



Clinical Practice Guideline for the Treatment of Patients with Axial Spondyloarthritis and Psoriatic Arthritis

ESPOGUÍA 2015 Update

This Clinical Practice Guideline is meant to help in healthcare decision-making. They are not mandatory and does not replace professional clinical judgement.

Published: 2018

Spanish Society of Rheumatology

Contents

Presentation	4
Authorship and Collaborations	5
Clinical Practice Recommendations	9
1. Introduction.....	12
2. Scope and Objectives	15
3. Methodology	17
4. Epidemiological Data and Clinical Manifestations	22
5. Clinical Questions	28
6. Treatment of Axial Spondyloarthritis (axSpA).....	30
7. Treatment of Psoriatic Arthritis (PsA)	64
8. General Advice for Patient Management	98
9. Perspective of patients suffering from AsP and AxSpA.....	99
10. Recommendations for Future Investigations.....	112
11. Therapeutic strategies.....	113
12. Appendix	118
Appendix 1. Levels of evidence and recommendations	119
Appendix 2. Glossary and Abbreviations	123
Appendix 3. Declaration of Interests	128
Bibliography	130

Presentation

The Spanish Society of Rheumatology (Spanish acronym SER), a non-profit scientific organization, has sponsored this clinical practice guideline (CPG). SER determined the need for such guidelines, as well as the initial group of investigators to develop it and the production schedule. It is also formulated the contract with the financing entity to guarantee the independence of the guidelines' contents.

The Research Unit (RI) of SER conducted the preselection of the principal investigator (PI) and expert panelists, developed the methodology, and coordinated the meetings and preparation of the CPG, including reviews of all evidence.

The content of the Espoguía collects evidence available until 2017. Based on advances in current knowledge and newly accumulating evidence, an update is expected in four years.

Authorship and Collaborations

The ESPOGUIA Development Group for the Treatment of Axial Spondyloarthritis and Psoriatic Arthritis

Coordination

Clinical Coordination

Juan D Cañete Crespillo. Senior Consulting Rheumatologist. Hospital Clínic, Barcelona.

Methodological Coordination

Petra Díaz del Campo Fontecha. Sociologist, Research Unit, Spanish Society of Rheumatology (SER), Madrid.

Expert Panelists

Raquel Almodóvar González. Rheumatology. Hospital Universitario Fundación Alcorcón, Madrid.

José Manuel Benítez del Castillo Sánchez. Ophthalmology. Hospital Universitario Clínico San Carlos. Ophthalmology Professor, Universidad Complutense, Madrid.

Juan D Cañete Crespillo. Senior Consulting Rheumatologist. Hospital Clínic, Barcelona.

Eugenio De Miguel Mendieta. Rheumatology. Hospital Universitario La Paz. Rheumatology Associate Professor, Universidad Autónoma, Madrid.

Fernando García Pérez. Physical Medicine and Rehabilitation. Hospital Universitario Fundación Alcorcón, Madrid.

Jordi Gratacós Masmitjà. Rheumatology. Hospital Universitario Parc Taulí Sabadell, Barcelona.

M^a José León Cabezas. Rheumatology Nurse Practitioner. Hospital Príncipe de Asturias. Alcalá de Henares, Madrid

Luis Francisco Linares Ferrando. Rheumatology. Hospital Clínico Universitario (HCU) Virgen de la Arrixaca, Murcia.

Carlos Montilla Morales. Rheumatology. Hospital Clínico Universitario, Salamanca.

María Victoria Navarro Compán. Rheumatology. Hospital Universitario La Paz, Madrid.

Ruben Queiro Silva. Rheumatology. Hospital Universitario Central de Asturias (HUCA), Oviedo.

Carlos Montilla Morales. Rheumatology. Hospital Clínico Universitario, Salamanca.

Julio Ramírez García. Rheumatology. Hospital Clínic, Barcelona.

Juan Carlos Torre Alonso. Rheumatology. H. Monte Naranco. Rheumatology Professor, Universidad de Oviedo.

Ricardo Valverde Garrido. Medical-Surgical Dermatology and Venerology. Hospital Universitario Infanta Sofía, Madrid.

2017 Update

- Juan D Cañete Crespillo.** Senior Consulting Rheumatologist. Hospital Clínic, Barcelona.
- Petra Díaz del Campo Fontecha.** Sociologist, Research Unit, Spanish Society of Rheumatology (SER), Madrid.
- Cristina Fernández Carballido.** Rheumatology. Hospital General Universitario de Elda, Alicante.
- Nieves Plana Farras.** Public Health and Preventive Medicine. Research Unit, Spanish Society of Rheumatology (SER), Madrid.
- Ruben Queiro Silva.** Rheumatology. Hospital Universitario Central de Asturias (HUCA), Oviedo.
- Sixto Zegarra Mondragon.** Rheumatology. Hospital Universitario Ramón y Cajal, Madrid.

Reviewers

- Miguel Ángel Abad Hernández.** Rheumatology. Hospital Virgen del Puerto. Plasencia, Cáceres.
- Gloria Candelas Rodríguez.** Rheumatology. Hospital Universitario Clínico San Carlos, Madrid
- Tatiana Cobo Ibáñez.** Rheumatology. Hospital Universitario Infanta Sofía, Madrid.
- Félix Manuel Francisco Hernández.** Rheumatology. Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria.
- Jesús Maese Manzano.** Rheumatology. Grupo de Trabajo de Reumatología Basada en la Evidencia (RBE), Madrid.
- M^a Victoria Navarro Compán.** Rheumatology. Hospital Universitario La Paz, Madrid.
- María Betina Nishishniya Aquino.** Rheumatology and Sports Medicine. Clínica Quirón, Barcelona.
- Ana Ortiz García.** Rheumatology. Hospital Universitario de la Princesa, Madrid.
- Virginia Villaverde García.** Rheumatology. Hospital Universitario de Móstoles, Madrid.

2017 Update

- Miguel Ángel Abad Hernández.** Rheumatology. Hospital Virgen del Puerto. Plasencia, Cáceres.
- José de la Mata Lord.** Rheumatology. Instituto de Salud Osteoarticular ARI, Madrid.
- Félix Manuel Francisco Hernández.** Rheumatology. Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria.
- Jesús Maese Manzano.** Rheumatology. Grupo de Trabajo de Reumatología Basada en la Evidencia (RBE), Madrid.
- María Betina Nishishniya Aquino.** Rheumatology and Sports Medicine. Clínica Quirón, Barcelona.
- Ana Ortiz García.** Rheumatology. Hospital Universitario de la Princesa, Madrid.
- Gloria Candelas Rodríguez.** Rheumatology. Hospital Universitario Clínico San Carlos, Madrid.
- Claudia Pereda Testa.** Rheumatology. Hospital Mediterráneo, Almería.

Patients

Irene Escribano Logroño. Patient. Member of the Psoriasis Action. Association of Psoriasis and Psoriatic Arthritis Patients and Families, Madrid.

Santos Yuste Zazo. Patient. Member of the Spanish League against Rheumatism (LIRE), Madrid.

Collaborations

Literature and Database Search

Mercedes Guerra Rodríguez. Documentalist, Research Unit, Spanish Society of Rheumatology (SER), Madrid.

Methodological Collaboration

Susana García Rodríguez. Research Unit, Spanish Society of Rheumatology (SER), Madrid.

Daniel Seoane Mato. Public Health and Preventive Medicine. Research Unit, Spanish Society of Rheumatology (SER), Madrid.

Evidence Review

Chamaida Plasencia Rodríguez. Rheumatology. Hospital Universitario La Paz, Madrid.

Patient Consultation

Petra Díaz del Campo Fontecha. Sociologist, Research Unit, Spanish Society of Rheumatology (SER), Madrid.

Patient Information Design

Petra Díaz del Campo Fontecha. Sociologist, Research Unit, Spanish Society of Rheumatology (SER), Madrid.

Irene Escribano Logroño. Patient. Patient. Member of the Psoriasis Action. Association of Psoriasis and Psoriatic Arthritis Patients and Families, Madrid.

Luis Francisco Linares Ferrando. Rheumatology. Hospital Clínico Universitario (HCU) Virgen de la Arrixaca, Murcia.

Santos Yuste Zazo. Patient. Member of the Spanish League against Rheumatism (LIRE), Madrid.

External Review

Jose A Gómez-Puerta. Rheumatology. Universidad de Antioquia, Colombia.

Helena Marzo Ortega. Rheumatology. Leeds Teaching Hospital Trust. Associated and Honorary Professor. University of Leeds, United Kingdom.

Acknowledgments

Special thanks to **Federico Díaz González**, Head of the SER Research Unit, for his contribution to ensuring the independence of this Clinical Practice Guideline (CPG).

Collaborating Organizations

Association of Psoriasis and Psoriatic Arthritis Patients and Families
Spanish Society of Rheumatology (SER)
Spanish Academy of Dermatology and Venerology (AEDV)
Spanish Society of Ophthalmology (SEO)
Spanish Society of Physical and Rehabilitation Medicine (SERMEF)
Spanish League against Rheumatism (LIRE)

Members from these organizations have contributed to the creation of this CPG.

Declaration of Interests:

All ESPOGUIA group members worked together on drafting a declaration of interests (see Appendix 3).

Public Display:

This guideline have been subjected to a Public Display process. The complete list of participants in this process can be found at www.ser.es.

Financing:

This CPG, sponsored by SER, was financed by AbbVie. The Spanish Foundation of Rheumatology (Spanish acronym, FER), which as the only intermediary employs the SER Research Unit staff and coordinates payments to panelists and reviewers, signed this contract with the pharmaceutical company. This agreement established total independence from the pharmaceutical company, which could not influence the panelist selection, the gathering and interpretation of evidence, or any other aspects of the final version of the CPG. The pharmaceutical company also committed to finance the CPG, even if the evidence contradicted any of its products' indications. Thus, the design, analysis, and interpretation of results have been carried out in a strictly independently fashion from AbbVie.

This guideline must be cited as:

Spanish Society of Rheumatology. ESPOGUIA development group. Clinical Practice Guideline for Patients with Axial Spondyloarthritis and Psoriatic Arthritis. Update. Madrid: Spanish Society of Rheumatology. 2017.

Clinical Practice Recommendations

Treatment of Axial Spondyloarthritis (axSpA)

2017	As soon as axial spondyloarthritis has been diagnosed we recommend commencement of pharmacological treatment (Grade D recommendation).
	Therapy with anti-TNF is recommended as the pharmacological treatment of choice for patients with active* non-radiographic axial spondyloarthritis who are refractory to NSAID (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 axial spondyloarthritis who are refractory to NSAID and/or treatment with anti-TNF (Grade C Recommendation).
2017	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).
2017	Predictive factors of structural damage progression should be assessed in the biological therapy indication (Grade D recommendation).
2017	After failure to a first anti-TNF, the patient should be treated with another anti-TNF or anti-IL17A (Grade D recommendation).
	In those patients with axial spondyloarthritis who reach the clinical objective, halting anti-TNF therapy is not recommended (Grade C recommendation).
2017	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).
2017	In the event of disease activity increase in patients whose anti-TNF dose was reduced, an increase should be considered returning to previous or standard dosage (Grade D recommendation).
	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).
	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 axial Spondyloarthritis (Grade D recommendation).
	Exercise programs must include aerobic exercises, preferably performed in supervised groups (Grade B recommendation).
	It is recommended that patients with axial spondyloarthritis be encouraged to stop smoking

from the time of diagnosis (Grade C recommendation).

Treatment of Psoriatic Arthritis (PsA)

2017

Early pharmacological intervention with conventional synthetic DMARDs (csDMARDs) is recommended in patients with PsA, chiefly in those with bad basal prognosis factors, to improve signs and symptoms, functional capacity and quality of life (Grade D recommendation).

2017

Biologic monotherapies have proven more effective than csDMARDs or a placebo in treating patients with psoriatic arthritis in its different manifestations: peripheral, axial, enthesitis, dactylitis, and uveitis (Grade D recommendation).

2017

Use of biological therapy is recommended for patients with peripheral PsA refractory to at least one csDMARD (Grade A recommendation).

Patients with predominantly ax-PsA refractory to NSAIDs, use of biological therapy (i-TNF or anti-IL17A) is recommended (Grade D recommendation).

Traditional csDMARDs (methotrexate, leflunomide, sulfasalazine) are recommended as first line treatment for active peripheral psoriatic arthritis (Grade C recommendation).

Among them, methotrexate is considered 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).

2017

The use of Apremilast is recommended in treating peripheral arthritis after failure or intolerance to csDMARD, when it is deemed more convenient than BT given the patient profile (Grade C recommendation).

2017

The use of biological therapy or tsDMARD (Apremilast) is recommended in patients with PsA and enthesitis refractory to NSAID and local treatment (Grade C recommendation).

2017

The use of biological therapy or tsDMARD (Apremilast) is recommended in patients with PsA and dactylitis refractory to NSAID and local treatment with corticoid infiltrations (Grade C recommendation).

2017

Use of biological therapy is recommended in both monotherapy and combined with csDMARD, for all peripheral manifestations of PsA. Combined therapy with MTX may increase survival of the TNFi monoclonal drugs, particularly the chimeric ones (Grade C recommendation).

2017

Switching to another biological therapy albeit another i-TNF or a drug with a different action mechanism like i-IL12/23 or anti-IL17A or tsDMARD (Apremilast), is recommended in patients with peripheral PsA and an i-TNF failure (Grade B recommendation).

2017

CVD risk profile should be considered both in assessing and treating these patients (Grade D recommendation).

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 center of reference ([Grade D recommendation](#)).

Treatment of Axial Spondyloarthritis (axSpA) and Psoriatic Arthritis (PsA)

Participation of clinical nurse specialists is recommended, either in person or by telephone, in follow-up consultations for patients with axial spondyloarthritis or with psoriatic arthritis due to evidence it increases patient satisfaction ([Grade D recommendation](#)).

Patients who are smokers and suffer from axial spondyloarthritis or psoriatic arthritis could benefit from implementation of educational tobacco cessation programs 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 lower 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 the patient opinions and preferences are not influenced ([Grade D recommendation](#)).

Patients with psoriatic arthritis could benefit from educational programs, preferably in a group setting led by a clinical nurse specialist. This would facilitate patient self-management and would treatment adherence ([Grade D recommendation](#)).

1. Introduction

Spondyloarthritis (SpA), traditionally described as spondyloarthropathies, is an umbrella term for a number of rheumatic diseases that share clinical, pathogenic, genetic, radiographic, epidemiological, and therapeutic response features. Both axial spondyloarthritis (axSpA) and Psoriatic arthritis (PsA), among others, are now included within this group. In addition, two subgroups are now classified within axSpA: Ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA).

AxSpA is a condition that affects sacroiliac joints and the vertebral column. Diagnosis was long based on the modified New York classification criteria of 1984 for AS (1). These classification criteria require the presence of a certain degree of chronic structural damage. Such damage is not reversible in sacroiliac joints and is detectable in a standard x-ray, which meant a significant delay in diagnosis. For this reason, the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axSpA (2) was introduced in 2009. These classification criteria incorporate magnetic resonance (MRI) of sacroiliac, which enables screening for acute alterations in sacroiliac joints (3) even when radiographic structural damage is not yet apparent. Currently, based on ASAS criteria for axSpA, there are two different patient types with axSpA: 1) those with AS who already have a certain degree of structural damage visible in a standard x-ray; and 2) those with nr-axSpA who suffer an early or less serious form of the disease. Answers to clinical questions related to AS, axSpA, and nr-axSpA will be found in this clinical practice guideline.

PsA is a chronic inflammatory disease of the musculoskeletal system usually associated with psoriasis. It may affect peripheral joints, axial skeleton joints (sacroiliac joints and vertebral column), entheses (sites where ligaments attach to the bone), tendon sheaths (dactylitis), skin, nails and other organs (bowels, eyes). Some years ago, its clinical heterogeneity and the absence of classification criteria made epidemiological studies and specific clinical trials problematic. Its various forms and musculoskeletal and cutaneous manifestations require complex treatment involving numerous specialists, particularly rheumatologists and dermatologists (4, 5).

In order to reduce variability in clinical practice and to improve patient care and quality of life for those with axial spondyloarthritis and psoriatic arthritis, the Spanish Society of Rheumatology (SER) has fostered the development of clinical practice guideline (CPG) under the aegis of a multidisciplinary team of professionals involved in the care of such patients. Clinical practice guideline document a “set of recommendations that aim to optimize patient care and are based on a systematic review of evidence and the risks / benefits of each option” (6).

Internationally, the most commonly used recommendations for the diagnosis and treatment of these rheumatic diseases have been those developed by the *European League Against Rheumatism* (EULAR) and of the *American College of Rheumatology* (ACR). In Spain, the reference guide (ESPOGUIA) was expanded upon by SER in 2009 (4). Significant advances made in recent years, mainly in areas of therapeutic intervention and diagnosis of early forms without structural damage, require an update to the CPG’s contents. ESPOGUIA 2015, Clinical Practice Guideline for Patients with Axial Spondyloarthritis and Psoriatic Arthritis, appears in this context.

This guideline, based on solid researched, provide users with information on available therapeutic interventions for these diseases, as well as assessments of their effectiveness.

This document reflects the work of many health professionals throughout Spain who are involved in the management of patients with axSpA and PsA. Recommendations are introduced at the beginning of each chapter with the summary of evidence appearing at the end.

The material detailing the methodology used in the CPG (search strategy for each clinical question, evidence tables, justification of recommendations, etc.) is available in the appendix.

SER, as sponsor of this guideline, hopes to promote effective, safe, and coordinated decision making on therapeutic interventions for patients suffering from axSpA and PsA.

2017 Update

After publishing ESPOGUIA 2015, the appearance of new treatment options for Axial Spondyloarthritis (axSpA) and Psoriatic Arthritis (PsA) led the Spanish Society of Rheumatology (Spanish acronym SER) to draw up two new documents with the SER’s Recommendations

regarding these pathologies. The results of the same have served to update this CPG. In the case of axSpA the new recommendations are an update on the assessment of illness activity and treatment goals. The new drugs available have also been included likewise their new indications and a review of the predictive factors for therapeutic response and radiographic progression of damage. Lastly, they tackle failure situations for a first anti-TNF, likewise the possible optimization of biological therapy. Regarding the PsA, apart from early diagnosis and treatment importance, emphasis is placed on the biological therapy indications and role of the new tsDMARDs with specific target like Apremilast, in the different clinical forms of the disease. Furthermore, the CPG have incorporated therapeutic algorithms drawn up in said Recommendations documents.

2. Scope and Objectives

2.1. Scope

This guideline focus on the care of those patients affected by axial spondyloarthritis (axSpA) or psoriatic arthritis (PsA). Only adult patients are included, and the clinical area being addressed is the treatment of these diseases.

Outside the scope:

- The population under 18 years of age.
- Recommendations about diagnosis, prevention, monitoring, and prognosis.

This guideline include different therapeutic options:

- Pharmacological treatment.
- Aspects in the treatment of patients with this pathology during the early stages of disease.
- Non-pharmacological treatment with exercise rehabilitation programs.
- Impact of smoking habits on clinical manifestations.
- Usefulness of health educational programs.
- In the case of PsA, the guideline only provide recommendations for inflammatory musculoskeletal manifestations, since management of moderate-severe cutaneous psoriasis is the responsibility of the dermatologist.

2.2. Objectives

Primary Objective: Provide guidance to rheumatologists on treatment recommendations based on the available scientific evidence; specifically, therapeutic interventions for the management of adult patients suffering from axSpA and PsA. In those situations, where sufficient evidence is lacking, recommendations are based on the consensus of the members who participated in the guideline development group.

Specific Objectives:

- Increase the skills of health professionals involved in caring for patients with axSpA and PsA in order to improve the quality of care offered.
- Reduce variability in clinical practice in the therapeutic management of these pathologies.

- Assess the effectiveness, safety, and efficiency of the different pharmacological and non-pharmacological approaches available.
- Summarize the scientific evidence in order to increase the knowledge of all professionals involved in the care process.
- Establish recommendations to standardize the care of patients with axSpA and PsA.
- Encourage collaboration between professionals from various specialties who are involved in patient management. In the specific case of PsA, collaboration between dermatology and rheumatology is considered essential for the satisfactory management of such patients.
- Develop general information material for the population affected by axSpA or PsA, as well as their relatives and caregivers, to afford them a better understanding of the process and aspects affecting disease progression.

2.3. Target Users

In addition to rheumatologists, these CPG are intended for other health professionals who may be involved in managing patients with axSpA and PsA, and/or who work in specialized care and primary health care: dermatology, gastroenterology, ophthalmology, rehabilitation, nursing, general practitioners, and other specialties. This guideline can also be used by patients and their relatives during consultations, allowing them to become more familiar with the existing therapeutic strategies and options. In this way, treatment regimens that are not supported by solid scientific evidence and/or the consensual opinion of experts can be avoided.

3. Methodology

In the creation of these CPG for the treatment of axial spondyloarthritis and psoriatic arthritis a number of steps were been taken, documented below:

1. Guideline Development Group

A multi-disciplinary work group was set up consisting of professionals involved in medical care, technical experts from the Research Unit (RU) of SER, and patient representatives. All participants are mentioned in the authorship and collaborations subsection. The composition of the group is described below.

- *Coordination*: A rheumatology specialist serving as the principal investigator (PI), and a methodology specialist, who is also a technical expert from the RU of SER, were charged with coordinating all clinical and methodological aspects of the CPG, as well as supporting the guideline development group.
- *Experts Group*: Rheumatology, dermatology, specialized nursing, rehabilitation, and ophthalmology specialists were selected through a public appeal via the participating scientific societies. As members of an expert panel, they supervised the drafting of recommendations for the CPG.
- *Reviewers*: Various reviewers from SER were responsible for systematically reviewing the available scientific evidence.
- *Patients*: Apart from health professionals, two patients also participated in the working group from its early stages.

A project calendar was set up establishing different phases and deadlines.

2. Scope and of Objectives

Updating the former Espoguía was deemed necessary due to the time elapsed since its last publication and because of new findings and advances. The former guideline have been partially updated and are hereby replaced with the new CPG. Delimitation in the scope and objectives of the CPG was consensually determined, drawing upon the clinical experience and information provided by the participating health professionals.

3. Formulating Clinical Questions

After defining the CPG's scope and objectives, the members of the guideline development group formulated the key clinical questions that had to be answered. A list of generic clinical questions was also created. Those questions that addressed the guideline's objectives were selected and rephrased using the Patient-Intervention-Comparison-Outcome (PICO) method.

2017 Update

The SER Recommendations documents on AxSpA and PsA have served to update some of the PICO questions included in ESPOGUÍA; in addition to providing new PICO questions whose aim was to review the most recent information obtained from scientific evidence based on therapeutic treatment of these patients.

4. Literature Search, Assessment and Synthesis of Evidence

A literature search was carried out using the MEDLINE database (via PubMed), EMBASE (Elsevier), the Cochrane Library (Wiley Online Library), and Cinahl (EBSCOhost). The question regarding physiotherapy was researched in PEDro (Physiotherapy Evidence Database). These databases were selected because they are not only readily accessible, but also constitute some of the main resources for biomedical information today.

Literature and database searches were limited to those studies published after the creation of ESPOGUÍA 2009 (4); i.e., from the beginning of 2008. These searches were completed at the end of 2014. Initially, all search strategies sought only to recover the primary studies in the aforementioned databases. However, if the results proved to be poor or inconsequential, then a supplemental search by hand among the bibliography in the most relevant documents was conducted. Further material was included after consulting with investigators and reviewers. This helped identify those studies published since the initial search until the current guideline were created, 2015. The studies examined included publications in Spanish, English, and French.

2017 Update

The methodology used to update ESPOGUÍA is based on the methodology manual for the Updating of National Health System Clinical Practice Guides (7).

