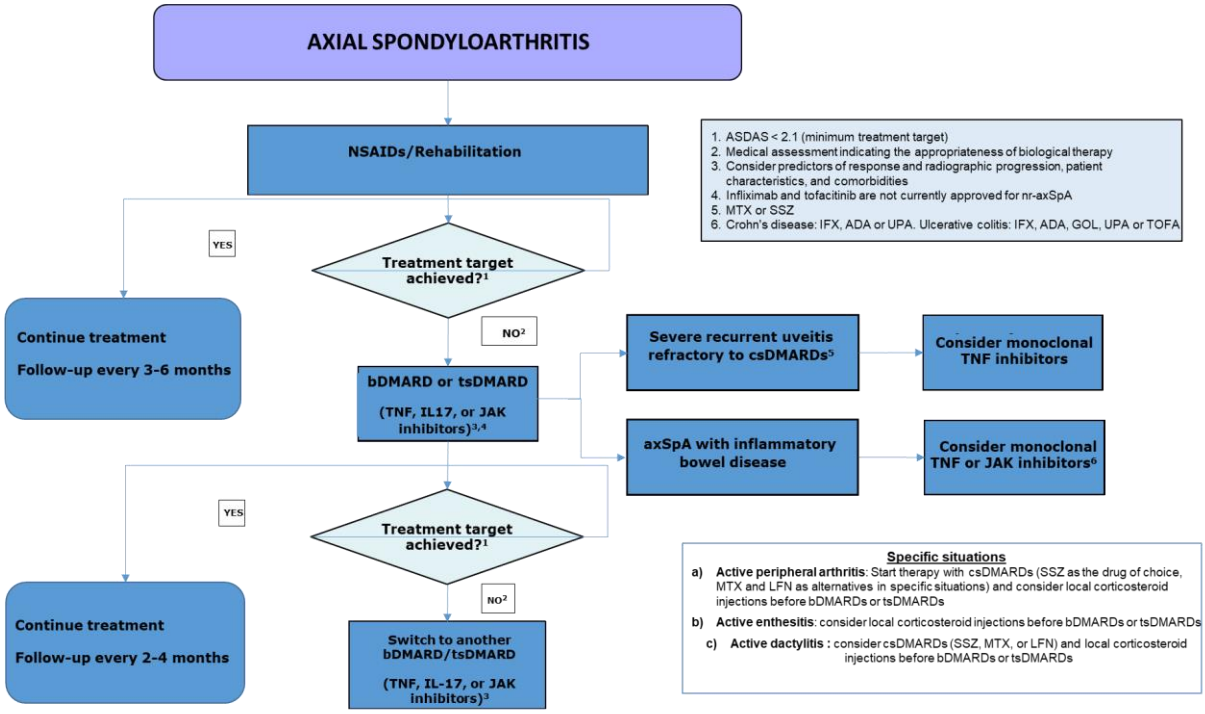
● Research should be conducted into the role of exercise programmes in axSpA, both in patients at the ankylosing stage and those with little loss of mobility and functional capacity.

● Additional studies are required, to assess the efficacy of csDMARDs and tsDMARDs (apremilast) in the treatment of axial manifestations, enthesitis, dactylitis and uveitis in PsA.

● Well-design long-term studies are required on the management of patients with PsA by multidisciplinary teams including rheumatologists and dermatologists in our setting.

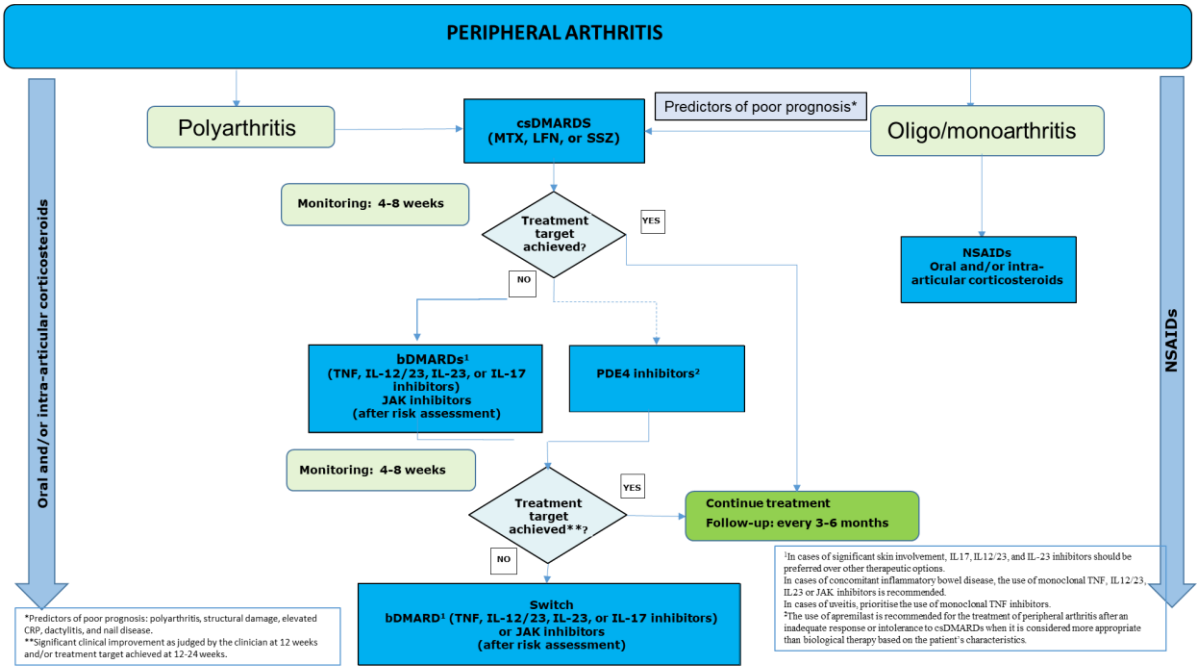
11. Treatment strategies

Treatment algorithm for axial spondyloarthritis

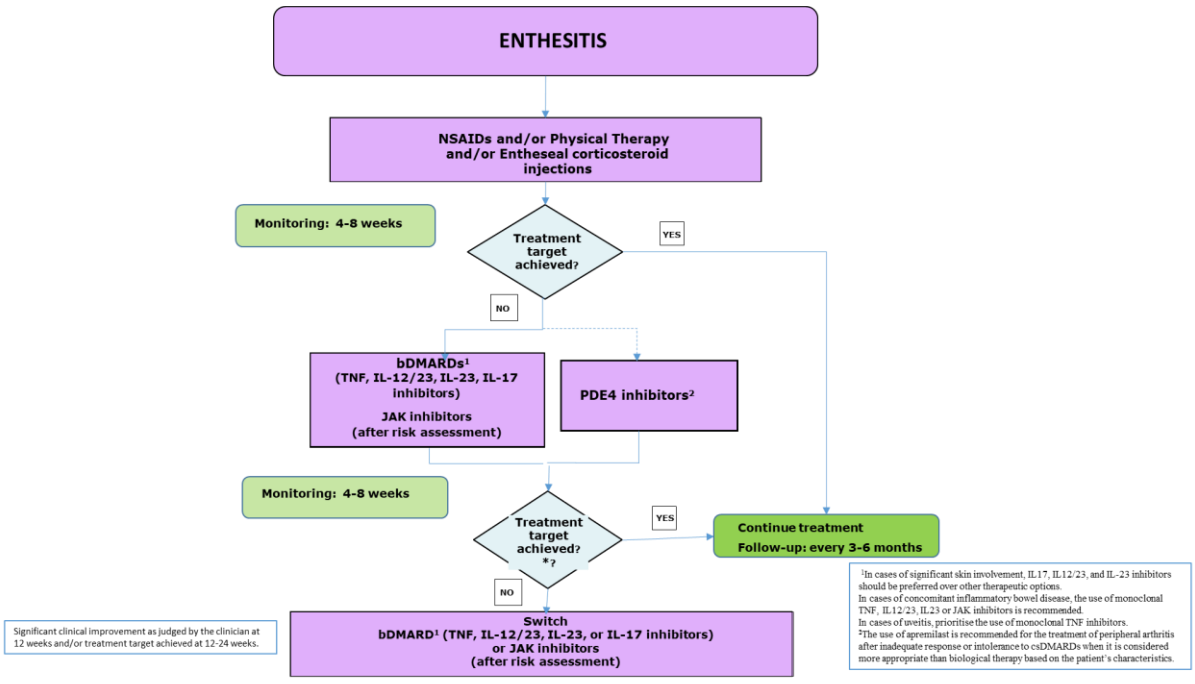


ADA: adalimumab; NSAID: non-steroidal anti-inflammatory drug; ASDAS: ASAS-endorsed disease activity score; DMARD: disease-modifying antirheumatic drug; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; tsDMARD: targeted synthetic DMARD; GOL: golimumab; IL-17: interleukin 17; JAK: Janus kinase; IFX: infliximab; TNF: tumour necrosis factor; LFN: leflunomide; MTX: methotrexate; SSZ: sulfasalazine; TOFA: tofacitinib; UPA: upadacitinib.