Following said method the reference, revision was completed in 2016; subsequently panelists identified some studies which had been published in 2017 and were included in the evidence corpus.

To manage the references found EndNote x7 reference agent was used. The search strategy for the different databases is detailed in the SER page methodology appendix.

http://www.ser.es/wp-content/uploads/2016/03/anexo_metodologico_Espoguia2015.pdf

<https://www.ser.es/wp-content/uploads/2018/04/Anexo-sobre-la-exposici%C3%B3n-publica-de-Recomendaciones-de-EspAax.pdf>

<https://www.ser.es/wp-content/uploads/2018/04/Anexo-sobre-exposici%C3%B3n-publica-de-Recomendaciones-en-APs.pdf>

Studies Inclusion Criteria

The included studies had the following characteristics:

Study Population: Adults diagnosed with axSpA, nr-axSpA, AS, or PsA.

Intervention: Early treatment, disease-modifying antirheumatic drugs (DMARDs), biological therapy (BT), multidisciplinary dermatology-rheumatology management of patients, health education programs, treatment discontinuation, rehabilitative intervention, smoking habits.

Outcome Variables: Efficacy in dealing with the disease cutaneous and musculoskeletal activity measured by the usual clinical parameters; axial and peripheral symptoms, enthesopathy by sonography or MRI, dactylitis, uveitis, visual prognosis, radiologic structural damage, functional capacity, quality of life.

Studies Design: Systematic reviews (SR) in randomized clinical trials (RCT), RCT phase III or IV double blind and observational studies that lasted a minimum of ≥ 6 months in ≥ 50 patients.

Exclusion Criteria

In this CPG were not included: 1) studies including children, adolescents, and pregnant women; 2) studies that did not adjust for PICO methodology variables related to patient sample size, intervention, comparisons, outcomes, or study design; and 3) abstracts, posters, narrative reviews, letters, editorials, and any studies that had not been published.

Quality Assessment of Studies

Studies were selected based on the inclusion and exclusion criteria specified above. A critical reading of the studies was conducted using the critical SIGN (Scottish Intercollegiate Guidelines Network) reading templates, and their internal and external validity measures were assessed. From the selected studies, the most significant data referring to methodology, outcomes, and quality (Appendix X) were extracted and entered in evidence tables. The level of scientific evidence was evaluated using a modified version of the Oxford Centre for Evidence-Based Medicine (CEBM) system (<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009>).

Formulation of Recommendations

After the considered review, recommendations were formulated. These formulations were based on the 'formal evaluation' or 'reasoned judgement' after previously summarizing the best available evidence for each clinical question. The strength of each recommendation was evaluated using a modified version of CEBM (<http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009>). Recommendations that proved controversial or that lacked sufficient evidence were submitted to the development group consensus.

Information from Patients

In addition to updating current treatment recommendations, the CPG encompass the patient's perspective.

Initially, information on how patients perceive the experience of living with axSpA and PsA was collected. Several patients voluntarily gave information about their experiences and concerns through qualitative research methodology, through focus groups and in-depth interviews.

Subsequently, the CPG coordinators developed a version of the document for patients that included their statements and submissions. This material was adapted to the patients' language and style, and collects the most helpful information related to the illness. It was created by a sub-working group consisting of professionals and the patients in the guideline development group that authored the CPG.

Guideline External Review and Final Document Edition

At this point, an advanced draft of the CPG was developed, and the work group reviewed it. Each section was analyzed, and any necessary amendments were considered for inclusion.

Subsequently an external revision was carried out by professionals selected based on their expertise in the relevant pathology and in the creation of clinical guidelines.

Scientific societies involved in this guideline development, which are represented by members of the work group are as follows: The Spanish Society of Rheumatology (Spanish acronym, SER); the Spanish Academy of Dermatology and Venerology (Spanish acronym, AEDV); the Spanish Society of Ophthalmology (Spanish acronym, SEO); the Spanish Society of Rehabilitation and Physical Medicine (Spanish acronym, SERMEF); and the Spanish League Against Rheumatism (Spanish acronym, LIRE).

Public Display

The draft CPG was subject to public comment by SER associate members and different interest groups (the pharmaceutical industry, other scientific societies, and patient associations). It was available for a 21-day period, at the SER website, together with a submission form that sought to collect scientific input on the methodology and recommendations put forth by the CPG.

How to Use the CPG

This CPG is organized into chapters. Each chapter, dealing with different areas of disease management, consists of the PICO question, a table showing the grade of quality plus an evidence summary; another table showing the grade of strength and the recommendations; a brief introduction to the question; the body of evidence and comments on its consistency, applicability, and relevance in this context.

The complete guideline is available at www.ser.es as is detailed information on the methodological process; i.e., the search strategies and the evidence profiles for the selected studies.

4. Epidemiological Data and Clinical Manifestations

Spondyloarthritis (SpA) is commonly encountered in both specialized and primary health care facilities. Such diseases affect a patient's health and quality of life, as well as his/her family, psychosocial, and work spheres. A better understanding of these diseases is imperative.

4.1 Prevalence

SpA diseases have a universal distribution. Their incidence and prevalence differs according to ethnicity, geographical location, and most importantly, the frequency of HLA-B27 among the general population (4, 8-10). Differences in classification criteria among various international studies have resulted in variable data sets. Prevalence figures range from 0.1% to 2.5% of the population, and an incidence rate of 0.84 to 77 cases per 100,000 inhabitants/year is estimated (4).

This tendency is also seen in Spain. One study that used the ESSG (European Spondyloarthropathy Study Group) criteria, considered a "gold standard" in the field, assessed the annual incidence rate of SpA at 62.5 patients per 100,000 residents (11).

AxSpA and PsA are chronic inflammatory and musculoskeletal diseases that are very common and have a significant medical and social impact. A recent systematic review of the prevalence of AS (per continent on average) concluded that although there are important differences from one to another, there is coherence among the figures reported in these areas. Indeed, there are enough studies to estimate that the number of possible patients suffering AS in Europe between 1.30 and 1.56 million (12).

Estimates of PsA incidence and prevalence show significant variations across different geographical areas and countries. According to the available data, psoriasis seems to affect approximately 3.2% of the population, and almost one third of patients with psoriasis suffer from arthritis. Therefore, PsA prevalence may vary between 0.3% and 1.0% (5).

There are only a few studies in Spain analyzing the prevalence of these pathologies (13, 14). Despite this fact, the available data is consistent with that obtained in other Western countries. Between 1% and 3% of the population may be affected by any one of these diseases

(15-18). Likewise, the annual incidence is estimated to be 3.6 cases per 100,000 inhabitants (95% CI: 2.7-19.0) for AS (9).

4.2 Impact, Quality of Life

The significance of these pathologies stems not only from their incidence and prevalence rates, but also from their impact on patients, society, and the medical system. SPA patients suffer higher comorbidity and mortality rates than the general population (19-27).

Although the clinical spectrum of these two diseases is heterogeneous, both can very negatively affect the quality of life in affected populations (28). Pain and functional limitations may lead to physical, psychological, and/or even sexual problems. In addition to this, rheumatic diseases are not widely understood or accepted, which may lead to socio-labor and socio-emotional problems (4). Data obtained from the study “Prevalence and Impact of Rheumatic Diseases in Adults in Spain” (Spanish acronym, EPISER) showed that when it came to measuring the burden of disease vis-à-vis quality of life, rheumatic diseases rank alongside other chronic neurological, cardiovascular, and respiratory diseases (26, 29).

4.3 Disease Burden

The burden associated with rheumatic and musculoskeletal diseases provides a measure about the loss of health in the general population, both in terms of fatal and non-fatal consequences. Moreover, even a single value (mortality, incidence, disability) enables some measure of the epidemiological data for each disease (30).

According to the World Health Organization (WHO), rheumatic diseases are the leading cause of physical disability in the Western world. Specifically, between 17% and 19% of occupational disability stem from some of the more than 250 rheumatic pathologies. In this regard, rheumatic and musculoskeletal diseases result in major expenditures as they are responsible for between 10% and 15% of primary care consultations and 10% of hospital emergencies. These diseases are also responsible for indirect costs such as sick leave, loss of productivity, social benefits, etc.

There are only a few prospective observational large-scale studies on the disease burdens of axSpA and PsA, but they show that these diseases result in significant socioeconomic costs. From a labor perspective, a high incidence sick leaves appears between 20 and 60 years of age;

and from a social perspective, major expenditures stemming from health problems and dependency in older patients increase significantly (31, 32).

Sick leaves due to AS vary between 6.5 and 18 days per patient/year. Between 15% and 20% of patients need assistance from relatives or other individuals (33, 34). Recent data show annual costs averaging between 4,782 and 5,806 euros per patient (35). From a socioeconomic perspective, European studies show that AS mainly impacts productivity. Indeed, functional disability values in these studies demonstrate just how expensive treatment is during the first and fifth years (36, 37).

Studies examining PsA burden have yielded scant data on economic and quality of life issues. For example, some European studies show that in Germany the average direct cost was 3,156 Euros per patient/year, while indirect costs can vary between 2,414 and 7,919 Euros depending on the method used to calculate. In Hungary, average total costs were 5,574 Euros per patient/year (direct costs 2,670, and indirect costs 2,904). These studies concluded that disease behavior, motor function disability, and severity of cutaneous symptoms were the determinant cost factors (38, 39).

In Spain, the average cost of PsA (both direct and indirect) is estimated at approximately 7,920 Euros per patient/year (4, 40), reaching 75,000 Euros in certain severe cases or those with poor prognosis (4, 41).

4.4 Organization and Assistance to Patients with Rheumatic and Musculoskeletal Diseases in the National Public Health System

The initial contact between a patient with rheumatic disease and the national public health system usually takes place at a primary care visit. The patient may then be referred to specialized care for consultation and possible diagnosis. Diagnostic techniques have improved greatly and a therapeutic resolution is usually possible without hospitalization. For a great number of rheumatic diseases, preventative measures and activities promoting a healthy lifestyle are key factors in not only lowering incidence and prevalence rates, but also in improving quality of life. Good coordination and communication between the health and social professionals involved lead to a more effective, comprehensive, and continuous patient care treatment plan (26).

Within this conceptual framework, efficient management of rheumatic diseases requires the coordinated participation of different professionals working in concert to address the specific needs of a patient at a particular time without redundancy or deficiency. Autoimmune and inflammatory diseases are the conceptual paradigm for this complex challenge (26).

Under Spanish health care guidelines, the patient must take into account two important factors: self-management education and risk management of medicinal products. Therefore, any initiative or program aimed at promoting and facilitating self-care (expert patient, patient education, or nursing consultation and rehabilitation/physiotherapy) will benefit patients, professionals, and the system as a whole. Likewise, it is also important to develop measures that guarantee patients' safety due to the high number of patients taking different medications, often simultaneously, throughout the course of the disease, particularly given the chronic nature of such diseases (26).

The national strategy for rheumatic diseases establishes a group of objectives, recommendations, and indicators, which will contribute to improve the quality of interventions and health outcomes in patients' health. This must be done from a realistic approach, according to the available resources and the field of competence of each Autonomous Community in Spain, and based on the available evidence (26).

It is difficult to assess the quality of health care and health outcomes for patients with rheumatic diseases. The Strategy proposes a group of indicators that enable a time analysis of these diseases using countrywide information sources. Other indicators must be provided by Autonomous Communities; and sometimes by scientific societies, and patient associations (26).

4.5 Clinical Manifestations

Spa are a heterogeneous group of diseases sharing certain clinical, immunogenic, and radiographic features that distinguish them from other diseases (42): 1) familial clustering, 2) pathogenic mechanisms, 3) association with HLA-B27 and with infections generally affecting the gastrointestinal or genitourinary tract, 4) entheses (area where tendons, fascia, and ligaments insert into bones in peripheral joints and vertebral spine) affection, and 5) clinical signs and symptoms.

These diseases are characterized by chronic inflammation of the entheses and other musculoskeletal structures with a tendency to produce bony ankylosis. The most typical and frequent clinical characteristics are: sacroiliitis, enthesitis, spondylitis, oligoarthritis or polyarthritis, uveitis (eye inflammation), psoriasis, and bowel inflammation. Other symptoms and extra-articular manifestations may appear, but are generally less frequent.

Each SpA has its own peculiarities. They are thus considered as specific entities with unique treatment and follow-up plans adapted to their specific characteristics (4).

Axial Spondyloarthritis (axSpA)

AxSpA is closely related to HLA-B27 (43). It is a chronic systemic inflammatory disease of unknown origin, which primarily affects the axial skeleton (sacroiliac joints and vertebral column) and entheses. Its most characteristic lesion is sacroiliitis (44).

The inflammatory process can provoke chondral ossification, as well as fibrous ankylosis leading to ankylosis during its advanced stages in up to 30% of patients. Less frequent, but no less important, is peripheral joint involvement, especially for joints in the lower limbs such as hips, knees, and feet. Extra-articular manifestations like uveitis can also appear (4, 45). AxSpA is also associated with major comorbidities, such as cardiovascular disease and osteoporosis (46). Less commonly associated comorbidities are renal, neurological, and pulmonary manifestations (47).

Psoriatic Arthritis (PsA)

PsA is a chronic inflammatory disease of the musculoskeletal system associated with cutaneous psoriasis and, generally, with a negative rheumatoid factor. Its clinical heterogeneity and absence of classification criteria until a few years ago have hindered epidemiological studies and specific clinical trials (4, 5).

The association between one of the various forms of cutaneous psoriasis with one or more of the different PsA clinical expression patterns may explain the difficulty in assessing the genetic profile of this disease (48). In particular, Cw6 has been associated with psoriasis, while HLA-B27, HLA-B38, and HLA-B39 are associated with PsA (49).

Certain environmental factors seem to increase susceptibility to developing PSA, including HIV infection, traumatic stress, and obesity. In addition, some forms of psoriasis (e.g., nail

dystrophy, scalp lesions, and intergluteal/perianal psoriasis) have been associated with a higher likelihood of developing PsA (50).

PsA increases risk factors for cardiovascular diseases such as hypertension and dyslipidemia, which are characterized by atherogenic lipid profiles. This increases the incidence not only of subclinical atherosclerosis (51-54), but also that of metabolic syndrome, especially in those patients with moderate-to-severe skin conditions. For such patients, the disease usually has a major psychological impact (55), all of which lowers quality of life.

5. Clinical Questions

Treatment of Axial Spondyloarthritis (axSpA)

2017

1. In patients with axial spondyloarthritis, does early pharmacological intervention improve functional capacity, structural damage and quality of life?

2. In patients with non-radiographic axial spondyloarthritis, 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?

2017
new

3. In patients with AxSpA, what are the prognostic factors regarding response to biological treatment?

2017
new

4. In patients with AxSpA, does pharmacological intervention with biological therapy (BT) control structural damage progression and axial radiographic lesion?

2017
new

5. In patients with axSpA who failed to respond to anti-TNF, would the intervention with another anti-TNF or biological therapy be efficient?

2017

6. In patients with axial spondyloarthritis, is it possible to stop treatment of TNF inhibitors? Is it possible to reduce the treatment dose of TNF inhibitors?

7. In patients with ankylosing spondylitis, does the use of biologics, compared with sulfasalazine, reduce the number of recurrences of uveitis and improve visual prognosis?

8. In patients with ankylosing spondylitis, what kind of exercise program is most effective in improving clinical and functional parameters?

9. In patients with axial spondyloarthritis, does smoking aggravate clinical manifestations (arthritis, axial involvement, enthesitis, and structural damage)?

Treatment of Psoriatic Arthritis (PsA)

2017

10. In patients with psoriatic arthritis, does early pharmacological intervention improve functional capacity, structural damage and quality of life?

2017

11. In patients with PsA, what is the efficacy of biological therapies in monotherapy regarding to peripheral, axial, enthesitis, dactylitis, uveitis, skin and nails clinical manifestations?

2017

12. In patients with PsA, what is the efficacy for DMARDs in its peripheral, axial, enthesitis, dactylitis, uveitis, skin and nail domains?

2017

13. In patients with psoriatic arthritis, is combined treatment with MTX and TB more effective than treatment with TB in monotherapy?

2017
new

14. In adults with PsA with axial and/or peripheral affection refractory to an anti-TNF, is treatment with a second BT efficient?

2017
new

15. In patient with PsA, does treatment with DMARDs or biological therapies reduce CVD mortality?

16. In patients with psoriatic arthritis 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?

Treatment of Axial Spondyloarthritis (axSpA) and Psoriatic Arthritis (PsA)

17. In patients with axial spondyloarthritis, are the health education programs offered by nurses beneficial? In patients with psoriatic arthritis and peripheral and/or axial affection, are the health education programs offered by nurses beneficial?

6. Treatment of Axial Spondyloarthritis (axSpA)

2017

Clinical Question 1

In patients with axial spondyloarthritis, does early pharmacological intervention improve functional capacity, structural damage and quality of life?

Summary of the Evidence

There is insufficient evidence on the effectiveness of early pharmacological treatment for patients with axial spondyloarthritis (56-61).	2b, 4
In secondary analyses evaluating the effectiveness of early pharmacological treatment in patients with axial spondyloarthritis, those with shorter disease durations responded better to treatment with anti-TNF (57, 62,63).	2b, 4

Recommendations

2017

As soon as axial spondyloarthritis has been diagnosed we recommend commencement of pharmacological treatment (**Grade D recommendation**).

For the majority of chronic complex diseases, particularly for rheumatoid arthritis (RA), there are consistent data demonstrating that early and effective treatment is the key to improving clinical response, and possibly, to reducing disease burden (disability, time off work, improved quality of life) (64-68). In the end, patients with axSpA endure significant burden diseases comparable to those of RA (39, 41). These patients often suffer delayed diagnosis (≥ 6 years) due to ignorance about the disease (69, 70). At present, there are different treatment options available that are very effective in controlling the disease (71). In the long term, early diagnosis and appropriate treatment could significantly improve patient health and reduce disease burden.

Quality of Evidence

Quality studies specifically designed to answer the clinical question have not been identified. There is only a secondary analysis from a RCT focused on the question. Moreover, its level of evidence was lowered in the Oxford Center of Evidence-Based Medicine scale (CEBM). However, the guideline development group has considered it appropriate to include in the evidence review other studies not meeting the initial inclusion criteria. In this way, the group can avail itself of considerably more information when formulating its recommendations.

There exists a double-blind RCT of 12 weeks, followed by an open extension up to 52 weeks, which evaluated the effectiveness of treatment with adalimumab (ADA) compared to placebo in patients with active nr-axSpA (BASDAI ≥ 4) who had failed to respond to at least one nonsteroidal anti-inflammatory drug (NSAID). Although the study was not designed to compare the response of an early intervention or a delayed intervention, the authors included an analysis of possible response predictors. When data were analyzed at 52 weeks, patients with a disease evolution of ≤ 3 years (in addition to those with CRP > 6 mg/L, and those ≤ 30 years old) presented a higher response rate; in terms of ASAS 40 ($P=0.006$) or BASDAI 50 ($P= 0.014$), than patients with a disease evolution ≥ 10 years. However, in multivariate analysis, the shortest disease duration lost statistical significance, although younger age and high CRP continued to be response predictors for BASDAI 50 and ASAS 40, respectively. According to the authors, the loss of meaning stems from overlap in the patients' age. They also concluded that, in addition to those who are younger and whose CRP is higher, patients with shorter disease duration responded better to treatment (57). [\(Evidence level 2b\)](#).

A 3-month prospective, observational, open study recently conducted at a single center, analyzed 95 patients with active (BASDAI $\geq 40/100$) AS (New York classification criteria), as well as the effectiveness of NSAID and the possible response predictors of these drugs. Patients who responded to treatment had shorter disease durations than those who failed to present any response (4 years (0.5-13) compared with 8 years (1-34); $p<0.001$). The authors contend that the best response in patients correlated with the shortest disease evolution, a finding similar to that observed with anti-TNF treatments). This suggests that this response predictor is not related to treatment, but to the clinical attributes of the patient (56). [\(Evidence level 4\)](#).

A univariate study from two clinical trials in 99 patients with AS treated with TNF-inhibitors (infliximab, etanercept, and 12 weeks in duration) with AS showed that shorter disease duration, in addition to lower BASFI, and increased ESR and CRP, and younger age predict a

higher BASDAI 50 response (OR: 0.93; 0.88 – 0.98; $p = 0.003$). When patients were stratified according to disease duration (≤ 10 years, 11–20 years, >20 years), the authors observed a higher percentage of BASDAI 50 response, which proved significantly higher in patients with lower disease durations, (73%; 58% and 31%, respectively; $\chi^2 = 11.7$; $p = 0.003$) (59) (Evidence level 2b). A later study based on data from these same trials, analyzed predictability in response to TNF-inhibitors vis-à-vis the presence and extent of inflammatory lesions in MRI, in sacroiliac joints, or in the spine. Three predicting parameters were taken into account: disease duration, CRP (mg/L), and MRI (Berlin). Although, individually, each parameter had a moderate predictive power at best, this predictive power improved when they were combined. Patients with two of these parameters reached a response of at least 45%, while those with one of the two parameters reached at least 25%. The authors highlighted the influence of inflammation in MRIs, and reiterated that the combination of the three parameters (disease duration, high CRP, and high Berlin MRI score) is what predicts the response to treatment with TNF-inhibitors (60) (Evidence level 2b).

Another study analyzing data from two clinical trials to investigate the possible decoupling between global patient scores and the objective parameters of inflammation in 66 patients suffering from nr-axSpA and treated with etanercept for 48 weeks. Patients were classified according to disease duration: < 4 years / ≥ 4 years, and < 2 years / 2–4 years / 4–8 years / ≥ 8 years. The authors argue that, based on patient reported outcomes (PROs), the response to TNF-inhibitors is better with early treatment. Finding no differences between the groups of < 2 years and 2–4 years led the authors to assert that 4 years is a desirable cut-off value for identifying the best window of opportunity (61) (Evidence level 2b).

In an analysis of data drawn from the British Biologics Register, a multivariate analysis of predictors of improvement of BASDAI and BASFI was carried out involving 261 patients who had completed 6 months of treatment with infliximab, etanercept, and adalimumab. Variables that reached $p \leq 0.2$ were chosen, using a logistic regression model and no connection was found between disease duration and response to treatment. The authors concluded that acute phase reactants best predicted the response to treatment at its beginning (58) (Evidence level 4).

In light of the scant evidence identified for this question, it was decided to include information from two additional studies that have only been published as abstracts submitted to congresses. One 5-year open clinical trial included patients with very early SpA, although the

specify classification criteria and progression times were not specified. This trial was the continuation of a 16-week RCT (n=39) in which infliximab (INF) was administered and compared with a placebo (PBO). After 40-week monitoring period, if an outbreak occurred (BASDAI ≥ 4), then the patients were included in an open study (n= 25). Fifty-eight per cent of the patients treated with INF continued with anti-TNF compared with 100% of patients treated with PBO. The authors concluded that one-third of patients treated early with INF for three months remained healthy and required no further treatment for 5 years. In contrast, patients who received PBO at the beginning need anti-TNF treatment along of those 5-years (69). A study with data from four clinical trials, each 12 weeks in duration, and involving 1281 patients, analyzed the relationships between disease duration, baseline characteristics, and the response to treatment with placebo/ sulfasalazine (SSZ) compared with etanercept. Disease duration was classified into four categories (< 2 years, 2 – 5 years, 5 – 10 years, and > 10 years). In general, a great percentage of patients responded to etanercept than those treated with SSZ or placebo. Patients with shorter disease durations experienced tended to respond better to ETA for most of the dichotomous variables, which was not observed in the case of SSZ or PBO. This tendency was significant for those ≤ 40 years of age at diagnosis. The authors concluded that ETA was more effective than SSZ and PBO irrespective of disease duration. Patients with a disease duration ≤ 2 years seemed to present the highest response rates (73).