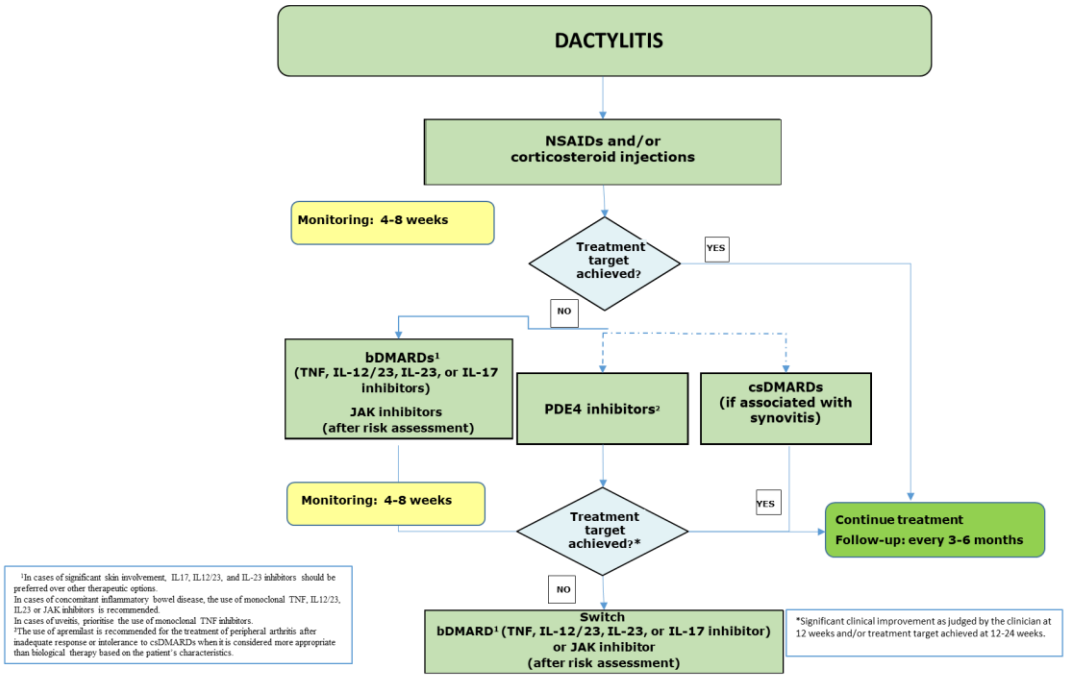
Treatment algorithms for psoriatic arthritis



DMARD: disease-modifying antirheumatic drug; bDMARD: biological DMARD; csDMARD: conventional synthetic DMARD; tsDMARD: targeted synthetic DMARD; JAK: Janus kinase; IL-17: interleukin 17; IL-12/23: interleukin 12/23; IL-23: interleukin 23; NSAID: nonsteroidal anti-inflammatory drug; PDE4: phosphodiesterase 4; TNF: tumour necrosis factor; LFN: leflunomide; MTX: methotrexate; SSZ: sulfasalazine.



DMARD: disease-modifying antirheumatic drug; bDMARD biological DMARD; csDMARD: conventional synthetic DMARD; tsDMARD: targeted synthetic DMARD; JAK: Janus kinase; IL-17: interleukin 17; IL-12/23: interleukin 12/23; IL-23: interleukin 23; NSAID: nonsteroidal anti-inflammatory drug; PDE4: phosphodiesterase 4; TNF: tumour necrosis factor.



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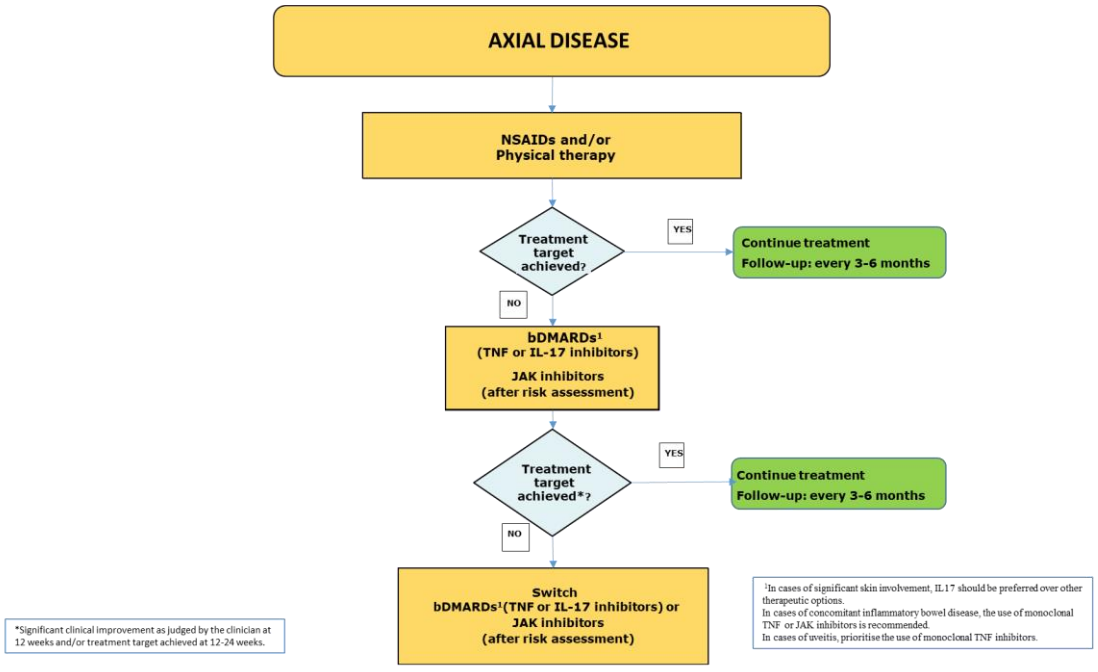

DMARD: disease-modifying antirheumatic drug; bDMARD biologic DMARD; tsDMARD: targeted synthetic DMARD; JAK: Janus kinase; IL-17: interleukin 17; NSAID: nonsteroidal anti-inflammatory drug; TNF: tumour necrosis factor.

12. Appendices

Appendix 1. Levels of evidence and grades of recommendation

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system

GRADE approach to rating the quality of evidence

Quality	Study design	Factors that can reduce the quality of the evidence*	Factors that can increase the quality of the evidence**
High ⊕⊕⊕⊕	RCT	• Limitations in study quality (design): Large (-1) Very large (-2) • Inconsistency: Large (-1) Very large (-2) • Indirectness of evidence: Large (-1) Very large (-2) • Imprecision: Large (-1) Very Large (-2) • High risk of publication bias: (-1)	Association: • Scientific evidence of a strong association (RR>2 or <0.5 based on observational studies with no plausible confounders) (+1) • Scientific evidence of a very strong association (RR>5 or <0.2 based on studies with a low risk of bias) (+2) • Dose-response gradient (+1) • All plausible confounding would reduce the demonstrated effect (+1)
Moderate ⊕⊕⊕⊖	--		
Low ⊕⊕⊖⊖	Observational studies		
Very low ⊕⊖⊖⊖	Studies with other designs		

* In the case of RCTs, the rating of the quality of the scientific evidence may decrease

** In the case of observational studies, the rating of the quality of the evidence may increase

RCT: randomised controlled trial; RR: relative risk.

Implication of the strength of recommendations in the GRADE system

Recommendation	Patients	Clinicians	Managers / Policymakers
Strong	Most people would agree with the recommended action, and only a small proportion would not.	Most patients should receive the recommended intervention.	The recommendation can be adopted as a healthcare policy in most situations.
Weak or Conditional	The majority of people would agree with the recommended action, but many would not.	Recognise that different choices will be appropriate for different patients and that you (the doctor) must help each patient make the decision that is most consistent with their values and preferences.	There is a need for considerable debate and the involvement of stakeholders.

Recommendations for good clinical practice*

Good clinical practice	Practice recommended based on the group's clinical experience and by consensus among members

*On some occasions, the GDG identified important practical issues it wanted to highlight but related to which there was unlikely to be any supporting evidence. In general, these issues concern aspects of treatment considered good clinical practice and which are not commonly questioned. Such issues have been evaluated as matters of good clinical practice.

Adaptation of recommendations using the GRADE-ADOLOPMENT approach*

Adapted	2018 ESPOGUÍA recommendations transformed to the GRADE system
New	*De novo* recommendations

*The clinical questions related to recognising when people are in the last few days of life, as well as communicating, shared decision-making and development of a care plan, hydration and symptom management in this context have been adapted from NICE guidance in *Care of dying adults in the last days of* life (NICE *guideline* [NG31]).

Appendix 2. Recommendations in the ESPOGUÍA 2018[8]

Treatment of Axial Spondyloarthritis (axSpA)

Early intervention

Clinical question: In patients with axSpA, does early pharmacological intervention improve functional capacity, structural damage, and quality of life?
As soon as axSpA has been diagnosed, we recommend commencement of pharmacological treatment (Grade D recommendation).

Biologic compared to conventional DMARD therapy

Clinical question: In patients with non-radiographic axSpA, what is the effectiveness of the different biological therapies compared with placebo or traditional DMARDs? What is the relative effectiveness of the different biological therapies?
Therapy with anti-TNF is recommended as the pharmacological treatment of choice for patients with active* non-radiographic axSpA who are refractory to NSAIDs (Grade A recommendation). * * Defined by objective inflammation characteristics (increase in CRP and/or MRI).
The use of tocilizumab is not recommended in patients with non-radiographic axSpA who are refractory to NSAID and/or treatment with anti-TNF (Grade C recommendation).

Treatment response

Clinical question: *In patients with axSpA, what are the prognostic factors regarding response to biological treatment?*
Assessment of the predictive factors of response should be considered when indicating biological therapy; however, it is in no way compulsory for treatment application (Grade D recommendation).
Clinical question: *In patients with axSpA, does pharmacological intervention with biological therapy (BT) control structural damage progression and axial radiographic lesions?*
Predictive factors of structural damage progression should be assessed in the biological therapy indication (Grade D recommendation).

Treatment failure

Clinical question: *In patients with axSpA who failed to respond to anti-TNF, would the intervention with another anti-TNF or biological therapy be efficient?*
After failure to a first anti-TNF, the patient should be treated with another anti-TNF or anti-IL17A (Grade D recommendation).

Treatment optimisation

Clinical question: *In patients with axSpA, is it possible to stop treatment of TNF inhibitors? Is it possible to reduce the treatment dose of TNF inhibitors?*
In patients with axSpA who reach the clinical objective, halting anti-TNF therapy is not recommended (Grade C recommendation).
The possibility of reducing the anti-TNF drug dose in patients with axSpA, who have achieved remission or maintain low disease activity, should be considered (Grade D recommendation).
In the event of disease activity increase in patients whose anti-TNF dose was reduced, a dose increase should be considered returning to the previous or standard dosage (Grade D recommendation).