2017 Update

The latest SER Recommendations update on using biological therapies for AxSpA includes new references supporting the benefit of early treatment in patients with AxSpA.

There are two RCTs which communicate the efficacy of anti-TNF therapy in early AxSpA. The first included patients with 'Inflammatory lumbar pain' (ILP) for at least 3 years and HLA-B27+ besides active *Sacroiliitis* in MRI. They were treated with Infliximab with favorable responses (ASAS20 and ASAS40, ASAS-PR, BASDAI), improvement or resolution of inflammatory MRI lesions (osseous edema), likewise functional (BASFI) and quality of life (ASQoL) improvements at 16 weeks, better than those of the placebo cohort (62).

In the second (63), patients diagnosed with active AxSpA and at least 3 years' evolution, active inflammation in MR SI, without prior NSAID use (or at least subjected to lavage if received prior) were included and assigned (2: 1) to receive Naproxen (NPX) 1000 mg a day plus IFX 5 mg/kg or placebo until week 24. More partial remissions of ASAS (ASAS-PR) in cohort with

IFX+NPX (61.9%) than that with PBO+NPX (35.3%) at week 28 ($p=0.002$). Furthermore, more patients in the IFXxNPX cohort had ASDAS, ASDAS-ID improvements, ASAS-40 response or improvements in BASDAI or BASFI among others.

Irrespective of whether it is therapy with anti-TNF or NSAID, these findings suggests that early treatment is a predictive factor of clinical response in such patients (56, 57, 60, 61, 73, 74).

In formulating recommendations, in terms of their applicability and the possibility of generalizing the results, the expert panel concluded that, though specific well-designed studies remain lacking, the results consistently demonstrate that the duration of disease is a predictive factor of clinical response in patients with axSpA. However, it is worthwhile noting two issues: First, there are no definitive data enabling the precise establishment of what is meant by early treatment. Some studies suggest that it could well be a period of less than 5 years from the onset of symptoms (57, 59, 61, 73), although a better clinical response has been documented in patients with less than 10 years of evolution (57, 59, 61, 73). Second, if the results using different treatments proved similar, this would suggest that response prediction is more closely linked to patient clinical characteristics than to the treatment itself. The guideline development group concluded that obtaining a good clinical response, even clinical remission, could ultimately minimize direct and indirect care costs. Evidence suggests that the earlier the treatment, the easier it is to achieve this objective.

Clinical Question 2

In patients with non-radiographic axial spondyloarthritis, what is the effectiveness of different biological therapies compared with placebo or traditional DMARDs? What is the relative effectiveness of the different biological therapies?

Evidence Summary

Biological therapies with anti-TNF (adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab) have proven effective in treating non-radiographic axial spondyloarthritis (57, 62, 70, 75-78).	1b
Biological agents such as adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab, versus placebo, contribute to (57, 62, 70, 75-78): <ul style="list-style-type: none"> Minimizing inflammatory activity. Improving functional capacity. 	1b
In non-radiographic axial spondyloarthritis, the biological agent tocilizumab does not improve clinical or functional parameters that have not previously responded to treatment with anti-TNF (79).	4

Recommendations

Therapy with anti-TNF is recommended as the pharmacological treatment of choice for patients with active* non-radiographic axial spondyloarthritis who are refractory to NSAID. (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 axial spondyloarthritis who are refractory to NSAID and/or treatment with anti-TNF. (Grade C Recommendation).

ASAS classification criteria for axial spondyloarthritis (axSpA) (80) have defined the non-radiographic axial spondyloarthritis (nr-axSpA), an entity which is characterized by the absence of structural damage in x-rays, as an early stage of axSpA. Several studies have revealed clinical manifestations and disease burden (81-85) that are comparable in patients with nr-axSpA and

those with AS, based on modified New York Criteria (1). Therefore, both stages require treatment, irrespective of the presence of structural damage. Current consensus holds that anti-TNF should be the treatment of choice for patients with axSpA (nr-axSpA included) who are refractory to NSAID (14, 86). There is clear evidence that treatment with anti-TNF is effective in improving signs, symptoms, and functional capacity with AS (75, 87, 88). There are even data supporting a possible slowing of spinal radiographic progression (89,90). Furthermore, for those AS patients who are refractory to NSAIDs (91, 92), clinical trials with ustekinumab (inhibitor IL-12/23) and secukinumab (inhibitor IL-17) are currently underway and show good preliminary results. Definitive results of these RCT probably will help to determine the real role of biological therapies for nr-axSpA.

Quality of Evidence

In one meta-analysis of 20 studies with data from 3096 patients (15 studies in AS, and five in nr-axSpA), the principal objective was to evaluate the effectiveness of therapy with anti-TNF, compared with placebo, in patients with AS and nr-axSpA. Regarding the latter, five studies of have been conducted – one with adalimumab, one with infliximab, one with certolizumab pegol, and one with etanercept – all at least 12 weeks in duration. Treatment with anti-TNF showed higher effectiveness than placebo in BASDAI (effect size 0.73; 95% CI: 0.44-1.01), BASFI (effect size 0.57; 95% CI: 0.29-0.85), and response ASAS 40 (HR 3.6; 95% CI: 2.5-5.3). In another systematic review (SR) an analysis based on data from some of the aforementioned studies found no significant differences in the efficacy of anti-TFN therapy among patients with AS and nr-axSpA (75) ([Evidence level 1a](#)).

Another systematic review (SR) of seven studies involving 117 patients suffering from undifferentiated spondyloarthritis, based on ESSG criteria (93), evaluated the effectiveness of different drugs (94). Only two studies, which were already part of the previous meta-analysis, examined the effectiveness of anti-TNF therapy compared with placebo in nr-axSpA. A British study compared the effectiveness of infliximab (IFX) (5mg/kg weight at weeks 0, 2, 6, 12) versus placebo over a 16-week period in 40 patients with inflammatory low back pain ≤ 3 years according to Calin's criteria (95), positive HLA-B27, and positive MRI of the sacroiliac joint. All patients included in the study, less 12%, met the nr-axSpA criteria, while only three patients met the New York Criteria. An improvement in response (ASAS 40) was observed in 61% of patients in the IFX group compared with 17% of those in the placebo group ($p=0.009$). A significant improvement was also observed in BASDAI, BASFI, and ASQoL scores in the IFX

group. Partial remission (ASAS) was higher in the IFX group (55.6% compared with 12.5%, $p=0.009$). Average reduction in the total RM score was significantly higher in patients treated with IFX -2.0 (IQR $-6.25, 0.0$) compared to those in the placebo group (IQR $-2.00, 1.5$). Afterwards, it was observed that three patients in the placebo group had a baseline score of 0 in MRI. Thus, the results were possibly biased due to the small sample size. Severe adverse events were not observed (62) ([Evidence level 1b](#)). The other study compared the effectiveness of adalimumab (40 mg every two weeks) versus placebo in 46 patients with nr-axSpA who were refractory to NSAIDs. At week 12, the adalimumab group ($n=22$) had higher response rates (ASAS 40 and ASAS partial remission) in 54% and 23% of patients compared with 12% and 0% in the placebo group ($n=24$), respectively. Significant improvements in response rates (ASAS 20, BASDAI 50 and in BASDAI, BASFI, PGA, GPV, CRP), as well as in nocturnal pain, were observed in patients treated with adalimumab. When patients previously given a placebo also began treatment with adalimumab, the effect remained evident at week 52 for the entire group. A young age (≤ 30 years) and a high baseline CRP ($> 6\text{mg/L}$) were the best predictors of response (ASAS 40 or BASDAI 50). Patients with positive HLA-B27 and positive MRI tended to have higher response rates (ASAS 40 and BASDAI 50), although the results did not reach statistical significance. There were no severe adverse events linked with adalimumab (57) ([Evidence level 1b](#)).

A multicentric study investigated the effectiveness of adalimumab (40 mg every two weeks) versus placebo in 185 patients with nr-axSpA, according to ASAS criteria (80), who were refractory to NSAIDs. At week 12, more patients treated with adalimumab ($n=94$) reached a response (ASAS 40 and partial ASAS remission) compared to those given a placebo ($n=91$) (36% vs. 15%, and 16% vs. 5%; $p \leq 0.001$), respectively. Significant improvements were also observed in responses (ASAS 20, BASDAI 50, ASAS 5/6, ASDAS and in BASDAI, GPV, CRP, total lumbar pain, HAQ, and SF-36). Regarding BASFI, the adalimumab group showed a trend to improve compared with the placebo group (-1.1 vs. -0.6 , $p=0.05$). The latter also showed a significant reduction, compared with the placebo group, in their Spine-SPARCC inflammation scores (-1.8 vs. 0.2) and sacroiliac joints (-3.2 vs. -0.6). Predictors of treatment response were analyzed and the following characteristics were associated with a higher response (ASAS 40) in the adalimumab group: symptom durations < 5 years ($p=0.02$), age < 40 years ($p=0.05$), and high baseline CRP ($p=0.03$). On the other hand, this effect was not observed according to the positivity of HLA B27 ($p=0.42$) and the presence of sacroiliitis in baseline MRIs ($p=0.65$). However, in those patients with baseline SPARCC MRI scores of sacroiliac joints ≥ 2 , or high baseline CRP, logistic regression analysis revealed that the adalimumab group had a higher

response rate (ASAS 40) compared to the placebo group (41% vs. 14%), although this interaction was not significant and the number of patients was small (70) ([Evidence level 1b](#)).

Another multicentric study analyzed the effectiveness of certolizumab pegol (CTZ) (200 mg every two weeks, and 400 mg every month) compared with placebo in 325 patients with axSpA based on ASAS criteria (80), including 178 EA and 147 nr-axSpA patients, with less than 5 years of disease duration. Patients had to have BASDAI ≥ 4 , and high CRP (> 7.9 mg/L) and/or sacroiliitis in MRI, and be refractory to NSAIDs. Eleven percent of patients with AS, and 20% of those with axSpA EA had previously been treated with anti-TNF. Regarding the nr-axSpA patient subgroup, a higher response (ASAS 40) in those receiving certolizumab pegol ($n=46$ CTZ 200mg, and $n=51$ CTZ 400mg) compared to placebo ($n=50$) (48% and 47% vs. 16%; 57% and 45% vs. 14%; $p<0.001$), was observed at weeks 12 and 24. Both doses of CTZ also showed significant differences in changes from baseline compared with the placebo in BASDAI, ASDAS, BASFI, and BASMI. Similar improvements were observed in both CTZ dose regimens (77). The effect continued until week 96 of treatment for the entire group after patients in the placebo group began to receive CTZ (96) ([Evidence level 1b](#)).

Another multicentric study analyzed the effectiveness of etanercept (50 mg / week) combined with NSAID compared with placebo in 215 patients with axSpA, according to ASAS criteria (78), whose disease duration was less than 5 years duration and who were refractory to NSAIDs. Patients with AS (New York Criteria), and those previously treated with anti-TNF were excluded. At baseline exams, 81% of patients had positive sacroiliac joints in MRI and 43% a high CRP (>3 mg/L). At week 12, a higher response (ASAS 40) in the etanercept group ($n=106$) compared to the placebo group ($n=109$) (32% vs. 16%; $p=0.0006$) was observed. There were significant differences in the changes since baseline evaluations compared with placebo in BASDAI (-2.0 vs. -1.3), ASDAS (-1.1 vs. -0.5), BASFI (-1.4 vs. -0.8), CRP (-3.0 vs. 0.1), low-back pain (-2.0 vs. -1.1) and MASES index (-1.4 vs. -0.7). At week 12, the etanercept-treated group showed a reduction, compared to the placebo group, in the SPARCC MRI indices of sacroiliac joint (-3.8 vs. 0.8; $p<0.001$), and spinal inflammation (-2.1 vs. -1.2; $p=0.04$). A *post hoc* analysis (ASAS 40) showed that etanercept was more effective at basal higher levels of CRP ($p=0.003$) or higher MRI index of sacroiliac inflammation ($p=0.146$). The effects remained until the open phase finished at week 24 (76) ([Evidence level 1b](#)).

A retrospective study of clinical cases in France investigated the effectiveness of tocilizumab (4 or 8 mg/kg every 4 weeks for at least 3 months) in 21 patients with axial (80) or peripheral (97)

SpA, according to ASAS criteria, who were refractory to two therapies with anti-TNF. Thirteen patients had axial disease; among these were four who showed no radiographic sacroiliitis. By the third month, no patient had reached a minimum reduction of 20 mm in BASDAI. Only one patient experienced a clinically significant improvement (ASDAS), and none reached the highest level of improvement according to the same criteria. One patient experienced a BASFI reduction greater than 20%. At month 6, with only 2 patients left, neither reached a minimum reduction of 20 mm in BASDAI, BASDAI 50 response, or ASDAS improvement. Only one patient showed a BASFI reduction greater than 20%. The 4 patients with nr-axSpA did not experience a reduction in acute phase reactants (ESR and/or CRP). Severe adverse events were not observed (79) (Evidence level 4).

Another 44-week multicentric study involving 197 nr-axSpA patients compared treatment with golimumab versus placebo. The study showed that at week 16 golimumab was significantly more effective than a placebo: ASAS 20 (71.1% vs. 40.0%, $p < 0.0001$); ASAS 40 (56.7% vs. 23.0%, $P < 0.0001$). A better response (ASAS 20 and 40 with GOL) among patients with sacroiliac inflammation (MRI) or high baseline CRP (subgroup OSI) was also observed. There were no differences in patients with normal MRI and normal levels of CRP. In addition, there were significant improvements with GOL compared to PB in BASDAI 50, ASASPR, and changes in SPARCC scoring of sacroiliac joints ($p < 0.0001$; $p < 0.014$; $p < 0.001$ respectively) (78).

In formulating recommendations, the group of experts found the results from the different reviewed studies to be relatively consistent. The group concluded that anti-TNF therapy (adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab) was effective in patients with nr-axSpA, both from a clinical and functional perspective. Indeed, the therapy even improved MRI inflammation, as some of these studies have shown. There is a need for more RCTs in patients with nr-axSpA to strengthen evidence on the effectiveness of anti-TNF therapy in this population.

Regarding the effectiveness of other biological therapies in nr-axSpA, the only available data draws from a case series involving intravenous tocilizumab. In this particular series, no clinical effectiveness in patients with axSpA was observed, despite the decrease in acute phase reactants.

The results from studies examining anti-TNF therapy are applicable to our national health system as the evaluated therapeutic agents have long been used for patients suffering SpA. In Spain, adalimumab, certolizumab pegol, and etanercept have approved indications of treatment for nr-axSpA. In some of these studies, high baseline CRP and/or sacroiliac

inflammation in MRI were shown to be predictors of better response to anti-TNF therapy (57, 70, 76). For this reason, recommendations made by ASAS/EULAR (86) and the European Medicines Agency (EMA) require an objective measure of disease activity, ESR or high CRP and/or sacroiliitis in MRI, before anti-TNF treatment can be administered in patients with nr-axSpA.

2017 Update

The latest SER Consensus also recommends biological therapy commencement in patients with Nr-axSpA when accompanied by high CRP and/or signs of inflammation in MRI (98).

The studies show the powerful anti-inflammatory properties of anti-TNF therapy in patients with nr-axSpA. Since the population is young and of working age, this will result in social and healthcare cost savings. Finally, published data also suggest that treatments with anti-TNF appear to have a good risk/benefit profile in patients with nr-axSpA.

2017
new

Clinical Question 3

In patients with axial spondyloarthritis, what are the prognostic factors regarding response to biological treatment?

Summary of the Evidence

Response predictive factors identified include: age, gender, smoking, weight, disease activity (including MRI), functional capacity, disease evolution time and HLA B27 (57, 70, 99-104).

2b, 3, 4

Recommendations

2017

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](#)).

Quality of Evidence

Numerous studies have associated certain disease variables with better response to treatment with anti-TNF drugs. A younger age at treatment commencement and shorter evolution period was associated with a better response in patients with SpA (59, 99-102) likewise those with Nr-axSpA (57, 70) ([Evidence level 2b, 3, 4](#)). The greater activity of the disease on treatment commencement is one of the greatest predictive factors of good response, which appears in most studies in both patients with PsA and those with Nr-axSpA (57, 70). Several studies suggest male patients would have a better therapeutic response (99, 100, 102) ([Evidence level 2b, 3, 4](#)), whereas female patients (103) with a lower functional capacity at treatment commencement (initial BASFI raised) would have a lower therapeutic response (59, 101, 102) ([Evidence level 2b, 3, 4](#)). Overweight expressed as a raised body mass index (BMI) is associated to a lower treatment response in some studies; furthermore, an independent association has been described between BMI>30 and treatment failure (103). Smokers present with a lower reduction of disease activity (BASDAI, ASDAS), especially when CPR is high, and a lower treatment response, even in ex-smokers (104). There are contradictory data regarding HLA

B27, although most studies suggest a better therapeutic response in positive B27 individuals (102). A recent study suggests that early response to anti-TNF therapy is one of the factors most associated to good long-term response (105).

At present there are contrasted predictive factors regarding response to therapy with Secukinumab.

There are numerous factors associated with the response to anti-TNF therapy; however, none individually or combined enables a firm prediction regarding the final observed response, so its absence should not prevent commencement of BT. Nevertheless, based on the results shown, it seems important to improve the therapeutic response to BT, by not delaying treatment in active patients despite NSAID treatment, and maintaining healthy life habits (avoid smoking and being overweight).

2017
new

Clinical Question 4

In patients with axial spondyloarthritis, does pharmacological intervention with biological therapy control structural damage progression and axial radiographic lesion?

Summary of the Evidence

Biological therapy is efficient in reducing vertebral and sacroiliac bone inflammation. Recent data suggest BT is also efficient in reducing radiographic progression in SpA (76, 89, 90, 106-108).	1b
Among the predictive factors of structural damage are: basal radiographic damage, MRI affection, gender, smoking and disease activity (109-111).	2b

Recommendations

2017

Predictive factors of structural damage progression should be assessed in the biological therapy indication ([Grade D recommendation](#)).

Quality of Evidence

Regarding radiographic damage progression, the presence of basal radiographic lesion (syndesmophytes on the spinal X-ray) is the most important predictive factor for progression (109, 111). Other factors associated to a greater progression of radiographic damage are: male gender, smoking and especially the persistency of inflammatory activity of the disease (clinically evaluated by CRP serum levels and/or presence of bone edema in MRI) (110, 111). Furthermore, a study with a 12 year follow-up of the OASIS cohort patients (112) ([Evidence level 2b](#)), noted that greater disease activity (ASDAS) is associated longitudinally with greater radiographic progression.

BT has been proven to have an early inhibitory effect on vertebral bone inflammation and the MRI assessed sacroiliac joints, already objectivable at 6 weeks from treatment commencement, which is higher than that obtained with NSAID or SSZ (76, 106-108) ([Evidence](#)

level 1b). Therefore, there is probably a 'therapeutic opportunity window' during the earliest stages of the disease (Nr-axSpA) where BT seems particularly efficient in inhibiting osteitis focal points at sacroiliac or vertebral level (113). Reduction of bone edema post-BT is associated with disease activity and CRP control, especially in Nr-axSpA. However, in the first studies at 2 years, disappearance of the bone edema post anti-TNF, particularly in patients with a more evolved disease, did not prove control of the onset of focal fat degeneration (FD) and structural damage progression (syndesmophytes) (114-116). In this sense there are data supporting the association of inflammation or FD or FD without prior inflammation is significantly associated with syndesmophyte formation after 5 years' treatment with Infliximab (117). Nevertheless, recent data suggest continuous treatment with anti-TNF for over 4 years is associated with a significative reduction in structural vertebral damage progression assessed by simple X-ray (mSASSS) (89, 90). Structural damage progression was less the sooner treatment was commenced, particularly in cases where disease evolution was less than 5 years, and the longer time treatment with anti-TNF was (90).

The data from major Secukinumab trials seem to indicate the reduction of osteitic lesion is associated with non-progression of fat lesions and a low rate of vertebral structural damage at 2 years (0.3(2.52) Units mSASSS), which was also low (0.38-0.52) in patients with predictive factors of progression like syndesmophytes or high baseline CRP (118).

Only preliminary data are available regarding radiographic progression and BT combined with NSAID. In a single study with a cohort of 40 patients with SpA, radiographic progression at 2 years assessed by mSASSS was lower in the combined treatment group taking anti-TNF + AINE than in the cohort treated with anti-TNF monotherapy (119).

2017
new

Clinical Question 5

In patients with axSpA who failed to respond to anti-TNF, would the intervention with another anti-TNF or biological therapy be efficient?

Summary of the Evidence

Treatment with a second anti-TNF in patients with AS who have failed to a previous anti-TNF is effective in a high percentage of patients (up to 30-50%) *. However, the clinical response observed is less than that experienced by patients receiving a first anti-TNF (120-125).	4
Evidence evaluating the efficacy of the change to a third anti-TNF in patients with SpA is very limited (120-122).	4
Treatment with Secukinumab in patients with SpA who failed an anti-TNF is efficient in a high percentage of patients (up to 30-50%). The response is lower than observed in patients anti-TNF-naïve (126).	4

Recommendations

2017

After failure to a first anti-TNF, the patient should be treated with another anti-TNF or anti-IL17A (Grade D recommendation).

Quality of Evidence

Treatment with a second anti-TNF or Secukinumab in patients with SpA who failed an anti-TNF previously, it is efficient in a high percentage of patients, although experience with Secukinumab is still limited. Nevertheless, the clinical response observed is lower than that experienced by patients receiving a first biological treatment (120-125, 127) (Evidence level 4). There are no data on the differences in efficacy or survival between switching to another anti-TNF or changing the therapeutic target (Secukinumab). Efficacy is reduced with the use of successive biological treatments; however, response is still obtained after the third BT (120-125, 127) (Evidence level 4). There are data which suggest a better response in patients who change to a second anti-TNF due to secondary inefficiency or toxicity of the first compared to patients with primary lack of response to anti-TNF.

Drug survival was lower in successive anti-TNF changes (120, 121, 123, 125), although differences were not significant probably due to small sample size. There does seem to have been survival differences in favor of those who changed due to secondary inefficacy and toxicity against primary inefficacy (128) ([Evidence level 4](#)). In this situation of primary inefficacy of anti-TNF, it would be reasonable to assess the change of therapeutic target and use Secukinumab.

There is still no evidence regarding efficacy on switching to anti-TNF after failure with Secukinumab; however, the AxSpA recommendations document panelists consider using anti-TNF in this situation reasonable. Perhaps the recommendation could be formulated changing 'first anti-TNF' for 'first biological drug'; however, on drafting the consensus document there was neither evidence nor experience regarding failure with anti-IL17A and subsequent use of anti-TNF.

There are no data regarding anti-TNF therapy change in Nr-axSpA, although it is assumed the response would not differ from that of patients with SpA.

There is no efficacy evidence with other biological drugs (like Rituximab or Abatacept) after anti-TNF failure.

Clinical Question 6a

In patients with axial spondyloarthritis, is it possible to stop treatment with anti-TNF?

Clinical Question 6b

In patients with axial spondyloarthritis, is it possible reduce the dosage of anti-TNF?

Evidence Summary

Discontinuation of anti-TNF therapy in patients with axial spondyloarthritis leads to a breakout within a few months in most cases (129-133).	4
Dose reductions during anti TNF therapy can effectively maintain remission or low disease activity in a great number of patients (>50%) with ankylosing spondylitis (134-141).	2b, 4
There is not enough data to clearly identify which factors predict a good outcome after reducing the dosage of anti TNF in patients suffering axial spondyloarthritis (134-141).	2b, 4

Recommendations

In those patients with axial spondyloarthritis who reach the clinical objective, halting anti-TNF therapy is not recommended (Grade C recommendation).

2017

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).

2017

In the event of disease activity increase in patients whose anti-TNF dose was reduced, an increase should be considered returning to previous or standard dosage (Grade D recommendation).