Visual outcomes

Clinical question: *In patients with ankylosing spondylitis, does the use of biologics, compared with sulfasalazine, reduce the number of recurrences of uveitis and improve visual prognosis?*
The guideline development group believes that in patients with ankylosing spondylitis, the use of anti-TNF, especially monoclonal antibodies, is effective in reducing the number of uveitis recurrences and improving visual prognosis. However, its superiority (or inferiority) in comparison with sulfasalazine cannot be established based on current scientific evidence (Grade D recommendation).

Exercise

Clinical question: *In patients with ankylosing spondylitis, what kind of exercise program is most effective in improving clinical and functional parameters?*
It is recommended that adults with ankylosing spondylitis exercise, preferably in supervised groups, as part of their disease treatment, to improve symptoms, quality of life, and health-related fitness (Grade B recommendation).
The previous recommendation is extended to patients with non-radiographic axSpA (Grade D recommendation).

Exercise programs must include aerobic exercises, preferably performed in supervised groups (Grade B recommendation).

Smoking

Clinical question: *In patients with axSpA, does smoking aggravate clinical manifestations (arthritis, axial involvement, enthesitis, and structural damage)?*
It is recommended that patients with axSpA be encouraged to stop smoking from the time of diagnosis (Grade C recommendation).

Treatment of Psoriatic Arthritis (PsA)

Early intervention

Clinical question: *In patients with PsA, does early pharmacological intervention improve functional capacity, structural damage and quality of life?*
Early pharmacological intervention with conventional synthetic DMARDs (csDMARDs) is recommended in patients with PsA, chiefly in those with poor baseline prognosis factors, to improve signs and symptoms, functional capacity and quality of life (Grade D recommendation).

Biologics as monotherapy

Clinical question: *In patients with PsA, what is the efficacy of biological therapies in monotherapy regarding peripheral, axial, enthesitis, dactylitis, uveitis, and skin and nail clinical manifestations?*
Biologic monotherapies have proven more effective than csDMARDs or placebo in treating patients with PsA in its different manifestations: peripheral, axial, enthesitis, dactylitis, and uveitis (Grade D recommendation).
Use of biological therapy is recommended for patients with peripheral PsA refractory to at least one csDMARD (Grade A recommendation).
Patients with predominantly axPsA refractory to NSAIDs, use of biological therapy (anti-TNF or anti-IL17A) is recommended (Grade D recommendation).

Conventional DMARDs

Clinical question: *In patients with PsA, what is the efficacy of DMARDs in its peripheral, axial, enthesitis, dactylitis, uveitis, skin and nail domains?*

Traditional csDMARDs (methotrexate, leflunomide, sulfasalazine) are recommended as first-line treatment for active peripheral PsA (Grade C recommendation).
Among them, methotrexate is considered the first-choice treatment due to its effects on arthritis and psoriasis (Grade D recommendation).
These drugs should not be used to treat symptoms of axial disease. There is no evidence supporting their use against enthesitis. There are questions about their effectiveness against dactylitis (Grade C recommendation).
The use of apremilast is recommended in treating peripheral arthritis after failure or intolerance to a csDMARD, when it is deemed more appropriate than biological therapy given the patient profile (Grade C recommendation).
The use of biological therapy or a tsDMARD (apremilast) is recommended in patients with PsA and enthesitis refractory to NSAIDs and local treatment (Grade C recommendation).
The use of biological therapy or a tsDMARD (apremilast) is recommended in patients with PsA and dactylitis refractory to NSAIDs and local treatment with corticoid injections (Grade C recommendation).

Methotrexate and biological therapy

Clinical question: *In patients with PsA, is combined treatment with MTX and biological therapy more effective than treatment with biological therapy as monotherapy?*
Use of biological therapy is recommended in both monotherapy and combined with csDMARDs, for all peripheral manifestations of PsA. Combined therapy with MTX may increase survival of the anti-TNF monoclonal drugs, particularly the chimeric ones (Grade C recommendation).

Treatment failure

Clinical question: *In adults with PsA with axial and/or peripheral involvement refractory to one anti-TNF, is treatment with a second biologic efficient?*
Switching to another biological therapy albeit another anti-TNF or a drug with a different action mechanism like anti-IL-12/23 or anti-IL-17A or a tsDMARD (apremilast) is recommended in patients with peripheral PsA and an anti-TNF failure (Grade B recommendation).

Cardiovascular morbidity

Clinical question: *In patients with PsA, does treatment with DMARDs or biological therapies reduce CVD mortality?*
CVD risk profile should be considered both in assessing and treating these patients (Grade D recommendation).

Multidisciplinary management

Clinical question: *In patients with PsA and moderate-to-severe skin conditions, what are the benefits of multidisciplinary management (dermatology-rheumatology consultations) in terms of improving clinical management and patient satisfaction?*
It is recommended that dermatologists and rheumatologists work closely together in order to gain optimal control over the psoriatic disease (Grade D recommendation).
This type of consultation is recommended whenever a multidisciplinary approach can be arranged at the health centre of reference (Grade D recommendation).

Treatment of Axial Spondyloarthritis (axSpA) and Psoriatic Arthritis (PsA)

Health education

Clinical question: *In patients with axSpA, are the health education programs offered by nurses beneficial? In patients with PsA and peripheral and/or axial involvement, are the health education programs offered by nurses beneficial?*
Participation of clinical nurse specialists is recommended, either in person or by telephone, in follow-up consultations for patients with axSpA or with PsA due to evidence it increases patient satisfaction (Grade D recommendation).
Patients who are smokers and suffer from axSpA or PsA could benefit from implementation of educational smoking cessation programmes provided by a nurse, since evidence shows they increase smoking quit rates (Grade D recommendation).
Nurse-run educational workshops prior to the start of subcutaneous therapy are recommended since they help reduce patient fear of this treatment type (Grade D recommendation).
The assistance of a nurse to clarify any doubts and help patients complete self-assessment questionnaires is recommended, provided that patients´ opinions and preferences are not influenced (Grade D recommendation).
Patients with PsA could benefit from educational programmes, preferably in a group setting led by a clinical nurse specialist. This would facilitate patient self-management and would improve treatment adherence (Grade D recommendation).

Appendix 3. Recommendations on refractory uveitis (extracted from the SER recommendations for the treatment of uveitis)[122]

Anterior Uveitis

Recommendation 5. In patients with refractory or recurrent anterior uveitis, adalimumab is recommended for patients who have failed to respond to conventional therapies. [Weak recommendation in favour].

Recommendation 6. In patients with refractory or recurrent anterior uveitis, other anti-TNF-α monoclonal antibodies, such as certolizumab, golimumab, or infliximab, could also be used. [Good clinical practice].

Non-Anterior Uveitis

Recommendation 10. For the treatment of patients with severe or refractory non-anterior, non-infectious, non-neoplastic uveitis not associated with demyelinating disease, the use of anti-TNF-α monoclonal antibodies is recommended, especially adalimumab [Strong recommendation in favour].

- Infliximab, golimumab, certolizumab, tocilizumab, and rituximab may be used as alternatives to adalimumab if deemed necessary [Good clinical practice].
- Etanercept is not advised for the treatment of non-anterior, non-infectious, non-neoplastic uveitis not associated with demyelinating disease. [Good clinical practice].

Recommendation 11. The GDG does not recommend the use of secukinumab to treat non-anterior, non-infectious, non-neoplastic uveitis not associated with demyelinating disease [Weak recommendation against].

Uveitic Macular Oedema

Recommendation 17. Intravitreal anti-vascular endothelial growth factor agents are suggested for uveitic macular oedema when there is a contraindication to corticosteroids [Good clinical practice].

Recommendation 18. In subjects with uveitic macular oedema, the use of anti-TNF-α monoclonal antibodies, and more specifically adalimumab, is advised on the basis of the positive results in clinical practice [Good clinical practice].

Recommendation 19. The GDG considers that the poor quality of the evidence available does not justify a recommendation for rituximab, sarilumab, or cytotoxic drugs in individuals with uveitic macular oedema [Good clinical practice].

If the uveitic macular oedema is refractory:

• Tocilizumab is suggested, or interferon alfa may also be considered depending on the person's experience with the drug, given the increased occurrence of adverse events and the difficulty in accessing the drug [Good clinical practice].

Appendix 4. Glossary and abbreviations

Glossary

Burden of disease: an indicator that measures the loss of health due to the fatal and non-fatal consequences of a disease (mortality and morbidity) in a population. It is measured in disability-adjusted life years (DALYs).

Case-control study: a study that identifies people with a disease (cases), for example, lung cancer, and compares them with a group of people without the disease (controls). The relationship between one or various disease-related factors (for example, smoking) is assessed by comparing the rate of exposure to these or other factors between cases and controls.

Case series: a type of study that describes a series of patients with a given disease or outcome.

Clinical practice guideline: a set of recommendations based on a systematic review of the evidence and the assessment of the risks and benefits of the options available, seeking to optimise the healthcare provided to patients.

Cochrane Library: collection of databases containing evidenced-based information, on effectiveness among other topics, to inform healthcare decision-making assembled by the Cochrane Collaboration including systematic reviews undertaken by this organisation (Cochrane Database of Systematic Reviews).

Cohort study: a study that involves following up one or more cohorts of individuals with different levels of exposure to a risk factor and assessing whether they develop the disease or condition of interest.

Cross-sectional descriptive study: a study that describes the rate of an event or exposure at a specific time (single measurement). Also called a prevalence study, it allows us to examine the relationship between a risk factor (or exposure) and an effect (or outcome) in a given population at a given time (cut-off point).

Dactylitis: inflammation/swelling of the joints and tendons in the digits. Commonly known as “sausage finger” or “sausage toe”.