In patients with axSpA, anti-TNF therapy has proven effective in improving disease signs and symptoms. However, it has not been shown to inhibit radiographic progression over the short

to medium term (within the first three years). On this basis, and considering the high cost of this treatment type, it remains unclear whether anti-TNF therapy should be withdrawn in those patients with axSpA who reach low activity disease or remission; or, conversely, whether therapy should continue for the long term. This same question applies when considering whether to maintain the same dose in those patients who reach low disease activity or remission; or, if instead, the dose can be safely reduced without leading to an increase in disease activity.

Question 3a

Quality of Evidence

Most of the scientific evidence on discontinuing anti-TNF therapy in patients with axSpA comes from studies involving patients with long-term disease. In addition, these studies are more descriptive in nature since they do not directly compare discontinuation anti-TNF with its maintenance; treatment is simply discontinued for all participants, and the results are analyzed.

Five studies were found that included data from 215 patients with axSpA, most with established disease: 76% ankylosing spondylitis, and 24% non-radiographic axial spondyloarthritis (129-133). In all five studies, standard-dose anti-TNF therapy was discontinued in patients, who were then followed-up to evaluate further disease outbreaks. The discontinued anti-TNF drugs were etanercept (130, 131, 133), infliximab (129), and adalimumab (132). The total number of patients in the studies ranged between 24 and 111, and the follow-up time after discontinuing anti-TNF therapy between 36 and 52 weeks. Average disease duration ranged between 3 and 15 years, and the time receiving anti-TNF therapy before discontinuation between 2.5 and 36 months. The percentage of patients who developed a recurrence during follow-up ranged between 69%-100%. Average time until recurrence was between 6 and 24 weeks. In addition, in the four observational studies, those patients who experienced a recurrence were again treated with the same anti-TNF drug that had been previously administered. In general, following a second round of anti-TNF therapy, an improvement similar to that observed at the beginning of the clinical trial was observed in most of the outcome variables. In summary, the available scientific evidence shows that discontinuation of anti-TNF therapy in patients with axial spondyloarthritis leads, in most of the cases, to a recurrence after a few months ([Evidence level 4](#)).

The results from these studies consistently confirm disease recurrence in most axSpA patients who discontinue anti-TNF therapy. These results are applicable to our own healthcare system since anti-TNF is commonly used. On the other hand, the majority of these studies involved patients with long-term disease. Therefore, studies examining possible recurrence in patients with an earlier stage of disease should be carried out to determine whether or not discontinuing anti-TNF therapy has the same effect.

The clinical impact of these results is significant. Anti-TNF therapy is among the major expenditures in our healthcare system. Since most studies have shown that the great majority of patients experience a recurrence of disease activity shortly after discontinuing anti-TNF therapy, treatment discontinuation is not recommended.

Question 3b

Quality of Evidence

All of the available scientific evidence on the effects of reducing anti-TNF therapy stems from studies involving axSpA patients; there is no evidence regarding patients with nr-axSpA.

Eight additional studies were identified, designed as follows: 3 involved retrospective cohorts (134, 137, 140), 3 prospective cohorts (136, 139, 141), and 2 clinical trials (135, 138). In all 8 studies, dose reductions were made according to an established protocol or based on the physician's judgement when patients had reached clinical remission (BASDAI<2 and normal CRP), or low disease activity (BASDAI<4 and normal CRP) after receiving standard doses of various anti-TNF drugs. The total number of included patients ranged between 8 and 136; those receiving a reduced dose ranged between 8 and 109. Average disease duration was between 3 and 13 years, while follow-up time after dose reduction was 6 to 21 months. The anti-TNF drugs used in these studies were etanercept (134-137, 139), infliximab (138), and adalimumab /etanercept/infliximab (140, 141). The remission or low disease activity time prior to dose reduction was recorded in only 4 of the studies and proved heterogeneous: < 3 months (136), at least 3 months (137), or 6 months (134,141). Five studies recorded the percentage of patients who maintained the level of clinical remission or low disease activity (47%, 75%, 53-81%, 86%, and 100%) (134-136, 140, 141). The other 3 studies showed the average change vis-à-vis disease activity measures after reducing the dose. Average BASDAI in these studies, before reducing the anti-TNF dose, was 2.3, 1.6, and 3.1, and at the end of the study 0.6, 1.4, and 2.1, respectively (137-139). Dose reduction was more often achieved by establishing longer

dosage intervals than by reducing the dose itself (injection or infusion). To sum up, the scientific evidence suggests that dose reduction in anti-TNF therapy is effective in a high percentage of patients with ankylosing spondylitis (>50%) to maintain clinical remission or low disease activity for a period of at least 1 year. Until now, such studies have failed to clearly identify factors predicting a good outcome following dose reductions in anti-TNF therapy (Evidence level 2b, 4).

2017 Update

The revision undertaken to draft the AxSpA Recommendations includes 5 more studies (142-146), with similar results to those previously obtained in the CPG. Likewise, the relapse rate in patients with SpA who underwent dose reduction strategies ranged between 0 and 47% (134-138, 140, 142, 144-146).

There are still no studies specifically designed to evaluate factors which predict the result after a reduction in the BT dose, although some suggest the shorter duration of remission prior to dose reduction, likewise the shorter treatment and disease duration are factors associated with relapses (144). Whereas, a greater ASQoL prior to optimization, male gender and not having received anti-TNF prior were associated with a good optimization response (140, 145).

The results from these studies consistently confirm the benefits of reducing the dosage in anti-TNF therapy in patients with axSpA once the clinical objective has been reached. These results are directly applicable to our own healthcare since anti-TNF therapy is commonly used. However, this evidence was drawn from studies that only included patients with AS; it remains to be seen whether these results are similarly applicable to cases involving earlier or less aggressive forms of the disease.

2017 Update

There are no data regarding optimization response in patients with Nr-axSpA to formulate an evidence based recommendation. However, the same burden of disease (82, 147) and response rate to BT are similar in both populations (70, 76-78), so the same guideline for Nr-

axSpA patients as for those with SpA is advised.

The clinical impact of these results is highly relevant. Anti-TNF is the largest pharmacologic expenditure for patients with axial spondyloarthritis in our healthcare system. However, it must be recalled that not all patients who underwent dose reduction maintained the initial clinical response. Therefore, additional studies are needed in order to identify beforehand which patients are best suited to dose reductions.

Clinical Question 7

In patients with ankylosing spondylitis, does the use of biological agents, compared with sulfasalazine, reduce the number of uveitis recurrences and does it improve visual prognosis?

Evidence Summary

Studies evaluating the effectiveness of biologics, compared with sulfasalazine, in reducing the number of uveitis recurrences and improving visual prognosis in patients with ankylosing spondylitis are scarce. Etanercept has not shown any superiority over the short term. For other anti-TNF drugs, there is no comparative evidence (148).	1b-
--	-----

Recommendations

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).

Previous bouts of uveitis are an important cause of morbidity in patients with AS and may lead to blindness. Sulfasalazine has been reported to decrease the number of episodes per year and their severity. On the other hand, biological therapy for treating AS (infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol) has been shown to be effective in treating uveitis in such patients. Uveitis *per se* does not appear in these drugs' data sheets. It is pertinent to assess the effectiveness of both treatments for eye inflammation (the number of episodes per year) and for visual function.

Quality of Evidence

The available evidence surrounding this clinical question remains small, and after being evaluated, quality studies to address this question could not be included (149, 150). One study that compared the effectiveness of a biological agent versus a traditional DMARD was identified.

This study evaluated the effectiveness and safety of etanercept (50mg /week), versus sulfasalazine (SSZ) (up to 3 g/day, minimum dose 1.5 g/day), in 566 adult patients with active AS (treated for ≥ 3 months with ≥ 1 NSAID maximum dose or maximum tolerated dose) at week 16 of treatment. The primary outcome variable of effectiveness was the percentage of patients who reached ASAS 20 at week 16. In addition, the study identified safety outcome variables such as the percentage of adverse events, and in particular, the rate of inflammatory bowel disease and uveitis. Etanercept proved more effective than SSZ (ASAS 20: 75.9% vs. 52.9%, ($p < 0.0001$), at week 16). It was also more effective in the remaining secondary efficacy variables that were analyzed. There were no statistically significant differences among the groups regarding the number or kind of events (including severe ones, or those forcing treatment interruption). There were no new cases of inflammatory bowel disease or recurrences among patients who had already been diagnosed with the disease at the beginning of the study. Regarding the uveitis rate, whether newly diagnosed or recurring in patients who had suffered previous episodes, the authors found no statistically significant differences between the two treatments [group etanercept 10.7 uveitis /100 patients-year (95% CI: 5.5-17.6) compared to group SSZ 14.7 uveitis /100 patients-year (95% CI: 6.4-26.5), ($p = 0.486$)] (148) ([Evidence level 1b-](#)).

In this study, we identified some potential bias to answer our question. The uveitis rate is not a primary outcome variable of effectiveness, but rather falls within the group of adverse events. On the other hand, disease monitoring took place over a short time frame (16 weeks). This limits interpretation of this uveitis rate in both groups. In addition, temporary inequality in reaching full dose in the compared treatments was observed. Patients in the sulfasalazine group received the doses progressively up to 3 gr at week 6, while the etanercept group received full doses of 50mg/week from week 1. At the same time, not all patients tolerated a dose of 3 g/day of SSZ. The evidence is considered inconclusive and has been assigned the mark “-“. More quality studies investigating the relative effectiveness of biological therapies, versus sulfasalazine, in decreasing the number of recurrences and improving visual prognosis in patients with ankylosing spondylitis are needed.

Clinical Question 8

For patients with ankylosing spondylitis, what kind of exercise program is more effective at improving clinical and functional parameters?

Evidence Summary

Exercise programs are effective for improving physical function, reducing disease activity, and thoracic expansion in patients with ankylosing spondylitis (AS) compared with those who do not exercise. There is not enough evidence on the relative effectiveness of different exercise programs on the clinical and functional parameters of AS (151).	2a, 2b
Beneficial effects have been found regarding improvements in pain, rigidity, spinal mobility, and cardiorespiratory function levels (151).	2a, 2b
Taking supervised exercise in groups has been shown to have better results, in terms of quality of life, than exercising at home unsupervised. There are no differences, however, regarding physical function, pain, rigidity or axial mobility (151).	2a, 2b
The combination of pharmacological therapy and exercise in patients with AS has proven effective in terms of functionality, mobility, quality of life, and in the disease activity index, especially with supervised exercise (152).	2a, 2b

Recommendations

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 axial spondyloarthritis (Grade D recommendation).

Exercise programs must include aerobic exercises, preferably performed in supervised groups (Grade B recommendation).

Exercise and educational programs are considered the cornerstone of non-pharmacological treatment for patients with ankylosing spondylitis (153,154). There are no quality studies on the role of physical exercise in patients with little mobility limitations and minimum functional repercussion. However, to be safe and effective, the precepts on physical exercise and activity outlined in the *American College of Sports Medicine* seem a reasonable guide for patients with chronic diseases (155). Most published studies on exercise programs focus on the intermediate-advanced stage of disease, and exclude, for example, patients suffering ankylosis. A wide range of exercise programs have been created for those who are moderately affected. In such patients, the predominance of classical stretching exercises is not justified since there is still lacking sufficient data on the superiority of one exercise over the other (156).

Quality of Evidence

A systematic review of adults with spondyloarthritis examined the effects of therapeutic exercise on parameters such as pain, rigidity, quality of life, physical function, disease activity, health-related fitness (cardiorespiratory function, muscle strength, flexibility, and body composition), and cardiovascular risk factors. Twenty-four controlled clinical trials (6 quasi-randomized studies, and 18 randomized studies) involving 1460 patients diagnosed with moderate-to-severe ankylosing spondylitis were included. At least one of the study groups partook in therapeutic exercises. The recommendations of the *American College of Sports Medicine* were followed in only two cases. Those interventions based solely on generalized recommendations, without prescribing specific exercises, and those in which exercise was combined with other types of passive intervention (e.g., manual therapy, physical means) were excluded in order to specifically analyze the effectiveness of these exercise programs. The characteristics of the exercise programs were quite heterogeneous in duration (from 3 weeks to 3 years), frequency (from two times per day to one time per week), type (flexibility, postural, respiratory, aerobic, strengthening, proprioceptive, global postural re-education, Pilates, hydrotherapy, sports activities), location (at a center in a group setting, at home), and supervision (with or without). The outcome measures used also varied greatly. In general, the conclusions indicated that, in patients with AS, therapeutic exercise is more beneficial than no intervention and must be practiced on a regular basis. The specific outcomes are as follows:

- There was moderate evidence supporting exercise-based interventions to improve physical function (expressed in BASFI), disease activity (expressed in BASDAI), and thoracic expansion compared with control groups.
- There is weak evidence on the effect of interventions to improve pain, rigidity, vertebral mobility, and cardiorespiratory function.
- Including aerobic exercises in stretching exercise programs does not improve cardiovascular risk factors, but does improve cardiorespiratory outcomes.
- Exercising in a supervised group, versus exercising at home without supervision, has a greater effect on quality of life, but has no effect on other outcome measures.
- It is not yet clear what the best exercise program is in order to improve clinical and functional parameters in ankylosing spondylitis.

This same review investigated comparisons between exercise programs and other rehabilitation strategies (in-patient rehabilitation, balneotherapy, respiratory kinesiotherapy through incentive spirometer, spa). There was no significant improvement in disease activity measures or in functional measures (151) ([Evidence level 2a, 2b](#)).

A review of 15 studies comprising 1516 AS sufferers who were clinically stabilized with biological drugs found a potentially synergistic benefits between therapeutic exercises and such drugs. The studies consisted of nine randomized controlled clinical trials, three non-randomized controlled clinical trials, and three clinical trials without control groups or randomization. In 10 of the 15 studies, an exercise-based rehabilitation protocol was associated with a statistically significant improvement in functional capacity (expressed in BASFI), and spinal mobility (expressed in BASMI). In six of the 15 studies, there was a significant improvement in quality of life (expressed by SF-36, HAQ, and ASQoI). In nine studies, BASDAI decreased significantly. In addition, beneficial effects were observed regarding psychological problems and fatigue, which are factors that contribute to improved quality of life. One of the studies showed that some treatment procedures such as Pilates are associated with significant improvements in BASDAI, BASFI, or BASMI. The authors of the review concluded that the positive effects of anti-TNF therapy do not justify dropping out of exercise programs due to the aforementioned synergistic benefits (152) ([Evidence level 2a, 2b](#)).

The outcomes from both reviews are consistent and in line with the noted efficacy of therapeutic exercises in patients with ankylosing spondylitis. However, since both included

studies with different designs and risks of bias, more quality studies are needed to properly evaluate the relative effectiveness of exercise programs in AxSpA patients.

Regarding applicability and possibility of generalization, the guideline development group finds that these interventions are, in general, directly applicable to our healthcare system. Although the disease course can vary greatly, exercise programs have been shown to positively efficacy numerous clinical and functional outcome parameters in adult patients suffering from intermediate-advanced phases of ankylosing spondylitis. However, data on patients in the initial phase (short duration of symptomatology) or those in the ankylosis phase remain lacking. However, there exists a prospective study in which a high number of patients with AS was followed-up for a period of 4.5 years. Two patient groups were identified: 1) those with a disease progression of less than 15 years. Within this population was a subgroup who regularly partook in recreational aerobic activities (more than 200 minutes/week); these individuals experienced less pain and rigidity than the subgroup who performed specific back exercises, although there were no significant changes in terms of functional limitations; and 2) those with a disease progression of more than 15 years in which a subgroup performed specific back exercises (at least 5 days per week). These patients experienced less pain and better physical function, and tended to be less prone to functional limitations. In short, the study suggests that, during the initial phase of AS, an aerobics-based exercise program of an intensity and duration similar to programs recommended for the general population is very appropriate. Specific back exercises must be reserved for those patients in the intermediate and advanced stages of the disease (157).

The authors observe that, in our healthcare system, traditional programs (vertebral and thoracic flexibility, postural, and respiratory exercises) still predominate over more innovative programs such as strengthening exercises, aerobic exercises, Pilates, etc. The guideline development group believes not only that mixed programs would be ideal, but also that, in general, any type of exercise is always better than inactivity. However, it is advisable to personalize exercise programs, as well as supervise and carry out appropriate monitoring to improve therapeutic compliance in the long-term. Patient associations and self-help groups can be useful from an educational standpoint by providing practical information with a positive tone, which is generally more appealing to patients (158).

In patients with AS there is an increase in cardiovascular risk (159), and aerobic exercise programs promote cardiovascular health by improving physical shape. The guideline experts

believe that physical exercise must serve an adjunct therapy to pharmacological treatment from the moment the disease is diagnosed. However, only 1 in 3 patients with AS exercise with the minimum desirable frequency, usually due to fatigue or lack of time (160).

Clinical Question 9

In patients with axial spondyloarthritis, does tobacco worsen clinical manifestations (arthritis, axial affectation, enthesitis, and structural damage)?

Evidence Summary

Active smoking is associated with spinal radiographic progression in patients with ankylosing spondylitis and in patients with non-radiographic axial spondyloarthritis (111).	1b
Being a smoker is independently associated with earlier onset of inflammatory low back pain, increased disease activity, higher axial inflammation in MRI, worse functional capacity, and worse quality of life in patients with axial spondyloarthritis with recent-onset disease (161,162).	4
In patients with ankylosing spondylitis, a smoking habit is associated with functional disability progression (163).	2b

Recommendations

It is recommended that patients with axial spondyloarthritis be encouraged to stop smoking from the time of diagnosis (Grade C recommendation).

In recent years, research has investigated prognostic factors in patients with ankylosing spondylitis. In particular, it has sought to identify those, which negatively impact prognosis from a radiographic and functional capacity standpoint. Several studies have identified tobacco as an important independent factor of poor prognosis. Nevertheless, homogenous studies are lacking and many questions remain. Among them, whether smoking is clinically significant in terms of radiographic and functional progression, and what its association with active synovitis or active enthesitis entails. In addition, does smoking affect other outcomes associated with the disease activity such as BASDAI, ASDAS, CRP, response to administered treatments, and others? Therefore, it is very important to obtain scientific evidence on the impact of tobacco on clinical manifestations of axial spondyloarthritis.

Quality of Evidence

A cross-sectional study evaluated the effects of smoking on 606 patients with AS. BASFI, NRS pain, ASQoL scores, and the four EASI-QoL domains (physical function, disease activity, emotional well-being, and social participation) were significantly higher in the group of patients who had smoked occasionally versus those who had never smoked. The authors concluded that there exists a dose-dependent relation between tobacco use and disease severity in patients with AS. Patients who are active smokers have higher disease activity, as well as worse functional capacity and quality of life irrespective of age, sex, disease duration, and social situation (162) ([Evidence level 4](#)).

Using New York Criteria, a longitudinal prospective study sought to identify the characteristics that can predict the progression rate of functional disability, as measured by HAQ's, over a 5-year period in 241 patients with AS. Patients were classified as smokers or non-smokers, though the intensity of the habit was not assessed. Only age, smoking habit, ISEL score, and the frequency of spinal exercises were independently analyzed. The results proved significant, in particular the progression rate of HAQ'S in the multivariate analysis, which increased by 0.025 units/year in patients who smoked compared to non-smokers (95% CI: 0.0071-0.0429; $p=0.007$). To evaluate if there were additional predictors of progressive functional disability in patients with recent-onset AS, those suffering the disease for less than 10 years at the time of study enrollment ($n= 58$) were selected. The HAQ rate of progression increased 0.0545 units/year in patients who smoked compared to those who did not ($p=0.004$). The authors concluded that tobacco is associated with progressive functional disability irrespective of age and other factors such as educational level, comorbidity, and the frequency of physical exercise. This progressive impairment was also observed in AS patients with less than ten years of disease evolution (163) ([Evidence level 2b](#)).

A 2-year follow-up observational longitudinal study assessed both the progression rate and predictors of spinal radiographic progression in 95 patients with non-radiographic axial spondyloarthritis, and 115 patients with AS. Parameters independently associated with radiographic progression ($mSASSS \geq 2$) were as follows: baseline presence of syndesmophytes, high ESR levels, high CRP concentrations, and active smoking habit. Except for the latter, these same parameters were associated with the appearance of new syndesmophytes, and/or progression of already existing ones. Regarding active smoking habit, the difference between active smokers and non-smokers was not significant. The authors concluded that active

smoking is independently associated with spinal radiographic progression in patients with ankylosing spondylitis, as well as in those with early non-radiographic axial spondyloarthritis (111) (Evidence level 1b).

A cross-sectional multi-center analysis in France involving a cohort of 647 patients (DESIR) evaluated the relation between an active smoking habit and clinical and functional outcomes, as well as structural damage in patients with recent-onset axSpA. The study included data on patient habits, though it did not take into account the number of cigarette packs smoked per year. An active smoking habit was independently associated with the early onset of inflammatory lower back pain in the multivariate analysis; this also occurred with ASDAS-CRP, BASDAI, and BASFI (dependent variables). The association between smoking and HAQ-AS found in the univariate analysis, was not evident in the multivariate analysis. In terms of quality of life, smoking was positively associated (irrespective of other factors) with Euro-QoL score, and negatively associated with other mental and physical measures. It was also associated with the existence of spine and sacroiliac inflammatory lesions in MRI, and with the presence of structural lesions. Finally, tobacco was associated with mSASSS, though not with radiographic sacroiliitis. The authors concluded that smoking is independently associated with the early appearance of inflammatory lower back pain, higher disease activity, and higher axial inflammation in MRI, higher axial structural damage in MRI and in X-rays, lower functional capacity, and worse quality of life in patients with recent-onset axial spondyloarthritis (161) (Evidence level 4).

In addition to the studies described above, others were excluded from the Evidence Summary Table due to methodologic limitations. All of them evaluated whether smoking can be regarded as an associated risk factor, or as a predictor of disease activity, functional capacity, or mobility in patients with AS. Some of the aforementioned limitations included: small sample size; the inclusion of ex-smokers in the same group as active smokers; failure to establish the degree of variation of functional limitations that led to differences in disease activity or treatment; and the failure to taking into account other possible confounding factors such as exercise or education level. Nevertheless, the panel believe it is worth summarizing the information provided as a means of orientating the guideline development group in formulating its recommendations. Although the majority of studies were cross-sectional in nature, some were cohort studies. The main outcomes are described as follows:

- Smoking is a risk factor significantly associated with BASFI and HAQ-S (164-166). In addition, data indicate significant associations with scores measuring thoracic

- expansion, lower back modified Schöber, occiput-wall distance (OWD), chin to manubrium sterni distance, and forced vital capacity (164, 167); other parameters included were morning stiffness, enthesitis index, finger-ground distance, total spine mobility, radiographic affectation (Dougados index) (167) (Evidence level 4).
- Active smokers had significantly worse VAS and VGP scores (164, 165). Moreover, quality of life (ASQoL), and disease activity (BASDAI) were worse in the active smokers group (164, 165, 168, 169) (Evidence level 4).
 - Being an active smoker was one of the variables independently and significantly associated with severe radiographic damage (pain 75th percentile BASRI-S/duration for AS) (170) (Evidence level 4).
 - Mobility (BASMI) was worse in the active smokers group than in the non-smokers group (168) (Evidence level 4).
 - Ankylosis was considerably more frequent in the active smokers group (168) (Evidence level 4).
 - In patients who were smokers, the intensity of the smoking habit (number of cigarettes per day / years) was significantly associated with BASFI, cervical rotation, finger-ground distance, and occiput-wall distance (171). There was also a significant correlation between intensity and worse BASDAI, ASQoL, and BASMI scores (130). Patients with a history of >20 packs of cigarettes per year were less likely to be included in the group with less radiographic pain (170). Moreover, the number of packs of cigarettes smoked per year was significantly higher in the patient group with radiographic ankylosis than in the group with minimal or moderate sacroiliitis (168) (Evidence level 4).
 - Smoking habit duration (starting age, years in duration) was also significantly associated with BASFI, finger-ground distance, and occiput-wall distance (171) (Evidence level 4).
 - In multivariate analysis, patients who smoked registered higher ESR, CRP, OWD, finger-ground distance (171), BASFI, and HAQ-S (166) scores. They also scored lower in BASDAI, quality of life (ASQoL), VAS, VGP (164, 165) or modified Schöber, lumbar and lateral flexion, and thoracic expansion (171) (Evidence level 4).
 - When the ex-smoker group was analyzed independently, the resulting BASFI and HAQ scores proved similar to those of non-smokers (165, 166, 168) (Evidence level 4).