Discussion group: a qualitative research technique used for investigating attitudes, opinions, appraisals or perceptions among a group of individuals regarding something or someone.

Embase: European (Dutch) database produced by Excerpta Medica containing medical and pharmacological information.

Enthesitis: inflammation of the entheses, sites where a tendon, ligament, joint capsule or fascia attaches to the bone. The most common symptoms are pain, swelling, and redness around the affected site.

In-depth interview: a qualitative research technique to obtain data through a conversation between an informant with pre-established characteristics and a skilled interviewer.

MEDLINE/PubMed: PubMed is a search engine that accesses the references and abstracts of the biomedical literature in the MEDLINE database maintained by the US National Library of Medicine available online.

Meta-analysis: a statistical approach that makes it possible to combine the results of different studies (diagnostic test studies, clinical trials, cohort studies, etc.) to obtain overall results, giving more weight to the results from larger studies. This term is also used to refer to systematic reviews that include meta-analysis.

Morbidity: having an illness or medical problems associated with a treatment or the amount of illness (incidence or prevalence) in a given population.

Mortality: the rate or proportion of people in a given population that die from a given disease in a given period of time.

National Institute for Health and Care Excellence: a public body in the United Kingdom that is independent of the National Health Service (NHS), whose role is to improve outcomes for people using the English and Welsh NHS and other public health and social care services by, among other activities, providing clinicians, public health and social care practitioners with access to the best available scientific evidence, in the form of clinical guidelines and advice concerning public health and healthcare technologies.

Odds ratio (OR): is a measure of the strength of association between two variables, e.g., an exposure and an outcome, and hence, serves as an indicator of the efficacy or effectiveness of a treatment. If the OR is 1, the effect of the treatment is not different from that observed in the control group. If it is above (or below) 1, the effect of treatment is higher (or lower) than that observed in the control group. It should be noted that the effect being measured may be negative (e.g., death or disability) or positive (e.g., smoking cessation).

Open trial: 1. Clinical trial in which the researcher knows details about the intervention given to the participant, also called an open-label trial. 2. Clinical trial with an open sequential design.

Placebo: A substance administered to the control group of a clinical trial, ideally identical in appearance and taste to the experimental treatment, which is thought to have no specific effect on the disease under study. In the context of non-pharmacological interventions, placebo is usually called a simulated treatment.

Prevalence: the rate or proportion of people in a given population who have a given condition or finding at a given time.

Primary research: the type of research that collects original data. Primary studies are different from reviews or syntheses which are based on data from individual primary studies. They also differ from systematic reviews that summarise the results of a set of primary studies.

Qualitative research: a concept that covers a wide range of theoretical, methodological and technical approaches and is characterised by studying phenomena in their natural context, attempting to make sense of, or interpret, them based on the meanings people attach to them. To this end, it uses the types of empirical material (interviews, observations, texts, etc.) that may best describe both routine and problematic situations, and what they mean in the lives of individuals.

Randomised clinical trial: an experimental study in which participants are assigned randomly (at random) to one of two (or more) groups: one (the experimental group) receives the treatment under study and the other/others (the comparison or control group/groups) receive the conventional treatment (or sometimes placebo). Both groups are monitored to assess any potential differences in outcomes. In this way, the efficacy of the treatment of interest is assessed.

Scottish Intercollegiate Guidelines Network (SIGN): A Scottish network of multidisciplinary groups that develop clinical practice guidelines containing recommendations based on the best available scientific evidence, as well as documents concerning the methods used to develop the guidelines.

Single- or double-blind trial: a clinical trial in which the participants (single blind) or neither the participants nor the clinicians involved (double blind) know which intervention each individual is receiving.

Systematic review: a summary of the evidence on a specific question has been gathered using systematic methods for identifying, critically appraising and synthesising information in the scientific literature in accordance with preset criteria. It may or may not include a meta-analysis.

Uveitis: inflammation in the middle layer of the eye, the uvea, which is responsible for supplying blood to the eyeball.

Abbreviations

ABA: abatacept

ACR: American College of Rheumatology

ADA: adalimumab

NSAID: nonsteroidal anti-inflammatory drug

PsA: psoriatic arthritis

ASAS: Assessment of SpondyloArthritis International Society and also a disease activity score endorsed by this society

ASQoL: Ankylosing Spondylitis Quality of Life scale

axSpA: axial spondyloarthritis

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

BASFI: Bath Ankylosing Spondylitis Functional Index

BASMI: Bath Ankylosing Spondylitis Metrology Index

bDMARD: biological disease-modifying antirheumatic drug

BMI: body mass index

BRD: brodalumab

BSA: body surface area

BZK: bimekizumab

CI: confidence interval

CPG: clinical practice guideline

CRP: C-reactive protein

csDMARD: conventional synthetic disease-modifying antirheumatic drug

CZP: certolizumab pegol

DMARD: disease-modifying antirheumatic drug

DAPSA: Disease Activity in PSoriatic Arthritis

DAS: Disease Activity Score

DLQI: Dermatology Life Quality Index

EASi-QoL: Evaluation of Ankylosing Spondylitis Quality of Life

EMA: European Medicines Agency

ESSG: European Spondyloarthropathy Study Group

ETN: Etanercept

EULAR: European League Against Rheumatism

FDA: Food and Drug Administration

FER: Foundation of the Spanish Society of Rheumatology

GDG: guideline development group

GOL: golimumab

GPR: global postural re-education

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

GUS: guselkumab

HAQ: Health Assessment Questionnaire

IFX: infliximab

IL-17: interleukin 17

IL-12/23: interleukin 12 and interleukin 23

IL-23: interleukin 23

IBD: inflammatory bowel disease

INX: infliximab

TNF: tumour necrosis factor

IXE: ixekizumab

JAK: Janus kinase

LDA: low disease activity

LFN: leflunomide

MACE: major adverse cardiovascular events

MASES: Maastricht Ankylosing Spondylitis Enthesitis Score

MDA: minimal disease activity

MRI: magnetic resonance imaging

mSASSS: Modified Stoke Ankylosing Spondylitis Spinal Score

MTX: methotrexate

nr-axSpA: non-radiographic axial spondyloarthritis

NRS: Numerical Rating Scale

PASI: Psoriasis Area Severity Index

PICO: Patient, Intervention, Comparison and Outcome

PROM: patient-reported outcome measure

~~33~~r-axSpA: radiographic axial spondyloarthritis

RCT: randomised controlled trial

RIS: risankizumab

RR: relative risk

SEC: secukinumab

SER: Spanish Society of Rheumatology (from the Spanish *Sociedad Española de Reumatología*)

SF-36: 36-item Short Form Health Survey

SPARCC: SpondyloArthritis Research Consortium of Canada

SpA: spondyloarthritis

SSZ: sulfasalazine

TNF: tumour necrosis factor

TJC: tender joint count

TOFA: tofacitinib

tsDMARD: targeted synthetic disease-modifying antirheumatic drug

SJC: swollen joint count

UPA: upadacitinib

UST: ustekinumab

Appendix 5. Guidance on the types of exercises that are suitable for patients with axial spondyloarthritis

Aerobic exercise:
• The best types of activity are ones that allow extension of the back and maintain hip and shoulder mobility to promote a good posture. • Activities like walking, stationary cycling, swimming and aquatic exercise are good for improving overall physical fitness. • This type of exercise should be done for at least 30 minutes, every day or most days, at moderate intensity, that is, while doing the activity it should be easy to talk, without feeling fatigue. • Walking should include long steps to fully extend the hips. • Footwear should have a cushioned flexible non-slip sole to minimise the impact of walking. • High-impact violent sports and activities with a risk of falls are discouraged at advanced stages of the disease.
Progressive strength training:
• This is important for maintaining spinal flexibility and function. • Exercises should focus on all the muscles involved in back extension as well as the abdominals, glutes, and quadriceps. • Ensure proper breathing during exercising: inhaling before movement, exhaling during movement and resting sufficiently between series (a couple of minutes) to avoid fatigue.
Stretches:
• This type of exercise is beneficial, especially in certain patients, to maintain or improve joint mobility when it becomes restricted. • Do three repetitions of each exercise, holding the position for around 30 seconds. In patients with axial spondylitis, who have greater stiffness and limited mobility of the spine, rehabilitation with physical therapy aimed at strengthening the back, reducing stiffness, and minimising mobility loss is a key part of the treatment, alongside pharmacological therapies. These exercises can be carried out in group sessions (rehabilitation rooms, physiotherapy, gyms, swimming pools, etc.) or at home. People with the greatest levels of disability should also move all their joints at least once or twice a day, with gentle movements. They can sit on a chair and move their arms, legs, and neck in circles or back and forth, to keep the joints flexible and prevent muscle atrophy.

Appendix 6. Declaration of interests

Juan D. Cañete Crespillo received funding from Abbvie, Janssen and UCB for attending courses/conferences and speaker fees from Nordic, and fees from IMIDomics for consultancy work for pharmaceutical and tech companies.

Petra Díaz del Campo Fontecha has no conflicts of interest to declare in relation to this guideline.

David Díaz Valle received funding from Esteve Pharmaceutica, Tedec Meiji and Thea Laboratories for attending courses/conferences and speaker fees from Abbvie, Bausch & Lomb, Esteve, Santen and UCB.

Agnès Fernández Clotet received funding from Abbvie, Dr. Falk, Ferring, Janssen, Pfizer and Takeda for attending courses/conferences and speaker fees from Janssen and Pfizer

Amparo López Esteban has no conflicts of interest to declare in relation to this guideline.

Clementina López Medina received funding from Abbvie, Lilly, MSD, Novartis and UCB for attending courses/conferences; speaker fees from Abbvie, Janssen, Lilly, Novartis and UCB; funding from Janssen for educational programmes and courses; speaker fees Abbvie, Lilly, Novartis and UCB for consultancy work for pharmaceutical and tech companies and a grant from Abbvie, Lilly, Novartis and UCB for a research project.

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