To sum up, these studies indicate that an active smoking habit was the variable most consistent in predicting worst outcomes in axial spondyloarthritis. Being an active smoker was associated with higher disease activity and worse functional capacity. Moreover, it negatively affected patient quality of life, which was reflected in worse disease prognoses.

In formulating the recommendations, the guideline development group took into account the consistency of outcomes from the various identified studies, all of which had similar findings in terms of smoking's impact on the disease. The clinical relevance and impact that implementation of the recommendation would have was also considered. Regarding the applicability and possibility of generalization, the experts believe that the health programs available at both primary and specialized care centers throughout Spain have sufficient resources to help patients to give up smoking. Therefore, the outcomes described in these studies could be easily and usefully applied to patient care in our health system.

7. Treatment of Psoriatic Arthritis (PsA)

2017

Clinical Question 10

In patients with psoriatic arthritis, does early pharmacologic intervention improve functional capacity, structural damage, and quality of life?

Evidence Summary

2017

Early therapeutic intervention and close follow-up improve the response rates (ACR20, ACR50 and ACR70), skin activity control, functional capacity and quality of life indices. However, there are no differences regarding radiographic progression (172).	4
Some secondary analyses conducted in different studies indicate that, from both clinical and radiographic points of view, the time of disease evolution might be a predictor of treatment response in patients suffering from peripheral psoriatic arthritis; specifically, a shorter time of evolution seems to predict a better response (173-179).	4

Recommendations

2017

Early pharmacological intervention with conventional synthetic DMARDs (csDMARDs) is recommended in patients with PsA, chiefly in those with bad basal prognosis factors, to improve signs and symptoms, functional capacity and quality of life (Grade D recommendation).

Psoriatic arthritis (PsA) may lead to joint destruction with a resulting impact on functional capacity and quality of life. In a case series of patients who experienced short (≤ 2 years) disease durations, joint erosions were identified in almost 50% of patients (180, 181). It is important to identify adverse prognostic factors during the first visits, since these factors can shape therapeutic decisions. Early pharmacologic interventions might not only prevent

structural damage, but also maintain functional capacity and quality of life for patients with PsA.

Quality of Evidence

2017 Update

Evidence is scarce in this field and only one new clinical trial has been identified that responds to the clinical question (TICOPA study). This trial assesses the benefits of treat to target strategy with strict control intervention (cohort 1: every 4 weeks) against standard clinical practice (cohort 2: every 12 weeks). 206 patients with early PsA (symptoms for <24 months) were included (172). It was noted that response rates ACR20, ACR50 and ACR70 at week 48 were higher in cohort 1 than cohort 2. Furthermore, greater benefit was noted in psoriasis control as well as functional capacity and quality of life indices in cohort 1 patients. On the contrary, no differences were objectified in radiographic progression at the end of follow-up (48 weeks) between both tracked cohorts (172) (Evidence level 4).

The rest of the available evidence is included in the ESPOGUÍA 2015:

In a 32-year prospective study with 1077 patients suffering from PsA, patients were divided into two groups according to the time of disease evolution: a) patients seen at clinics within the first two years after diagnosis (early PsA, n = 436); b) patients diagnosed more than two years before their first visit (established AsP, n = 641). Both groups presented a similar number of swollen joints and psoriasis activity, and a similar frequency of axial involvement. Radiographic deterioration was higher in the group with established PsA, making them more likely to receive therapy with DMARD or biological drugs. In the multivariate analysis, the group with established PsA presented a higher progression rate compared with the early PsA group. This correlation was even more clear when stratified according to disease duration at the first visit. (1-2 years compared to < 1 year: 1.53 (0.99–2.36) p = 0.05); (2-4 years compared to < 1 year: 1.70 (1.11-2.62) p = 0.01); (5-9 years compared to < 1 year: 1.83 (1.16 – 2.88) p = 0.009); (10-20 years compared to < 1 year: 1.83 (1.14 – 2.96) p = 0.01); (> 20 years compared to < 1 year: 2.96 (1.64–5.34) p=0.0003) (173) (Evidence level 4).

Another study conducts a *post hoc* analysis of a previous double blind RCT involving randomized patients treated with ETA 50 mg/week (n=372). The patients were stratified according PsA duration: a) those with a disease duration \leq 2 years (early PsA), and b) those

with a duration > 2 years (established PsA). Average disease duration was 0.5 years in the first group, and 7.7 years in the second. After 24 weeks the early PsA group showed greater improvement compared with the established PsA group in terms of the outcome measures reported by patients (PRO). The main limitations of the study were the *post hoc* analysis, and the fact that it was not designed to evaluate the effect of early treatment on patients with psoriasis and PsA (175, 178) (Evidence level 4).

An open study of 35 patients with the early oligoarticular/enthesitic form of PsA (< 2 years of evolution) compared the efficacy of full dose NSAIDs for 3 months (afterwards adding MTX) with combined treatment from treatment onset using AINE and MTX. After 3 months, patients given the combined treatment from the beginning exhibited significant improvement in the numbers of painful joints and swollen joints compared with those on the NSAID regimen ($p < 0.05$). However, after 6 months there were no differences in any of the analyzed variables ($p < 0.05$). The authors suggested that in patients with early oligoarthritis, a delay of 3 months before introduction of MTX makes no difference in terms of clinical effectiveness (177) (Evidence level 4).

An observational longitudinal multicentric study of 24 weeks' duration evaluated the effectiveness and safety of anti-TNF therapy in a group of 29 patients with early PsA (disease duration < 12 months) with poor response to standard treatment using NSAIDs and DMARDs. At week 24, 82% of the patients showed improvement (DAS28 > 1-2; EULAR response); 13.8% responded poorly, and 3.5% did not present any response. Baseline DAS28 of 5.3 (4–6.8) was also reduced to 3 (0.5-5.2) at week 24. All evaluated variables improved in relation to baseline ($p < 0.001$). In light of the results, the authors suggested that anti-TNF therapy in patients with early PsA is effective (176) (Evidence level 4).

A 5-year prospective study followed 197 patients with early PsA (< 2 years' evolution) to investigate predictors of clinical outcome measures. In the multivariate analysis, independent predictor factors of minimal disease activity (MDA) were as follows: a shorter delay in symptom onset, the inclusion of patients in the register, and a lower HAQ at the time of enrollment. The short duration of symptoms at the time of a patient's enrollment proved to be the main response predictor and was the most important finding of this study (179) (Evidence level 4).

A cross-sectional study with a cohort of 283 patients analyzed the effect of a delay in the first rheumatology consultation on several functional and structural outcomes. The average delay was a period of 1 year (IQR 0.5-2.9). Thirty percent of patients were seen 6 months after symptom onset, 53% within the first year, and 71% within the first two years. Using multiple regression analysis, a clear correlation was observed among patients who were attended later involving erosion in the peripheral joints and worse HAQ scores (HR 4.25 $p=0.0019$, and HR 2.2 $p=0.004$, respectively). A delay in diagnosis longer than 1 year was associated with arthritis mutilans, a lower possibility of remission without medication, and worsening functional capacity. Delays in diagnosis beyond 2 years correlated with lower education levels, lower Body Mass Index (BMI), erosion in the peripheral joints, and worse HAQ scores. The authors concluded that the delays in diagnosis from symptom onset until the first rheumatology consultation were associated with erosion in the peripheral joints, and more severe functional impairment in the long-term. However, they acknowledged certain study limitations such as the absence of time measures, and the lack of documentation as to why patients were late for primary care appointments. In addition, there was no research addressing the time taken to refer patients to rheumatology, potential inaccuracies stemming from the gathering of data retrospectively, or the possibility that patients attended in rheumatology may present more severe disease (174) (Evidence level 4).

In formulating their recommendations, the guideline development group was aware of the scant evidence on the effectiveness of early pharmacologic intervention and on some questions regarding the quality level of the selected studies. Specifically, the group's rationale and reservations are as follows: a) Although *post hoc* analyses were considered inadequate, requiring careful interpretation, theirs was justified as much of the clinical trial information proved useful, particularly in its exploratory nature; b) One must remain cognizant of the potential bias to which open non-randomized studies are usually prone; c) if a study did not include radiographic assessments, and only patients with oligoarticular-enthesitic form were analyzed, then the data cannot be extrapolated to other peripheral forms of PsA.

Nonetheless, the results of these studies are quite consistent regarding the effectiveness of early pharmacologic intervention. Their stated conclusions are fundamentally based on secondary analyses indicating that the duration of disease evolution could serve as a response predictor in treating those with peripheral psoriatic arthritis. This holds true from both clinical and radiographic points of view. In fact, shorter disease evolution seems to predict a better

therapeutic response. It was also noted that a delay in the first visit to a rheumatologist was associated with greater structural damage, a poorer response to treatment with DMARDs, and worse functional capacity. By extension it can be concluded, albeit without solid evidence, that early pharmacologic intervention could be accompanied by better outcomes from a clinical and radiographic standpoint, and in terms of physical functions, patient reported outcomes, and quality of life.

The guideline development group felt that given the weakness of the evidence at hand, early pharmacologic intervention cannot be generalized to any cases of peripheral PsA treated by our country's national healthcare system. Early pharmacologic intervention, and possibly closely controlled strategies aimed at objective treatments (T2T), could improve clinical and radiographic prognosis of peripheral PsA. Nevertheless, treat to target strategies are often beset by higher prevalences of secondary effects.

2017

Clinical Question 11

In patients with PsA, what is the efficacy of biological therapies in monotherapy regarding to peripheral, axial, enthesitis, dactylitis, uveitis, skin and nails clinical manifestations?

Summary of Evidence

<p>There is not enough evidence on the effectiveness of biological monotherapy compared with conventional DMARDs or to a placebo. In those studies in which biological treatment is compared with a placebo, the percentage of patients treated with methotrexate in each comparison group proved variable (182-187).</p>	<p>2b</p>
<p>The following results were obtained from secondary analyses on subgroups of patients treated without methotrexate:</p> <p>In patients treated with golimumab in monotherapy, irrespective of dose (50 mg, 100 mg), radiographic progression after 24 weeks of treatment was lower than in those given a placebo. Parameters of clinical activity were not assessed (183).</p> <p>Ustekinumab in monotherapy, irrespective of dose (45 mg, 90 mg), was significantly more effective (ACR 20 response) than the placebo, and also more greatly reduced radiographic progression after 24 weeks of treatment (RR=2.37; 95% CI: 1.59-3.53 and RR=3.31; 95% CI: 1.60-6.86) (182, 184, 185).</p> <p>Secukinumab at doses of 150 and 300 mg in monotherapy was significantly higher (responses ACR20 and ACR 50) with placebo (without MTX) at 24 weeks' treatment (186, 187).</p>	<p>2b</p>

2017

Patients with predominantly ax-PsA refractory to NSAIDs, use of BT (i-TNF or anti-IL17A) is recommended.

2017

Biological monotherapies have proven more effective than csDMARDs or a placebo in treating patients with psoriatic arthritis in its different manifestations: peripheral, axial, enthesitis, dactylitis, and uveitis ([Grade D recommendation](#)).

2017

Use of BT is recommended for patients with peripheral PsA refractory to at least one csDMARD ([Grade A recommendation](#)).

Patients with predominantly ax-PsA refractory to NSAIDs, use of BT (i-TNF or anti-IL17A) is

recommended (Grade D Recommendation).

A great percentage of the patients with psoriatic arthritis seen in clinical practice receive biological monotherapy. However, most clinical trials compared biological treatment with methotrexate and a placebo, which is often methotrexate in monotherapy). For this reason, a literature review was needed to analyze the effectiveness of biological therapy in monotherapy versus a placebo or conventional DMARDs for PsA in its different manifestations (peripheral, axial, enthesitis, dactylitis, and uveitis), and in terms of radiographic progression.

Quality of Evidence

Scientific evidence addressing this question remains scant, and quality studies specifically designed to answer it could not be identified. Sub-analyses were made of each of the three studies included. Although a double-blind methodology was maintained, this could not ensure baseline homogeneity in each group. For this reason, it was decided to reduce the Evidence level to that of a low quality RCT based on the Oxford CEBM scale.

A double-blind RCT in a 1-year extension stage evaluated radiographic progression in PsA patients treated with golimumab. The patient subgroup treated with golimumab in monotherapy (146 patients, 50mg dose, or 146 patients, 10mg dose, every 4 weeks) had lower radiographic progression than those given a placebo [GOL50 monotherapy 75/146 (51%): 0.01 (1.47); GOL100 monotherapy 75/146 (51%): 0.11 (1.28); placebo (without baseline MTX) 58/113 (51%): 0.31 (1.28)]. Both doses conferred a protecting effect upon the appearance of erosions compared with the smallest change detectable with placebo (RR= 0.40; 95% CI: 0.16-0.98) (183) (Evidence level 2b).

Two separate RCTs assessed the effectiveness and safety of ustekinumab in patients with active AsP, while another study carried out an integrated analysis of radiographic progression for the two RCTs at 52 weeks. A double-blind RCT (PSUMMIT 1) evaluated 615 biological-naïve patients with active polyarticular PsA. When the patient subgroup treated with ustekinumab in monotherapy was analyzed (44 patients, dose 45 mg, and 55 patients, dose 90 mg) and compared with those given a placebo (22 patients without methotrexate), data relating to the ACR20 variable were only available after 24 weeks. The response proved significantly higher in patients treated ustekinumab in monotherapy, irrespective of dose, than a placebo (ACR20

2.37; 95% CI: 1.59-3.53) (184) ([Evidence level 2b](#)). A double-blind RCT (PSUMMIT 2) evaluated 312 patients with polyarticular PsA, including patients refractory to anti-TNF- α therapy. One patients subgroup who received ustekinumab in monotherapy (18 patients dose 45mg, and 25 patients dose 90mg) while another group was administered a placebo (7 patients without MTX), although data from variable ACR20 were only available after 24 weeks. The ustekinumab monotherapy subgroup, irrespective of dose, showed an ACR20 response significantly higher than the placebo group after 24 weeks (RR response ACR20 3.31; 95% CI: 1.60-6.86) (185). ([Evidence level 2b](#)). Combined data from patients who partook in the two aforementioned studies was used to evaluate the effects of ustekinumab on radiographic progression. Those treated with ustekinumab in monotherapy, regardless of dose (155 patients with dose 45mg, and 155 patients with dose 90mg), showed lower radiographic progression after 24 weeks [average of change 0.3 (DE 2.6)] than those on a placebo (without MTX) [average of change 1.1 (DE 5.0)] (182,188) ([Evidence level 2b](#)).

2017 Update

Regarding evidence available on Secukinumab efficacy, RCTs stage 3 FUTURE 1 and 2 assess Secukinumab efficacy and safety in patients with active PsA refractory to csDMARD or anti-TNF. FUTURE 1 study (186), showed patients treated with Secukinumab (cohort 150 mg + 75 mg) in monotherapy had an ACR20 response at week 24 significantly higher than those treated with placebo (without MTX) [RR response ACR20 3.48 (IC95% 1.97-6.14)]. The same occurred for individual doses of 150 and 75 mg in monotherapy [RR 3.28 (IC95% 1.81-5.95) and RR 3.68 (2.05-6.60), respectively] (186) ([Evidence level 2b](#)).

In the FUTURE 2 study (187), on analyzing the patients treated with Secukinumab in monotherapy and those with placebo (without MTX), data were only available for the variables ACR20, 50 and 70 at 24 weeks. Patients treated with Secukinumab (cohort 300 mg + 150 mg) in monotherapy showed an ACR20 response significantly higher at week 24 than those treated with placebo (without MTX) [RR response ACR20 5.14 (IC95% 2.20-12.00)]. It was the same for individual doses of 300 and 150 mg in monotherapy [RR 5.14 (IC95% 2.20-12.00), for both] but not with Secukinumab 75 mg in monotherapy [RR response ACR20 1.48 (IC95% 0.52-4.20)] ([Evidence level 2b](#)).

Patients treated with Secukinumab (combined 300+150) in monotherapy had an ACR50 response significantly higher at week 24 than those treated with placebo (without MTX)

[RR response ACR50 5.57 (IC95% 1.81-17.15)]. It was the same for individual doses of 300 and 150 mg in monotherapy [RR 5.14 (IC95% 1.61-16.4) and RR 6.00 (1.91-18.89), respectively] but not with Secukinumab 75 mg in monotherapy [RR response ACR50 1.54 (IC95% 0.39-6.09)]. Patients treated with Secukinumab (combined 300+150) in monotherapy had an ACR70 response significantly higher at week 24 than those treated with placebo (without MTX), especially with 150 mg dose, but not with 75 mg (187) (Evidence level 2b).

In researching this question, the guideline development group could find no studies evaluating the specific effectiveness of infliximab, etanercept, adalimumab, certolizumab pegol, abatacept, brodalumab, tocilizumab, anakinra, or rituximab in monotherapy compared with a placebo or synthetic DMARD in patients with PsA in its peripheral form, axial form, enthesitis, dactylitis and uveitis.

The group took into account the need to conduct subanalyses of RCTs involving patient subgroups not receiving methotrexate in order to determine the effectiveness of different biological therapies in monotherapy compared to placebo. For this reason, the body of evidence gathered to form their conclusions was smaller. Nonetheless, guideline development group believes biological therapies in monotherapy should be made available in our healthcare system since the patients selected for these studies had similar characteristics to those seen here. The group also believes the results to be significant and promising particularly given that many patients receive biological monotherapies in everyday clinical practice for a variety of circumstances (intolerance to standard DMARDs, hypertransaminasemia, etc.).

2017 Update

In patients with peripheral PsA where DMARDs were inefficient or were removed due to intolerance, use of BT would be indicated. Regarding the iTNF agents, different clinical trials have shown they are efficient in all the PsA domains. They are also shown to have a significative effect on structural damage inhibition (189-192). Furthermore, we have 2 new agents with different mechanism of action, i.e. Ustekinumab (i-IL12/23) (182, 184, 185) and Secukinumab (anti-IL17A) (187, 193), which have proven efficacy in controlling PsA manifestations and inhibiting radiographic damage, so they are equally valid options for patients with PsA and inadequate response to DMARD, particularly in those cases with

serious skin involvement.

Due to lack of specific studies on PsA with predominant axial affectation, the Guide Preparation Group (GEG Spanish Acronym) considers it convenient to following recommendations formulated for AxSpA; therefore, the first biological agent should be an iTNF according to standard clinical practice. Nevertheless, recently published data on Secukinumab in AS are equally optimal, although there is still no indication regarding this drug for the non-radiographic form.

The guideline development group further believes that addition of high-quality RCTs are needed, in particular ones that might prove the effectiveness of biological drugs used in monotherapy with patients with psoriatic arthritis under its different manifestations: peripheral, axial, enthesitis, dactylitis, and uveitis.

2017

Clinical Question 12

In patients with psoriatic arthritis, what is the efficacy for DMARDs in its peripheral, axial, enthesitis, dactylitis, uveitis, skin and nail domains?

Evidence Summary

The use of methotrexate in patients with psoriatic arthritis leads to significant results; e.g., improvements in the global assessment of the disease by both patient and doctor, and reductions in the number of swollen and painful joints (177, 194, 195).	2b
The early use of methotrexate at high doses in patients with psoriatic arthritis is associated with a decrease in radiographic progression (196).	4
The use of leflunomide in patients with psoriatic arthritis shows significant beneficial effects as regards peripheral manifestations in PsARC variables, average painful and swollen joint counts, and in physician and patient global assessment measures; it also correlates with a significant improvement in the dactylitis variable (197-199).	4
The use of Apremilast in patients with peripheral PsA after an inadequate response or intolerance to DMARD shows greater efficacy than the placebo (measured as ACR20 response increase and decrease of DAS28 (CRP)), functional capacity (HAQ-DI) and global assessment of doctor and patient). It also improves enthesitis measured by MASES and dactylitis (200-202). However, there is no evidence Apremilast reduces radiographic progression or that it improves axial manifestations or uveitis.	1b

2017

Recommendations

Traditional csDMARDs (methotrexate, leflunomide, sulfasalazine) are recommended as first line treatment for active peripheral psoriatic arthritis ([Grade C recommendation](#)).

Among them, methotrexate is considered 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](#)).

2017	The use of Apremilast is recommended in treating peripheral arthritis after failure or intolerance to csDMARD, when it is deemed more convenient than BT given the patient profile (Grade C recommendation).
2017	The use of biological therapy or tsDMARD (Apremilast) is recommended in patients with PsA and enthesitis refractory to NSAID and local treatment (Grade C recommendation).
2017	The use of biological therapy or tsDMARD (Apremilast) is recommended in patients with PsA and dactylitis refractory to NSAID and local treatment with corticoid infiltrations (Grade C recommendation).

Due to the clinical heterogeneity of psoriatic arthritis, therapeutic recommendations have been separated into five domains based on the disease manifestation (peripheral arthritis, axial arthritis, enthesitis, dactylitis, and skin and nail involvement) (203, 204). Methotrexate (MTX) has traditionally been used as a csDMARD in psoriatic arthritis (PsA) for joint and skin manifestations (205), and is among the most frequently used treatments for this pathology (204, 206). However, the shortage of clinical trials documenting its effectiveness in PsA poses questions as to its suitability for treating PsA, as well as on PsA manifestations in which MTX is effective (204, 207).

Different systematic reviews (SR) (205, 208-210) accord with studies in the relative effectiveness of DMARDs on the peripheral forms of PsA. This has prompted groups such as GRAPPA and EULAR to develop recommendations for active peripheral arthritis treatment using such traditional csDMARDs as methotrexate (MTX), sulfasalazine (SSZ), and leflunomide (LEF). However, there are not enough quality studies to definitively support this assertion.

There is also insufficient consensus on the utility of these drugs for other musculoskeletal manifestations (axial, dactylitis, or enthesitis), or uveitis. Consequently, it is necessary to update the evidence to reevaluate the efficacy of traditional DMARDs in the treatment of PsA.

Quality of Evidence

Clinical trials of MTX, due to different circumstances of a methodological nature, have not been able to show conclusive data on their effectiveness in PsA (195). However, the clinical experience with MTX, based on the usual clinical practice, observational studies and records of patients with PsA, has placed MTX as the csDMARD of choice in this disease.

Three studies evaluating the effectiveness of MTX on PsA were identified. An RCT evaluated the use of MTX, versus a placebo, in 221 patients. After 6 months the comparison showed no significant results in PsARC (OR 1.77; 95% CI: 0.97-3.23), ACR20 (OR 2.00; 95% CI: 0.65-6.22) or DAS-28 (OR 1.70; 95% CI: 0.90-3.17). There were also no significant differences in terms of joint counts, inflammatory markers (ESR, CRP), functional capacity (HAQ), or pain scale. The only observed benefits were decreases in the patient and physician global assessments, as well as in skin involvement ($P = 0.03$; $P < 0.001$, and $P = 0.02$ respectively). However, inclusion criteria resulted in the selection of low-activity patients. In addition, the recruitment period was extremely long, mean doses of methotrexate were lower than habitual doses, and a high number of patients dropped out of the study (only 65% and 69% in the active and placebo groups completed the study, respectively). All of these factors limited the validity of the study (194, 195) (Evidence level 2b). A retrospective study, conducted in Toronto between 1994 and 2004, compared radiographic progression and evolution of peripheral arthritis in a cohort from a previous study conducted by the same authors (1978 – 2003). The patients in the more recent cohort, who experienced shorter PsA disease durations received higher doses of MTX than those in the previous cohort. After 24 months, 68% of patients in the recent cohort improved joint count by 40%. This figure is higher than that obtained in the prior cohort. Radiographic progression was also significantly lower (1.5 ± 1.8 vs. 2.3 ± 1.2). These results suggest that the use of MTX at higher doses (16.5 mg/week vs. 10.6 mg/week) during early disease stages is associated with better clinical response and with a greater effect on radiographic progression (196) (Evidence level 4).

The remaining scientific evidence used to evaluate MTX stems from a systematic review of 3 RCTs that compare MTX in monotherapy with a placebo, and 7 open or retrospective studies that evaluated MTX in PsA. However, the review does not offer detailed information on results contained in these studies. Moreover, data on radiographic progression proved inconclusive as only a small case-control study was analyzed (74).

Two studies were identified that evaluated the effectiveness of leflunomide (LEF). The first was a 24-week observational prospective multinational study involving 440 patients diagnosed with active PsA and without previous LEF treatment. Eighty-six point four percent of patients (95% CI: 82.8%-89.4%) were responsive to PsARC after 24 weeks, with an average decrease in the number of painful joints (NPJ) and the number of swollen joints (NSJ) of 18.5-8.9 and 12.9-5.4, respectively; $P < 0.0001$. In addition, 51.2% ($n=467$) of patients with dactylitis experienced

a significant improvement compared with 46.7% of patients who presented no changes. The study concluded that LEF is an effective and well-tolerated option for treatment against PsA in routine clinical practice. Moreover, it found that LEF had beneficial effects on peripheral arthritis and dactylitis, though to a lesser extent on psoriasis, as well as on other symptoms such as fatigue and pain (197) ([Evidence level 4](#)).

The second was a prospective observational study that evaluated the effectiveness and safety of LEF alone (n=43; 50.6%), and in combination with MTX (n=42; 49.4%), under routine clinical practice conditions. Thirty-eight percent, 48%, and 56% of patients experienced a decrease of $\geq 40\%$ in swollen joint counts after 3, 6, and 12 months, respectively. 27%, 28% and 38% of patients obtained a PASI 50 response after 3.6 and 12 months; 19%, 19% and 32% of the patients obtained a PASI 75 response after 3, 6 and 12 months, respectively. Evaluated data between patients treated with LEF alone, and those treated with LEF and MTX proved similar. It was concluded that LEF had resulted in improvements in at least 50% of patients / year. The use of concomitant MTX was a predictor of a response (PASI 50) after 12 months (OR 6.19; 95% CI: 0.20-31.97). The proportion of patients who stopped treatment was 35% (16 patients in the LEF group, and 14 in the LEF+MTX group) (199) ([Evidence level 4](#)).

In evaluating the effectiveness of sulfasalazine (SSZ) only one systematic review (SR) was identified. Although published in 2012, it examined evidence prior to 2008 that had been included in ESPOGUIA 2009. The review, which not providing detailed information on results of these studies, offered the following conclusions: SSZ was effective for treating peripheral arthritis; two studies contained data on dactylitis, but found no significant differences between the use of SSZ or a placebo; one study concluded that there were no significant benefits with a placebo against enthesitis; another small case-control study (20 patients) found that SSZ had no effect on radiographic progression (74).

The evidence to answer this clinical question is scarce, and is also hampered by unequal quality of the methodology at work. The guideline development group therefore decided to include other studies which, although not conforming in a strict sense with the inclusion criteria, since the comparisons did not involve traditional DMARDs and placebo, could still be helpful in formulating recommendations.

One RCT evaluated the effectiveness of MTX in 35 randomized patients with PsA who had been divided into two groups. Group A was treated with a NSAID for 3 months, then in combination

with MTX (10mg/week intramuscular) the subsequent 3 months. Group B was treated with a combination of NSAID and MTX (10mg/week intramuscular) during the entire 6-month period. After 3 months, all variables improved significantly ($p<0.05$) in both groups. However, the group B, that had continued treatment of MTX, experienced a faster and marked improvement which was statistically significant ($p<0.05$), in terms of their clinical symptoms (*SJC and TJC*). (177) (Evidence level 2b).

An open RCT with a small sample size ($n=32$) compared the effectiveness and safety of LEF with MTX. The LEF group ($N= 17$) received a dose of 100 mg for the first three days, then continued at a dose of 20 mg/day. The MTX group ($n=15$) was treated with 10 mg/week. In both groups, ibuprofen was allowed at a maximum dose of 1,400 mg/day. In both groups, a significant improvement was observed in SJC, TJC, VAS pain, and PASI after 6 months. The authors concluded that LEF seems to be as effective and safe as MTX in treating psoriatic arthritis (198) (Evidence level 2b).

2017 Update

By way of new evidence, a study with a Nordic cohort (179) in patients with PsA assessed MTX efficacy during first 6 months of treatment obtaining results similar to those obtained in the cohort of patients with RA. Furthermore, drug survival at 2 years was also similar in both cohorts (approx. 66% per cohort), and revealing treatment discontinuation was related to sub-cohorts of younger and advanced age patients, likewise those with greater functional deterioration.

In the TICOPA study (172) corresponding to “*treat to target*” strategy in British patients with early PsA diagnosis and under 2 years of symptomatology; 22% who received MTX as monotherapy reached the target minimum disease activity. It is important to highlight MTX should be prescribed at an efficient dose generally between 15 and 25 mg/weekly, via the appropriate administration medium in each case (subcutaneous or orally), together with folic acid supplements.

Regarding the role of csDMARDs in inhibiting structural damage and radiological progression, there are discrepancies and at present insufficient evidence. One study indicates that MTX at high doses (average dose 16.2 mg/weekly) (196) may have some effect compared to a preliminary study by the same authors on patients receiving an average dose of 10.8 mg/weekly. A subsequent revision of 3 studies on patients with PsA

treated with MTX, reported discrepancy regarding structural damage progression and absence of benefit in 2 and favorable results in the other (189).

No new registers were found regarding the efficacy of LEF or SSZ in controlling the inflammatory activity of peripheral PsA or evidence of results regarding association of either of these 2 drugs with MTX to control the activity of this pathology.

The guide update includes not only evaluation of the efficacy of traditional DMARDs but also those with specific target (tsDMARD). Apremilast is a small molecule which inhibits phosphodiesterase 4 (PDE-4). The inhibition of PDE-4 causes an increase in intracellular levels of Cyclic adenosine monophosphate (cAMP) modulating the expression of cytokines, reducing the pro-inflammatory (IL-23, IL-17, IL-6, etc.) and increasing the anti-inflammatory (IL-10) (211). Efficacy data for Apremilast in peripheral PsA based on results of clinical trials appear to be lower than BT, since they demonstrate clinical benefit which is only significant in clinical response indicators like ACR20 and PASI50, besides physical function scales like SF-36. In Schett's RCT the efficacy of Apremilast (20 mg/12 h or 40 mg/24 h) was assessed against placebo for 28 weeks. Apremilast proved to be significantly more effective than placebo in peripheral arthritis (ACR20), enthesitis and dactylitis. Information obtained from post-hoc analysis concluded there were no differences in the ACR20 response rate in 2 subgroups, i.e. Apremilast in monotherapy or combined with MTX (200) ([Evidence level 1b](#)). PALACE 1 clinical trial randomized 504 patients to Apremilast branches (20 mg/12h or 30 mg/12h) and placebo. Results at 16 weeks showed an ACR20 response percentage significantly greater for Apremilast branches (31%, 40% vs 19%) (201). At week 52, the ACR20 response percentage was 63.0% and 54.6% for patients with Apremilast at doses of 20 and 30mg/12h (202) ([Evidence level 1b](#)).

The absence of radiographic progression data, lack of experience in its use and comparative studies with csDMARD or BTs leads to doubts regarding the place of Apremilast in the therapeutic algorithm for peripheral PsA. However, its safety profile is good based on its use in those patients who due to the presence of comorbidities or a history of severe infections, the use of other therapeutic options is contraindicated (212). Despite its safety, its follow-up must be monitored in patients with depressive profile due to risk of suicidal thoughts described in some patients (213).

As to **axial affectation** in PsA, use of csDMARD is unjustified due to lack of evidence

regarding its efficacy at this level. At present there is insufficient scientific evidence to indicate the use of Apremilast in patients with AxSpA. A pilot study in double blind stage II controlled with placebo performed in a single centre, assessed the efficacy of Apremilast 30mg against placebo during 12 weeks on patients with active SpA (214). Despite the differences in favor of patients treated with Apremilast, they did not achieve statistical significance including the change in BASDAI at week 12 which was the main target of the study.

In those forms of SpA with predominant **enthesitic** form, the first use recommended is NSAID, physiotherapy and local perienthesitic infiltrations with glucocorticoids, despite the fact that to date there are no randomized trials controlled with placebo to support their efficacy. There is no evidence which supports the use of csDMARD in enthesitis; although in patients with SpA and enthesitis use of csDMARD could be considered provided there is associated peripheral arthritis. If despite the foregoing treatment a good response was not obtained, then BT or Apremilast would be the correct option.

Imaging studies have identified **dactylitis** as a complex multicompartiment ailment affecting tendinous structures and soft tissues, with its own characteristics that include: tenosynovitis, synovitis, capsulitis and inflammation of these soft tissues within the spectrum of PsA manifestations (215). In those forms of SpA with dactylitis the first use recommended is NSAID and local infiltrations with corticoids, although at present there are no randomized placebo controlled studies available supporting their efficacy. In patients with SpA and dactylitis, it could be considered provided there is associated peripheral arthritis. The csDMARD generally have a small effect on pure dactylitis (216).

Scientific evidence on the effectiveness of traditional DMARDs against uveitis was not found.

csDMARDs have emerged as a cost-effective and safe alternative for the initial treatment of PsA, mainly in its peripheral forms. Early use of csDMARDs, in tandem with corticosteroids infiltration and NSAIDs, in dactylitis and enthesitis must be individually evaluated, although it might represent a suitable choice in certain cases (e.g., when there is also peripheral arthritis). However, the use of DMARDs in axial forms of PsA, or in unambiguous forms of enthesitis is not justified.

In terms of applying and generalizing these results, the guideline development group recognized that the therapeutic agents in question are commonly used in our healthcare system. In addition, the population examined in the studies is similar that encountered in our own system, since both patients with long-term and recent-onset PsA are treated in our system.

2017

Clinical Question 13

In patients with psoriatic arthritis, is the combined treatment of MTX and biological therapy (BT) more efficient than treatment with BT in monotherapy?

Summary of Evidence

In analyzing secondary subgroups (<i>post hoc</i> analysis, no direct comparisons), no significant differences were observed in the effectiveness biological monotherapy (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) compared with the combined use of methotrexate and biological therapy (183, 217-219).	2b
When the effectiveness of ustekinumab in monotherapy (doses of 45mg and 90mg) was compared with the combined of ustekinumab and methotrexate, patient response proved quite similar (184, 185).	2b-
There are no differences in the safety profiles of biological monotherapy and combined use of biological therapy and methotrexate (183-185, 200, 217-219).	2b
Data from population registries have shown that the maintenance rate of biological therapy (adalimumab, infliximab) can be extended when used in combination with methotrexate (220-222).	2b, 4
There are no available studies evaluating the effectiveness of the following biological therapies in monotherapy: abatacept, alefacept, anakinra, brodalumab and tocilizumab.	

Recommendations

2017

Use of biological therapy is recommended in both monotherapy and combined with csDMARD, for all peripheral manifestations of PsA. Combined therapy with MTX may increase survival of the TNFi monoclonal drugs, particularly the chimeric ones ([Grade C recommendation](#)).

In rheumatoid arthritis, treatment with anti-TNF in combination with methotrexate (MTX) has proven to be more effective than anti-TNF in monotherapy. As a result, combined therapy is recommended for treating this disease. MTX is recommended as the csDMARD of choice for

psoriatic arthritis, but neither EULAR nor GRAPPA has recommend its use in combination with anti-TNF. Nevertheless, combination of MTX with anti-TNF has been presented as an effective method for obtaining better responses in patients with severe-moderate psoriasis (223). Some studies observe a higher effectiveness using this treatment regimen than with monotherapy (224) while others suggest a lower anti-drug-antibody formulation in order to lower immunogenicity (225). For this reason, it is important that clinicians, when treating patients with PsA, be aware of the scientific evidence supporting the concomitant use of MTX and anti-TNF treatment.

Quality of Evidence

Scientific evidence to answer this clinical question remains scarce. In all studies save one, there are no direct comparisons on the effectiveness and safety of combined treatment of methotrexate (MTX) and biological therapy (BT) versus BT in monotherapy. They are studies that assess BT at different doses compared with a placebo. Therefore, additional information was obtained from a study (from the systematic review) that addressed this question, as well as from analyses of secondary subgroups (no direct comparisons) in which the percentage of patients administered MTX was quite variable. For these reasons, the level of evidence has been lowered in the CEBM scale (Oxford).

A systematic review (SR) included various types of studies (RCTs, population registers, and cohort studies) that evaluated the effectiveness of adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab at different doses in comparison with a placebo. These studies provide secondary information (*post hoc* analyses) on BT in monotherapy compared to a combination of MTX and BT. The latter showed little beneficial clinical effects in compared to BT in monotherapy (217) ([Evidence level 2b](#)). Some population studies included in this SR found that the maintenance rate of anti-TNF agents – in particular infliximab, but also adalimumab in certain studies – could be extended when used in combination with MTX (220-222) ([Evidence level 2b, 4](#)).

An RCT with measures at 52, 104, and 256 weeks evaluated the effectiveness of golimumab at doses of 50 mg and 100 mg in comparison with a placebo. In a *post hoc* analysis, secondary information on the effectiveness of BT in monotherapy versus a combination of MTX and BT is obtained. The latter showed very limited beneficial effects (clinical improvement) compared with BT in monotherapy (183, 218, 219) ([Evidence level 2b](#)).

Two studies with results from the randomized controlled PSUMMIT trial, published separately, evaluated the effectiveness of ustekinumab after 6 and 12 months at doses of 45 mg and 90 mg, compared with a placebo. In the post-hoc analysis there were no significant differences in the efficacy of ustekinumab in monotherapy or combined with (184, 185) ([Evidence level 2b](#)).

In all of these studies, the safety profiles of BT in monotherapy, versus a combination of BT and MTX, revealed no differences (183-185, 200, 217-219) ([Evidence level 2b](#)).

Studies meeting inclusion criteria and/or not discriminating among results from the MTX + BT subgroup for biological treatments (abatacept, alefacept, anakinra, brodalumab, and tocilizumab) were not found. However, an RCT phase III has proven that the effectiveness of secukinumab at week 24 was unrelated to the patient being in concomitant treatment with methotrexate (186, 187).

2017 Update

There are no studies with direct comparisons of efficacy and safety between the combined therapy of MTX and BT against BT in monotherapy to treat PsA. The data from clinical trials did not find significative differences regarding the efficacy (ACR responses) or safety in patients undergoing combined treatment compared to those with BT in monotherapy (178, 183, 187, 191, 212, 217, 219, 226-234) ([Evidence level 2b, 4](#)).

Valid conclusions regarding efficacy or safety cannot be extracted for every biological drug combined with MTX compared to BT in monotherapy. Generally speaking, the combination with MTX did not show a significative clinical improvement against monotherapy (217). However, therapy combined with MTX did contribute to greater drug survival in some patient registers, particularly monoclonal antibodies and above all with Infliximab, so its use might be considered in this circumstance (220, 221, 235, 236). Experts conclude quality studies designed to assess the efficacy of combined MTX and BT treatment against BT treatment in monotherapy are required

2017
new

Pregunta clínica 14

In adults with PsA with axial and/or peripheral affection refractory to an anti-TNF, is treatment with a second biological therapy efficient?

Summary of the Evidence

Favorable response rates (ACR20/50/70, EULAR and DAS28) were shown in patients when changed to a second iTNF agent, although generally with lower values than those obtained in patients not previously exposed to these drugs (125, 185, 191, 237-239).	1b
Some studies show a slight reduction in the survival of the second biological therapy compared to the first and clearly worse in the third (221, 222, 240-243).	2b
There are no studies comparing the usefulness of a using a second iTNF against a change in the therapeutic target (IL12/23 or anti-IL17A).	

Recommendations

2017

Switching to another biological therapies albeit another i-TNFi or a drug with a different action mechanism like i-IL12/23 or anti-IL17A or tsDMARD (Apremilast), is recommended in patients with peripheral PsA and an i-TNF failure ([Grade B recommendation](#)).

Quality of Evidence

Evidence available to answer this question is based on the results of registers/registrations, i.e. standard clinical practice in RCT and some retrospective studies. Data from clinical trials indicate the response to a second iTNF agent is good although lower than generally obtained in patients not previously treated with these drugs. The ACCLAIM (238) study and different RCTs with biological disease modifying antirheumatic drug (bDMARDs) generally show that patients TNFi- naïve have higher ACR response rates than those with a previous treatment with TNFi (125, 185, 191, 237-239) ([Evidence level 1b](#)), although without significative differences between the first and second iTNF in most studies.

The registers show the second BT has a lower effect on disease activity compared to the first TNFi (221, 222, 241, 243) (Evidence level 2b), which drops even further with the third iTNF (222). No differences were observed due to reason of suspension of the first iTNF (adverse effect or lack of efficacy) (221, 222, 241, 243) or among the different TNFi molecules (222, 240) (Level of evidence 2b). Coates et al (240) and Ruward et al, (242) showed a good response to the second and third TNFi but lower than in naïve patients, and a slight reduction in survival of the second BT compared to first and clearly worse in the third. In a Norwegian register (241) survival at 3 years was 36% for the second TNFi compared to 57% for the first ($p<0.001$). In the Danish register (221), the median survival of the first TNFi was 2.2 years (confidence interval [CI] 95% 1.9-2.5) and the second TNFi was 1.3 years (CI 95% 1.2-1.6) ($p<0.001$). In the French register (243) the median survival of the first TNFi was 2 years (0.1-15.7), second 1.3 years (0.1–9.7) and 1.6 years for the third TNFi (0.1–7.3). And in the Swedish register (222) the survival median of the second anti-TNF was 64 months (CI 95% 31-97) compared to 14 months (CI 95% 5-23) for those changed to a third anti-TNF. There are no studies comparing the usefulness of a second iTNF against change to a distinct therapeutic target (IL12/23 or anti-IL17A) so both options are equally valid at present. In both Ustekinumab and Secukinumab studies as with TNFi drugs, it was shown that response to these drugs in patients not previously treated with BTs was higher when compared to those where a TNFi had already failed. Therefore, the expected efficacy will always be greater the sooner a BT is used, regardless of which is used (96, 186, 187). Apremilast also demonstrated better ACR20 responses in patients who had not received BT previously (201).

2017
new

Clinical Question 15

In patient with PsA, does treatment with DMARDs or biological therapies reduce CVD mortality?

Summary of the Evidence

There are insufficient studies assessing the effects of using biological agents and other DMARDs in CVD events in patients with PsA (244, 245).	2a
Some studies suggest TNFi and MTX acting as inflammation inhibitors may have cardioprotective effects. However, long-term quality prospective studies are required to explore the effects of said drugs on CVD morbimortality (244, 245).	2a

Recommendations

2017

CVD risk profile should be considered both in assessing and treating these patients. (Grade D recommendation).

Quality of Evidence

Tackling CVD risk in patients with chronic inflammatory diseases is important since knowing the connection between inflammation, endothelium dysfunction and atherogenesis increase (246). Associated to the role of inflammation in PsA patients an increase in CVD risk factors (HBP[Hypertension], diabetes, dyslipemia, etc.) has been observed, ergo a greater prevalence of CVD events (247). Another significative aspect we wish to insist upon is preventing obesity, since besides being a CVD risk factor, it may be associated with a worse response to immunomodulator treatments and greater difficulty to reach a state of minimal disease activity (51).

Systematic revision of this field infers epidemiological data are insufficient to reach definitive conclusions regarding the effects of biological drugs and csDMARD on CVD events in patients with PsA. However, the TNFi and MTX acting as inflammation inhibitors may have cardioprotective effects (244, 245) (Evidence level 2a).

Moreover, the specialist's therapeutic decision must be the most cost efficient possible with the greatest clinical benefit for the patient without extra charge to the national health system.

Clinical Question 16

In patients with psoriatic arthritis and moderate-severe skin psoriasis, what are the benefits, in terms of improving clinical control and patient satisfaction, of using a multidisciplinary management approach (dermatology-rheumatology consultation)?

Summary of the Evidence

Adult patients with psoriatic arthritis and moderate-severe psoriasis showed clinical improvement from baseline (referral from their primary care provider) after some therapeutic adjustments were made following a multidisciplinary consultation (248, 249).	4
In adult patients with psoriatic arthritis and severe psoriasis, multidisciplinary consultation results in a higher level of satisfaction (250).	4
Adult patients with psoriasis and severe psoriatic arthritis provide more positive assessments of multidisciplinary consultations than with standard consultations (250).	4

Recommendations

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 center of reference. (Grade D recommendation).

The frequently established association between psoriasis and psoriatic arthritis (5-30% of the former are associated with the latter in some series), and the fact that cutaneous manifestation precedes joint manifestation in most cases (only 10-15% of patients first present psoriatic arthritis) (251), makes PsA a source of frequent consultation among specialists who treat both manifestations. There are theoretical arguments (regarding early diagnosis, improved control, and disease prevention); economic arguments (cost savings); as well as human reasons (comfort and satisfaction) that favor multidisciplinary consultations and its implementation in hospitals. It should be stated that the suitability of a multidisciplinary

consultation should be measured by its capacity to achieve the main goals of PsA management: early diagnosis and early treatment.

Quality of Evidence

A 6-year study evaluated the impact of multidisciplinary consultation (dermatology-rheumatology), on a weekly basis, in terms of diagnosis and treatment of psoriasis and psoriatic arthritis in 270 adult patients (with cutaneous and musculoskeletal symptoms). Patients were referred from dermatology (43%), rheumatology (27%) and primary care. Fifty-three percent of patients received a “de novo” diagnosis of PsA. In addition, by modifying previous care with more frequent interventions, the use of topical treatments was reduced (from 50% to 38.8%). In addition, indications rose for the use of non-biological systemic DMARDs (from 14.6% to 25.4%) and in biologics (from 15.7% to 36.9%) in those patients referred to both rheumatology and dermatology (OR 5.1). The study has some limitations since it does not include validated indices of joint and cutaneous effectiveness as outcomes. A significant confounding factor, which is referral from primary care, is also present (248) ([Evidence level 4](#)).

A second study evaluated the satisfaction level in 48 adult patients seen in monthly multidisciplinary consultations (dermatology-rheumatology). Patients were given a satisfaction survey and data interpreted by an independent clinician. Patients scored their experiences in multidisciplinary consultation, on average, at 4.91 (scale 0-5) compared with 2.85 (0-5) in stand-alone dermatology or rheumatology consultations. Up to 94% of patients showed a high level of satisfaction, with waiting being marked as an area for improvement. Among the limitations of the study are its small sample size, and the one-time nature of the survey. Thus, patient satisfaction cannot be assessed in the long run. No comparison with another series of patients seen in standard rheumatology or dermatology consultations was made (250) ([Evidence level 4](#)).

There was a third study involving 199 patients referred from dermatology (40% of cases), or rheumatology (57), who had been diagnosed with psoriasis and/or psoriatic arthropathy during multidisciplinary consultation (dermatology-rheumatology) in 188 of the cases. A “de novo” diagnosis of PsA was made in 30% of the patients referred from dermatology due to cutaneous psoriasis. Therapeutic adjustments were made in 53.6% of patients, 44% of the time due to bad cutaneous control, 26% to bad joint control, and 15% due to both. These

adjustments consisted, for the most part, of administering phototherapy (27%), methotrexate (54%), and/or biologics (11,2%). Using a multidisciplinary approach, improvements were observed in 56% of cases after an average follow-up period of 9 months (249) (Evidence level 4).

After considering the results previously cited, the few existing studies on multidisciplinary management (rheumatology-dermatology) of PsA point to improvement in accurately diagnosing “de novo” psoriatic arthropathy, as well as a striking level of satisfaction in patients seen at such consultations. The generalization of findings is, however, problematic given the limited evidence, design, quality of available studies, and limited follow-up time.

In formulating the recommendation, the guideline development group believes that, in terms of cost optimization, multidisciplinary consultations (dermatology-rheumatology) would translate to a decrease in the overall frequency of consultations. Moreover, patients’ perception of quality and comfort seems to improve, while the duplication of visits and tests is reduced. The ability to detect de novo psoriatic arthritis also seems to increase, making it possible to treat the disease from its earliest stages, and to improve diagnosis. However, further well-designed studies with larger patient samples, and under long-term disease conditions, are needed to confirm these potential benefits. Finally, although dermatology-rheumatology consultation management is desirable, such changes are generally gradual in pace, and across Spain currently remain relatively few in number.

Clinical Question 17

For patients with axial spondyloarthritis, are health education programs offered by nurses beneficial?

For patients with psoriatic arthritis, and peripheral and/or axial affectation, are health education programs offered by nurses beneficial?

Summary of Evidence

There is little evidence documenting the benefits that nurse-run health education programs can provide patients specifically diagnosed with psoriatic arthritis (252-259).	1b,2b,4
Nurse consultations do increase treatment adherence rates, mainly when the education programs are conducted in a group setting (252, 253).	1b
Educational programs provided by nurses facilitate patients' self-management (252, 253, 259).	1b
Nurse consultations increase patient satisfaction levels regarding care received, as well improving adherence to treatments prescribed by the rheumatologist (259).	2b
Nurse involvement in intervention programs for smokers suffering from rheumatic diseases may contribute to smoking decrease or cessation (255).	4
Follow-up consultations conducted in person, or by telephone, for those suffering inflammatory arthropathies increase patient satisfaction with this type of assistance programs (254, 257).	1b, 4
Most patients with chronic inflammatory diseases find nurse-run educational workshops to be useful or very useful when conducted prior to subcutaneous therapy, since they help to decrease their fear of this new treatment (256).	4

Recommendations

Participation of clinical nurse specialists is recommended, either in person or by telephone, in follow-up consultations for patients with axial spondyloarthritis or with psoriatic arthritis due to evidence it increases patient satisfaction (**Grade D recommendation**).

Patients who are smokers and suffer from axial spondyloarthritis or psoriatic arthritis could benefit from implementation of educational tobacco cessation programs provided by a nurse, since evidence show they increase smoking quit rates (Grade D recommendation).

Nurse-run educational workshops prior to the start of subcutaneous therapy are recommended since they help lower 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 the patient opinions and preferences are not influenced (Grade D recommendation).

Patients with psoriatic arthritis could benefit from educational programs, preferably in a group setting led by a clinical nurse specialist. This would facilitate patient self-management and would treatment adherence (Grade D recommendation).

Patients suffering from AxSpA with peripheral and/or axial affectation, or from PsA, undergo a process which is generally chronic and causes pain, functional disability, and even psychological problems such as anxiety, depression, etc., all of which affect their family and social environment. Health professionals must provide comprehensive and multidisciplinary care, in which nurses have an important role through the development and administration of educational programs for patients and their families. This includes structured activities aimed at increasing the patient's knowledge about the disease, or fostering educational programs (individual-, group-, or community-based) (260). Rheumatology nurse may help patients with managing their disease and controlling comorbidities associated with this pathology. The most salient points included in any such educational programs would include: information on diagnostic procedures, disease types, treatments, physical exercise, pain control, and joint protection (261).

Patient educational programs are essential to any intervention with this type of patient. A patient educated in all of these aspects is a patient who can more actively partake in his/her health care.

Quality of Evidence

There is little evidence documenting the benefits that nurse-run health education programs can provide patients with AxSpA or psoriatic arthritis. Nearly all of the published studies

involve a mix of patients with different pathologies grouped under the labels polyarthritis, inflammatory arthritis, or rheumatic diseases.

One RCT analyzed the effect of clinical consultations carried out by nurses to manage disease in patients suffering inflammatory arthritis (RA, PsA, AS, JIA, or undifferentiated polyarthritis). Sixty-eight patients were randomly assigned for a follow-up appointment with a clinical specialist nurse or the patient's rheumatologist at 3, 9, and 21 months. Statistically significant differences were found regarding patient satisfaction -Leeds Satisfaction Questionnaire (LSQ)- in all the subscales in the follow-up group, as were measures of general satisfaction after 9 months (average difference adjustment between groups of -0.74; 95% CI: -0.96 to -0.52) and 21 months (-0.69; 95% CI: -0.87 to -0.50). DAS28 improved in both groups, at 9 and 21 months, though there were no statistically significant differences between the two groups (254) ([Evidence level 1b](#)).

An interventional study without a control group evaluated the effects of an educational program run by a rheumatologist and a nurse for 152 patients who were smokers with rheumatic diseases (RA, spondyloarthritis including AS and PsA, and connective tissue diseases). During the initial visit of the intervention, the rheumatologist provided verbal and written counseling, with an emphasis on quit smoking strategies. The patients completed a questionnaire that addressed tobacco dependency and previous attempts to stop smoking. In follow-up consultations, carried out by a nurse over the phone, patients were asked about their smoking habits, and previously provided information was reiterated. Finally, patients were offered a further visit or pharmacological treatment to stop smoking. Smoking cessation rates were 11.8%, 14.4%, and 15.7% after 3, 6, and 12 months, respectively. Nineteen percent of patients reduced their cigarette consumption by 50% after 12 months (OR 3.8; 95% IC: 1.8 – 8.1). Linear regression analysis showed that a lower dependency score ($p = 0.03$) and previous attempts to stop smoking ($p = 0.04$) were significantly associated with smoking cessation after 12 months (255) ([Evidence level 4](#)).

A prospective study carried out in two phases (2011-2012) evaluated the usefulness of information provided by a nurse to 29 patients with inflammatory chronic diseases regarding the use of pen injectors and syringes for administration of etanercept. Twenty-one percent of patients had AS and 3% of patients had undifferentiated spondyloarthritis. The patients' fear to prior administration, post-injection pain, difficulty in handling, and satisfaction level

regarding the use of one over the other, as well as their preferences after trying both were also assessed. Baseline and follow-up questionnaires, both developed for this purpose, were used to collect data; variables were evaluated using visual analog scales [VSA] at 2, 4, and 6 months. In comparing the syringe and the pen injector, there were no statistically significant differences in terms of fear, pain, or difficulty in handling the implement ($p = 0.469$; $p = 0.812$, and $p = 0.169$ respectively). After 6 months, 59% of patients stated they were satisfied or very satisfied with the pen; 93% found the workshop useful or very useful; and 55% preferred the pen (256) (Evidence level 4).

Another study evaluated the help a nurse provided to 162 patients diagnosed with AS in completing a BASDAI. The BASDAI was first completed by the patient (self-reporting), and then repeated with the nurse's assistance. If the absolute value of difference between both questionnaires was ≥ 1 cm (the minimum difference that is clinically important), the patients were defined as discordant. There were no high average differences between the patient self-assessed BASDAI scores (3.07, SD 2.31) and those completed with the nurse's guidance (2.89, SD 2.31); 23.4%, of the results were discordant. Compared to non-discordant subjects, discordant patients presented more active disease; were older; more often female; had ≤ 8 years of education; and read newspapers less often. Logistic regression analysis revealed the main discordance factors to be extent of education 3.1 (range from 1.21 to 7.88); age 1.19 (range from 0.97 to 1.46), and frequency of newspaper reading 2.63 (0.96 to 7.18) (262) (Evidence level 4).

An open RCT analyzed the effect of a nurse-run educational program for 141 patients with polyarthritis (RA, PsA, and unspecified polyarthritis). The intervention consisted of 3 workshops in a group setting and one individual training session. The comparison was carried out with the habitual assistance and without considering the educational program. The intervention group experienced a global improvement with regard to well-being after 4 months of educational programs (AIO 8.21; 95% CI: 2.3 – 14.1; $p = 0.01$), as well as better self-management of the disease (SE 4.17; 95% CI: 0.2–8.1; $p = 0.04$) to a greater degree than did the control group. A positive trend was observed in disease activity improvement (DAS28 -0.23; 95% CI: -0.5 – 0.0; $p = 0.10$), as was a significant change in patient involvement (5.98; 95% CI: 1.8 – 10.2; $p = 0.01$) and pain levels (VAS -9.41; 95% CI: -16.6 to -2.2; $p = 0.01$) (252) (Evidence level 1b). The same authors analyzed the study 12 months later, and noted an overall improvement in the well-being of the intervention group (8.2; 95% CI: 1.6–14.8; $p = 0.015$). No

significant differences were observed regarding disease self-management between the two groups. Analyses of each group revealed a statistically significant improvement (DAS 28) for the intervention group after 12 months, as measured from baseline (-0.3; 95% CI: -0.5 to 0.1; $p = 0.001$). In regards to disease self-management, the control group experienced a significant deterioration after 12 months (-5.0; 95% CI: -8.6 to 1.3; $p = 0.008$) based on scales measuring psychosocial impact (AIMS2 0.3; 95% CI: 0.1 to 0.5; $p = 0.008$), anxiety and depression (HADS 1.4; 95% CI: 0.3 to 2.5; $p = 0.013$) (253) ([Evidence level 1b](#)).

An RCT compared group (3 to 6 patients) and individual counseling, both conducted by a nurse, in 62 patients with PsA who were about to start treatment with a DMARD. Patients in the counseling group demonstrated better adherence to medication (tested by tablet counts) (90% compared to 69%). Patients who received individual counseling missed at least one analytical follow-up and one clinical follow-up visit compared to their counterparts in the other group (25% vs. 17% and 19% vs. 3%, respectively). Patient levels of satisfaction regarding the information provided proved similar in both groups. Continuation of medication intake rates were higher in the training group (after 4 months, 73% vs. 63%; after 12 months, 47% vs. 38%). The authors emphasized that the trend towards better outcomes, both in adherence and in continuation of medication intake rates, in the training group likely indicated the potential benefits of group interactions. However, all of the obtained results remained inconclusive (259) ([Evidence level 2b](#)).

Due to the lack of evidence surrounding this clinical question, two studies identified through a manual search were included. One evaluated the impact on waiting times, as well as satisfaction levels with over-the-phone clinical consultations provided by nurses to patients with rheumatologic diseases. For 1 month, 71 patients who were on the waiting list for a regular consultation were recruited for a follow-up phone call from a nurse in the rheumatology department. This phone consultation was used the same parameters as a standard outpatient visit. The results showed that 72% of patients appreciated this type of care and were not opposed to receiving this type of assistance again. Eight percent of patients preferred an in-person consultation with the nurse. The average wait time was reduced by 2 months (257) ([Evidence level 4](#)). Another study evaluated the effectiveness of educational interventions in reducing barriers to health literacy and in improving health outcomes for 127 patients with inflammatory arthritis. The intervention consisted of information provided in plain language, and/or two individual sessions with an educator trained in joint inflammatory diseases. This was compared with a standard outpatient visit. The intervention group showed

improvement in their mental health scores after 6 and 12 months (4.6% and 4.8% of change), while the control group's score dropped (-4.3% and -0.8% of change). In terms of self-efficacy, the intervention group improved more from the initial intervention up to 12 months (1.5% and 3.6% change vs. -3.2% and -2.0% change). Differences between individual care and standard care were statistically significant at 6 and 12 months, except in the percentage of change in mental health scores at 12 month. Adjusted multivariate analysis showed significant improvements regarding the mental component of SF-36 in the individual care group (average difference between groups = 7.5 points, $p = 0.003$). This improvement was higher after 6 months (7.5 points, $p = 0.01$) than after 12 months (6.3 points, $p = 0.03$). In univariate analysis, however, the intervention had a significant impact on self-effectiveness, which was not the case in multivariate models ($p = 0.12$) (258) ([Evidence level 1b](#)).

The guideline development group also deemed it appropriate to mention content from other publications on the role of nurses in rheumatology care. The work of nurse practitioners can be as a caregiver directly treating the patient and his/her disease and/or as an interface between the patient and his/her rheumatologist, other health professionals, patient associations, or official bodies. The range of duties discharged by nurses in patient care is broad: follow-up through systematized clinical evaluations, including the measurement of metrological parameters and/or questionnaires; compliance control, self-administration, dosing responsibilities, and secondary effects of treatments; administration and monitoring of biological drugs, both subcutaneous and intravenously, which can be carried out according to protocols and/or clinician directed. A nurse benefits the patient by solving different problems related to his/her disease, greatly assisting with a rheumatologist's workload. Nurses also benefit the healthcare system by greatly lowering operating costs (4, 263-266). Recent project SCORE abstracts submitted to the SER and EULAR congresses report that nurse-led rheumatology clinics contribute to less frequent primary care consultations and improvements in clinical results and patient quality of life, knowledge, treatment adherence, and perceived quality of healthcare provided (267).

In light of all this, the guideline development group recognizes the many advantages of having clinical nurse specialists help in the management of patients with ankylosing spondylitis or with psoriatic arthritis. Their assistance is particularly valuable in tasks such as clinical metrology, monitoring patient compliance, self-administration, ensuring correct dosage, secondary treatments effects, educational programs and liaising between patients and other professionals or entities.

Based on the experience of the guideline development group, another important role played by nurses is in the prevention and management of adverse effects and complications, medication issues, and other special situations (vaccinations) (268). Nursing care represents the first intervention in patient care, encompassing infections, surgeries, dietary and hygienic habits, exercise programs, control of cardiovascular risk factors, tobacco cessation and restriction, and alcohol intake. The desirability of turning patients into active participants, and not mere recipients of their care, by offering them information and monitoring, as well as giving them and their families the attitudes and technical skills to deal with the disease and increasing their quality of life, is also to be emphasized (269).

8. General Advice for Patient Management

The management of patients with axial spondyloarthritis or psoriatic arthritis must be carried out by taking into account each patient's individual characteristics ([Grade D recommendation](#)).

Before early implementation of treatment for axial spondyloarthritis or psoriatic arthritis, patients must be properly informed regarding pharmacological properties and side effects, treatment duration, expected benefits and possible secondary effects, taking their preferences into consideration ([Grade D recommendation](#)).

In prescribing biologics particular attention must be paid to the patient's age, preferences, tolerance, previous treatment, secondary effects, possibility of pregnancy, and cost benefits ([Grade D recommendation](#)).

The Patient and/or family should be instructed regarding self-care of joints, and self-management of biological therapy ([Grade D recommendation](#)).

Health professionals will offer information to patients with axial spondyloarthritis regarding the most appropriate physical exercise ([Grade D recommendation](#)).

The health professional will give patients with axial spondyloarthritis information regarding tobacco cessation programs ([Grade D recommendation](#)).

9. Perspective of patients suffering from AsP and AxSpA

“The illness: an invisible companion for one’s entire life”

(A patient's reflection)

It is important to obtain information on how patients understand and perceive the diseases they suffer. In formulating this clinical practice guideline, the perspective of patients suffering from axSpA and PsA was included by having two of them directly partake in the process. This included reviewing the existing scientific studies regarding and moreover asking patients that volunteered to share their experiences and concerns.

Systematic Review

The review examined the available scientific literature, whether quantitative or qualitative in methodology. In addition, patient concerns, worries and needs (adherence, quality of life...) regarding a given treatment, as well as those areas in which patients, their families and caregivers need more information and support were all addressed.

Below is a summary of the information gained through review of the selected studies.

Diagnosis	
<p>The elapsed time between the onset of symptoms and the diagnosis is too long for patients and is described by them as frustrating and discouraging. This feeling of frustration stems from the pain they suffer, from lack of sleep, and from the fact that they do not know why this is happening. The diagnosis alters the patient's, his/her caregiver's, and family's daily life. The difficulty of obtaining an accurate diagnosis has a deep psychological impact. This stage involves going through a period of undiagnosed symptoms, which affects aspects of daily life. Until they are properly diagnosed, patients are unable to understand what is happening to them and cannot explain it to others. Finally, they are unable to know how their future is going to be affected.</p> <p>Diagnosis is seen as a relief, as the disease is finally identified, and this uncertainty is resolved. Afterwards, however, comes a new stage fraught with worries and negative expectations regarding their ability to handle what the future holds for them. Patients begin to wonder if, in a few years, they will increasingly have to rely on others in their everyday lives (270-275).</p> <p>Hereditary Disease:</p> <p>Regarding diagnosis, there is another aspect related to the uncertainty a patient feels: the fact that his/her disease may be hereditary. The chance that other members of their family might develop the same disease causes “self torture” and worries the family. The perception of themselves as “sick people for life” also generates anxiety, although some patients do realize</p>	<p>Experts</p> <p>Opinion 4</p> <p>Q+, Q++</p>

<p>that the disease will not be transmitted to offspring. The studies highlight the importance of the doctor's help in alleviating much uncertainty if he/she can explain the role of genetics in a sympathetic manner and in plain language (276).</p>	
<p>The Symptoms of the Disease</p>	
<p>General tiredness or asthenia:</p> <p>One of the more obtrusive symptoms is general tiredness or asthenia. It constitutes an unknown, unpredictable, and uncontrollable physical experience for the patient, as if he/she had "another body". It appears suddenly, without any previous physical effort that might explain it. Things that are tolerated one day become unbearable the next. This can be difficult for those around them to fully grasp. Asthenia is described as a lack of energy and a general tiredness that prevents one from carrying out daily activities, particularly at work, but also in family life.</p> <p>Mothers can identify with this problem, and note their inability to bear the workload associated with childcare. Fathers describe as very important the turmoil they feel at being unable to play with their kids, a problem that adds to the lack of energy for helping with household chores.</p> <p>However, the majority of patients find a way to deal with these problems. Among the most effective coping mechanisms are: resting and sleeping, adjusting activity levels and avoiding stress, dividing tasks between big and small, and asking other family members for help.</p> <p>Patients would also like to see more research into non-pharmacological solutions for battling tiredness and asthenia (271, 273, 277-282).</p> <p>Pain:</p> <p>The main frustration of asthenia is the difficulty patients experience in trying to describe it. Patients feel great uncertainty about when their disease might lessen in severity. In addition, fear of its recurrence is a cause of considerable distress.</p> <p>Their relationship with their own body changes when the pain becomes chronic, when there seems no possibility of returning to a life without pain. Pain becomes part of daily life, "part of the family". This constant "partner" paradoxically makes the patient feel his/her own body more acutely, instead of less self-conscious. For patients suffering psoriatic arthritis, the symptomatology of the pain is more unbearable than skin lesions.</p> <p>Patients understand that it is a symptom that only they register due to its invisibility. Patients often feel that people around them do not believe in their suffering, and that this disbelief extends to all spheres: family, clinical,</p>	<p>Q+, Q++</p>

<p>and social (275, 283).</p> <p>External Appearance:</p> <p>Patients, especially those with psoriatic arthritis, tend to perceive a stigma of the “visibility of the illness”. This visibility is two-fold in nature: in addition to skin lesions, they must also suffer articular changes (284).</p>	
<p>Treatment</p>	
<p>Before starting a prescribed treatment, patients search for information on the medicine in question, either through the doctor, or via the drug's information sheet (or leaflet) and/or the internet.</p> <p>Patients express fear of what are regarded as new drugs i.e., biological therapies. Fortunately, the majority of patients experience an improvement in both their functional and work capacities. However, many state continued difficulties with other symptoms of the disease and often request occupational therapy.</p> <p>Patients understand that to achieve compliance (adherence to treatment), they need to trust their rheumatologist. The most effective way to positively influence a patient's perception of a new medication is by maintaining an open and informative dialogue between themselves and their rheumatologist (285, 286).</p>	<p>Q+, Q++</p>
<p>Living with the Disease</p>	
<p>Living with Spondylitis:</p> <p>Spondylitis is considered by patients to be a fluctuating illness. There are stages in which the disease allows them to have a more or less normal life. To achieve this, they often must modify certain daily habits that enable improved mobility and avoidance of overstraining. This may also involve turning to less demanding sports activities. There are other stages of the disease in which they must slow their activity level, due to stiffness, asthenia, and general fatigue. There are also stages in which they must cease certain activities as their pain becomes unmanageable (287).</p> <p>Living with SpA:</p> <p>For patients with psoriatic arthritis, an outbreak is much more than just an inflammation of the joints. Patients in the early stages of the disease learn to identify the pre-outbreak phase. As time goes by, they even learn how to manage the trigger factors and the pre-outbreak phase in order to halt its progress. This is typically achieved either through self-management techniques or medication. However, patients also admit that there are times when the outbreak cannot be controlled (288).</p>	<p>Descriptive Study 3</p> <p>Q+, Q++</p>

Disease Management:

There are different ways to manage the disease depending on how long the patients have been living with their illness. Those with more experience can generally face it in a more positive way. They know which adjustments must be made in order to better navigate the difficulties ahead of them. Patients who have been more recently diagnosed have a harder time in making these adjustments.

In general, the most important aspects of effective self-management include: a positive attitude, an ability to adapt to the disease, to remain indifferent to what other people may think, to safely self-medicate, and to integrate the aforementioned into their daily life and routines (283, 289).

Changes in the Perception of Oneself:

The disease provokes a feeling of vulnerability in patients. The difficulty they often face in maintaining family roles is considerable. Pain, asthenia and tiredness, lack of mobility and physical limitations all combine to interfere with the fulfillment of their roles as parents and/or grandparents.

These feelings are strikingly more pronounced in male patients. They no longer feel like a “superman” able to do everything and this seriously undermines their masculinity. The disease affects their abilities to be the ideal father according to established social criteria. In addition, the situation continuously reminds them of being ill. They feel guilty and indignant because they cannot do certain things such as keeping their jobs and are forced to stay at home (273, 290).

Work:

The aforementioned symptoms - tiredness, “invisibility”, fluctuations, and unpredictability - act as barriers that complicate and burden patients' lives.

There are two particularly important aspects to this:

- Workplace issues: Difficulty getting to work and inadequate facilities.
- Difficulty with interpersonal relationships at work: Specifically, the lack of understanding on the part of bosses and colleagues. The health problem is not readily visible to bosses and this can lead to fear of losing one's job, stigmatization, and/or negative reaction from workmates. Thus, many suffering this disease “wear a mask to hide their arthritis, pretending that everything is fine.”

Patients understand that continuing to work may involve complex emotional challenges. Feelings of guilt, sadness, and depression brought on by various disease-related losses and limitations are commonplace. However, most patients prefer to continue working even if it means sacrificing other important things.

Patients did describe some solutions that might make their situations more manageable: more flexible scheduling and workplace conditions such as

<p>well-designed ergonomic modifications supervised by a professional therapist (279).</p> <p>Social Relationships:</p> <p>The disease has a considerable impact on social relationships.</p> <p>Patients express difficulty in dealing with the perceptions of friends who cannot understand their illness, particularly when there are no visible signs of it. This causes suffering because, little by little, their relationships with old friends grow more distant.</p> <p>On a positive note is the formation of new relationships with fellow patients who do understand the disease (273, 275).</p> <p>Sexuality:</p> <p>This type of disease can also negatively affect a patient's sexuality. Tiredness or asthenia is the most limiting factor on sexual relations, followed closely by joint and muscular pain. In addition, particular emphasis is placed on the compounding effects of anxiety and depression (280, 291).</p> <p>Patients understand that sexual function plays an important role in quality of life, and that there is a negative correlation between sexual problems and quality of life and/or health levels. Indeed, tiredness, low energy levels, poor mental health, limitations in daily life due to physical problems all act to lower quality of life, thus contributing to sexual problems (292).</p>	
<p>Relationship with Health Professionals:</p>	
<p>The experience of the patients with health professionals is positive, but they also express various needs they have in this regard. They want their physicians to listen to them and see them. Health professionals must be accessible, with real patient-doctor interactions (293).</p>	<p>Q+, Q++</p>
<p>Caregiver's Perspective:</p>	
<p>Relatives or caregivers living with patients suffering from spondylitis or psoriatic arthrosis can also experience difficulties. The role of caregivers is crucial since they contribute to the patient's physical and emotional well-being. However, caregivers and relatives must also incorporate important changes in their own daily lives and leisure activities. This can entail certain problems:</p> <ul style="list-style-type: none"> - From a mental health point of view: emotional overload, feelings of guilt, discouragement. - Workplace problems due to absenteeism to care for a relative. - Effects on relationships and social networks: decreases in spare time 	<p>Q+, Q++</p>

and leisure activities. Caregivers understand that their workload will increase as the patient becomes more dependent. They also lament the lack of institutional aid they receive (270).	
Need for Information	
<p>The three main sources of disease information patients rely on are: first, the internet; second, written information obtained in hospitals; and third, information provided by health professionals.</p> <p>Based on patient profiles, women are more likely to ask for additional information, while older patients tend to be more satisfied with the amount of information they receive.</p> <p>For patients, it is very important to have information about their prognosis. It is also important that this is conveyed in a hopeful yet realistic way, and that they understand their options so that they can better adapt to living with a chronic disease (158, 273, 293).</p>	<p>Descriptive</p> <p>Study 3</p> <p>Q+, Q++</p>

Qualitative Study

In order to understand the disease experience among patients from the same cultural background, a primary qualitative investigation was carried out. This involved holding discussion groups, as well as in-depth interviews, with patients suffering ankylosing spondylitis and psoriatic arthritis. Such feedback helped identify questions more relevant to these patients. It is hoped that such information will augment what is available in the current literature.

The most important conclusions of the qualitative investigation are summarized in the following table:

Categories	Analysis
Diagnosis	<p>Calvary</p> <p>A definitive diagnosis serves as a sort of Calvary for these patients. For example, it can be interpreted as a stage of the pilgrimage undertaken by professionals to alleviate a patient's anxieties. It is a process that starts with a family doctor, continues with a physiotherapist and, sometimes, also with a traumatologist, until the right diagnosis is found. Unfortunately, for the patient all of this can feel like a waste of physical and mental energy.</p> <p><i>"You go to your family doctor and they attribute it to lower-back pain."</i></p>

	<p><i>"My family doctor and the traumatologist told me that it was just a knock. They gave me infiltrations. These were effective for a while... they then sent me to the surgeon, who examined me and asked me if I wanted to have my finger amputated. Then someone had the idea to send me to the rheumatologist."</i></p> <p><i>"I have had problems since I was a kid. Even when in the military service I had problems as I couldn't maintain the same pace as the others... After a check-up at a military hospital they told me: "Get out of here, you are just a lazy ass. Or that this was a pain caused by the sciatic nerve, a herniated disk, that I should have surgery, that I shouldn't...."</i></p> <p>Impact and Relief</p> <p>To obtain the right diagnosis means to put a name to the illness, which can be a great to patients.</p> <p><i>"You finally know what you have! It is very important to get a name for it. You know that then there will be a treatment"</i></p> <p><i>"I didn't know what ankylosing spondylitis was; it was even difficult for me to learn to say the word. But now it is very rewarding to help other people by sharing my experiences."</i></p> <p>Later, must assimilate the fact that they have a chronic disease, and the difficulty of accepting this will have a deep emotional impact on their lives.</p> <p><i>"When they tell you, you don't know what questions to ask; it all comes rushing in: is this for life?"</i></p>
<p>Prognosis</p> <p>Follow-up</p>	<p>A companion for life</p> <p>The core worry of patients relates to the chronic nature of the illness.</p> <p><i>"The shock you feel following diagnosis leaves you puzzled. After that, when they explain to you that you have a degenerative disease, that it is for life... it keeps you thinking. The first thing you ask is: But, can I do anything to stop it? They tell you you can't."</i></p> <p><i>"It is difficult to imagine that you are going to have this illness forever."</i></p> <p>Uncertainty</p> <p>A recurring complaint among patients concerns the information on disease evolution and prognosis, and the manner in which it is conveyed, by professionals. Time constraints during patient consultations could be offset by greater sensitivity on the part of the doctors.</p> <p><i>"The doctor has no more than 10 minutes' time. You leave with a lot of doubt that you cannot express. The doubts surface when you arrive home".</i></p> <p><i>"They must explain everything that the illness entails. They should also explain that the disease could evolve in different ways... The attitude the</i></p>

	<p>doctor conveys is very important, even if they tell you that you can end up in a wheelchair.”</p> <p>“You don't know whether your evolution will be good or bad until a considerable amount of time has passed”</p>
<p>Clinical Manifestations</p> <p>Symptomatology</p>	<p>To Live with Pain and Getting Used to It</p> <p>Although spondylitis and psoriatic arthritis having their own specific characteristics, some symptoms are common to both diseases. Pain is perceived as the main symptom in terms of its negative impact on quality of life.</p> <p>“I used to have joint pain... overall pain in my back that often made it impossible to sleep at night... There are times in which the pain in my arm feels as if it is being torn off.”</p> <p>“Physiotherapy and painkillers made me feel better, but it wasn't enough.”</p> <p>“I have experience various things, but spondylitis is the most painful illness I have ever had. It is a very annoying disease, and causes a lot of pain.”</p> <p>“When I'm in pain I don't want to speak to anyone until it's over. Even my wife, when she sees a certain look on face, know to leave me alone. I would rather be alone, since I can make strange gestures and movements that help relieve the pain. The good thing is that I anticipate these episodes;, I tell myself that this is going to happen.”</p> <p>Not only is the illness chronic, the pain is as well, a realization the patient must become accustomed to, it and which is difficult to quantify or describe.</p> <p>“You suffer from pain daily... how can you tell someone else how you feel?”</p> <p>“You get used to pain. You are always going to suffer from pain.”</p> <p>“One gets used to pain. I carry on with pain every day and have gotten used to it. You get to a point in which it is very difficult to evaluate the extent of it and you must simply bear with more and more.”</p> <p>Tiredness, eternal tiredness</p> <p>Another major physical limitation suffered by patients is general tiredness or asthenia. This is a recurring symptom that is often exacerbated by the additional efforts that daily activities require.</p> <p>“I have always become easily tired... There are days in which I can do nothing; I feel very tired... even my voice, it disappears and I just have a tiny voice”</p> <p>“How are you? Tired... It is a constant tiredness.”</p>
Treatment	As regards treatment, the most important development has to do

	<p>with new pharmacological therapies. Patients are often of two mind about this: some have doubts about these drugs while others prefer them to their former medications.</p> <p><i>"Among the patients I know, I must be the one who has been reluctant to start with biologicals. I have objections, but started with them because my doctor said there was no other choice. I was terrified of getting the injections."</i></p> <p><i>"I pushed very hard for treatment with biologicals, because I had asked around and everybody told me they felt better on them."</i></p> <p>Almost universally, patients' concerns about side effects will affect their acceptance or refusal of such treatments.</p> <p><i>"You start getting some information about the treatments that is alarming. I read through pages and pages about the side effects. They used to tell me not to read them. What happens is that, since there aren't many more options, you tell yourself that you are in good hands."</i></p> <p>A more individualized and continuous follow-up plan would increase patient adherence to these types of medicines.</p> <p><i>"Another thing is that although they gave me the medicine, they don't make certain whether you are taking it or not. It is not an easy treatment; it is not just swallowing a pill and that's it."</i></p>
Genetic Profile	<p><i>The Shadow of Inheritance</i></p> <p>The fear that the illness can be inherited is especially pronounced in those patients who have children. There is a special sensitivity regarding this aspect that makes these patients acutely sensitive to any symptoms or sign that their children may exhibit.</p> <p><i>"I started to think that my daughter had problems, but I kept quiet and didn't share my fears. The doctor didn't know what to say... And now, when my grandson says that something hurts, then I..."</i></p> <p><i>"It is like a lottery, you never know."</i></p> <p><i>"I have relaxed regarding my kids as the years have gone by. Since it all started for me when I was very young, seeing one more year pass by without any symptoms felt good."</i></p> <p><i>"My son felt pain in the lumbar area and the heels and I panicked."</i></p>
Impact on Daily Life	<p><i>Changes in Daily Activities</i></p> <p>The illness causes significant changes in the patients' daily lives because it affects their work life, social life and emotional life. For many, it involves a traumatic break with the daily routine they once</p>

followed, forcing dramatic changes their everyday activities.

"I have hardly ever been able to hold my grandchildren in my arms. It seems trivial, but it is not. When I am with my granddaughter and she says: hold me, grandpa, I have to tell her 'No, no, I can't'"

Problems at Work

Physical limitations diminish the functional ability to work. Such changes vary with the personal situation of each patient.

"It became harder and harder to adopt certain postures at work. There were things that I didn't sense as normal, but I couldn't link them. I used to go to the doctor because of the pain and because I bumped myself... I used to think I was clumsy. I felt myself clumsier and clumsier, bending over was hard."

"Quitting my job was traumatic."

"I have always liked my job."

The most physically demanding jobs more often force patients into a disability-based retirement due to their inability to do the work.

"Age affects you (at 49 "total incapacity", and then at 53 "absolute incapacity"). It is a relatively young age to quit working, and you have a hard time. I didn't want to reach absolute incapacity, but rather to maintain total incapacity, since being at work helped me not to think about my illness. Even if my duties were lighter, it was very helpful. This activity helped me."

It is difficult to accept the possibility that one might have to resign from work. When this finally occurs, patients look for other options to help them feel more useful professionally.

"When I resigned from work I told myself I had to be proactive, change my life. I have tried to get used to my new life and I'm not doing badly. I like to be called and be able to help, although there are days in which I can't do a thing, I feel awful and I can't do a thing. The advantage of not working is that I do it when I can... although my work is limited to advising my colleagues, it still helps me a lot. This activity helps me"

Obstacles to Leisure Activities

The disease also forces patients give up leisure activities they once enjoyed. This has a negative impact on their mood and registers as one more loss in their quality of life.

"Since I was young, I used to see my brothers and other people who got less tired than I did. I used to make an effort and I felt exhausted while they kept going. That was traumatic during my youth. I used to practice sports, but there comes a time when you can't practice sports, because you just can't. It was traumatic not to be able to participate anymore."

	<p style="text-align: center;">Personal and Social Relationships</p> <p>These illnesses are unknown to the general public. This relates to patients stating that they feel their diseases are neither understood nor accepted by the people surrounding them.</p> <p><i>"When I wake up tired, when I'm slow to react... but then others see you and see how you look and they don't see you badly. The people I encounter regularly know I suffer from psoriatic arthritis because I mention it, because they don't see you when you are doing badly. The illness is unknown to many people."</i></p> <p><i>"I used to arrive bent over to the factory; you started there, started greasing, and at 10 you were feeling fine. My co-workers used to say: 'You are just pretending'. It is not understood."</i></p> <p><i>"This feeling of being misunderstood never goes away. If you manage, they say you are doing fine and you are the one saying I feel bad."</i></p> <p><i>"When I finally found something that explained what the illness was, the first thing I did was to call my family and tell them: I need you to read this."</i></p> <p style="text-align: center;">Emotional Level</p> <p>Emotional problems can have serious consequences. It is easy to lose control. However, patients find resources to face depressive stages. They try not to let the disease take control over their lives. The role of the family and their support are of key importance to overcoming emotional crises.</p> <p><i>"Everything affects you a lot. My father died recently from a very hard illness and I've had a bad time. Because I'm disabled, I couldn't help my father as I would have liked because my illness hasn't allowed me."</i></p> <p><i>"I have downs, I must admit. I wake up many nights... I haven't suffered from depression because thank God my family supports me a lot. I get up at night, I start crying, I get over it, I go back to bed and nobody finds out... Family is the main support. If I had been alone, I would have gotten depressed. My personality is changing."</i></p> <p>Fostering relationships with other patients suffering from the same illness and learning about their experiences can be emotionally therapeutic.</p> <p><i>"I went to a patients' association; I saw other people in my same situation."</i></p> <p><i>"I try to cheer other people up, and it cheers me up."</i></p>
Coping	<p style="text-align: center;">Keep Active</p> <p>Practicing any type of physical activity is a lifesaver for many patients. In order to alleviate the disease's symptomatology, patients have</p>

	<p>found that regular exercise can relieve the symptoms and improve their performance and quality of life.</p> <p><i>"They prescribe me pain killers, but as I could be taking them for life, I asked: Are there any other choices? To exercise as much as possible. Pilates, swimming... With Pilates it is now rare that if I have to get up at night, when before the normal thing was that I could sleep. By doing exercise I have less pain and I feel more flexible. But I can do Pilates because I don't have to work."</i></p> <p><i>"You have to do something, spend your time doing something, because if I think too much, I get down."</i></p> <p>Adapting to Limitations</p> <p>Although the physical and emotional impacts of the disease vary with each patient, most develop coping mechanisms allowing them to properly face the disease and adapt to the limitations imposed on their lives.</p> <p><i>"As these are diseases that start at an early age, you learn to live with them."</i></p> <p><i>"You get used to limitations. I know that I can't do certain things, but I manage to do them in a different way."</i></p> <p><i>"You know that there are a lot of things you can't do, but you overcome the limitations, put your shoes on, your socks, sitting down... you do it your way and you live a normal life."</i></p> <p>Always Maintain a Positive Attitude</p> <p>One coping mechanism that patients develop seems related to the human survival instinct. It is all about adopting positive attitudes so that their health doesn't undermine their lives emotionally. However, many patients express the need for psychological support to achieve this goal.</p> <p><i>"Knowing how to face the disease and knowing how to live with it."</i></p> <p><i>"I don't have any problem talking about my disease."</i></p> <p><i>"The way you face the disease and your attitude are very important. One thing you lose with this disease is the psychological support you should have. When you are 20 and they tell you that you have a degenerative disease... you have to have a positive attitude to endure all that is coming"</i></p> <p><i>"Although pain goes on inside, I try not to show it publicly."</i></p>
Relationship With Professionals	<p>Good Treatment</p> <p>There are various aspects to consider in the doctor-patient relationship. For example, the very concept of "good treatment". It is remarkable that the majority of patients rate the treatment received from their specialist rheumatologists as excellent. However, there are</p>

	<p>still issues regarding positive and effective two-way communication with the doctors: personalized attention and training in “caring know how” to improve patients' relationships with professionals.</p> <p><i>“I couldn't get better care.”</i></p> <p><i>“Doctors calling you by your name is important. Personalized attention on both the specialist and family doctor's parts.”</i></p> <p><i>“That they know your name, and smile at you.”</i></p>
--	--

10. Recommendations for Future Investigations

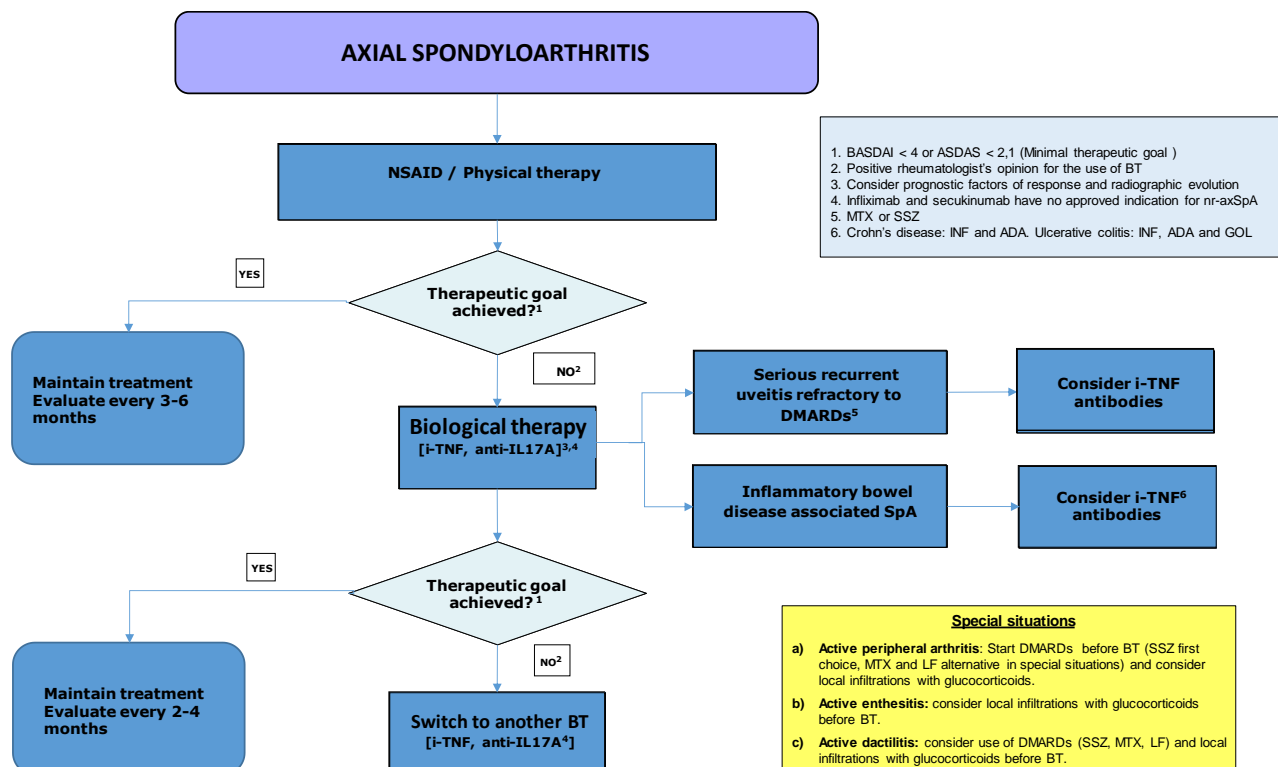
- Future investigations must advance our understanding of the effects of early pharmacological treatment on functional capacity, structural damage, and quality of life in patients with axial spondyloarthritis or psoriatic arthritis.
- There is a need for studies comparing effectiveness of treatments for non-radiographic axial spondyloarthritis versus new biological therapies that utilize a mechanism of action different from anti-TNF (ustekinumab, secukinumab).
- Additional studies must be conducted to identify beforehand in which patients with axial spondyloarthritis it is possible to reduce the dosage of anti-TNF, and in which patients this is not feasible.
- More long-term studies are needed comparing the effectiveness of biological therapies, versus sulfasalazine, in reducing the recurrence rate of uveitis and in improving visual prognosis in patients with ankylosing spondylitis.
- The role of different exercise programs must be investigated for both patients with axial spondyloarthritis in the ankylosis phase and in those with mild mobility and functional limitations.
- More RCTs with proven methodologies must be undertaken to investigate the effectiveness of biological monotherapy for patients with psoriatic arthritis in its different manifestations: peripheral, axial, enthesitis, dactylitis, and uveitis.
- Additional studies must be conducted to evaluate the effectiveness of traditional DMARDs on axial manifestations, enthesitis, dactylitis, and uveitis for patients with PsA.
- Also warranted are further investigations directly comparing whether there is an added advantage to treating patients with a combination of biological drugs and MTX compared to biological treatment in monotherapy.
- Well-designed long-term studies on managing patients with AsP using multidisciplinary consultations (rheumatology-dermatology) would similarly be welcome in this context.
- There is need for studies using proven methodologies to identify those nurse-administered health educational programs that might prove applicable to our own healthcare system for patients with AsP and axSpA.

2017 Update

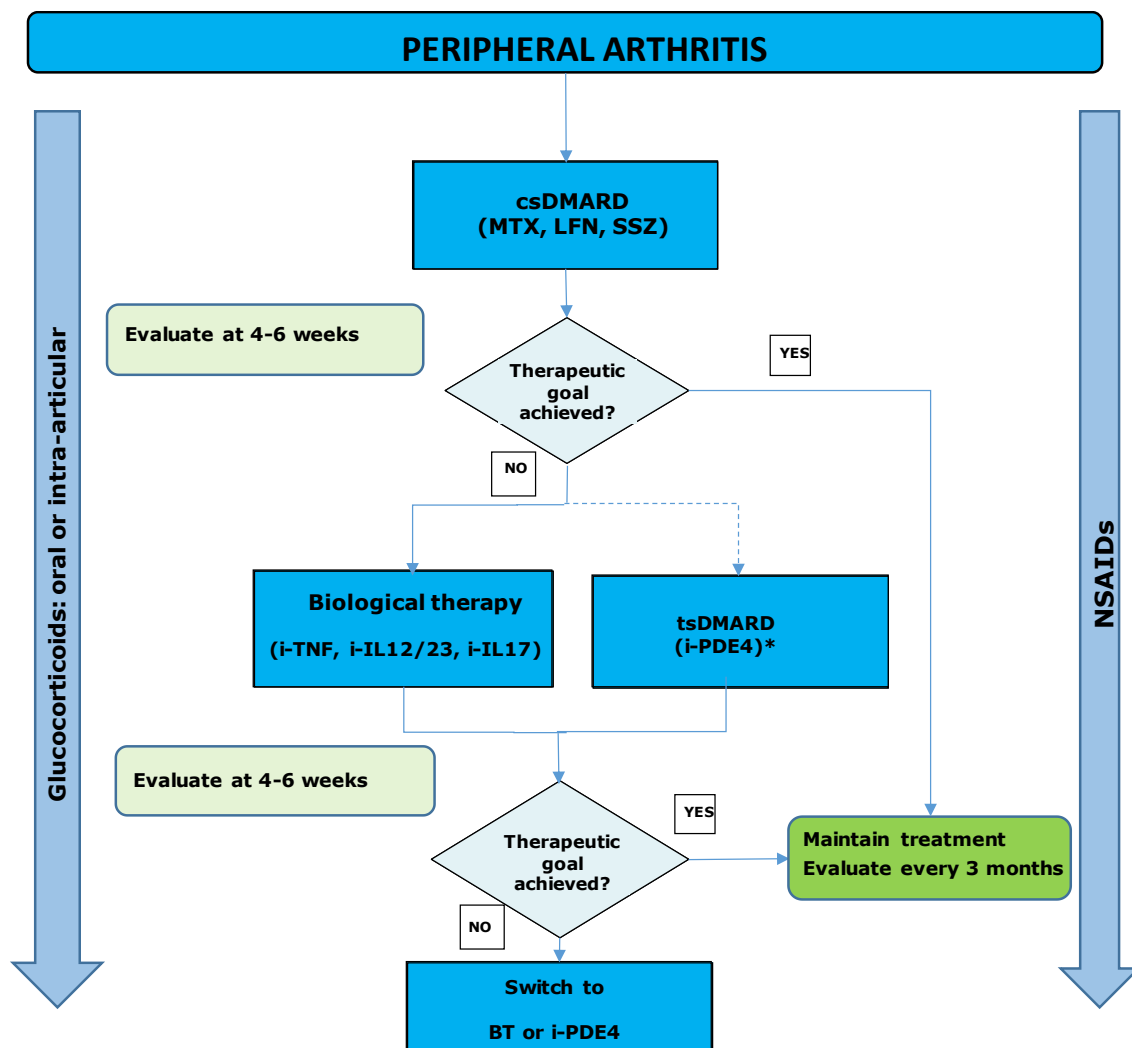
11. Therapeutic strategies

Below are the different treatment algorithms based on the recommendations proposed in the guide

11.1. Algorithm 1: Treatment of axSpA

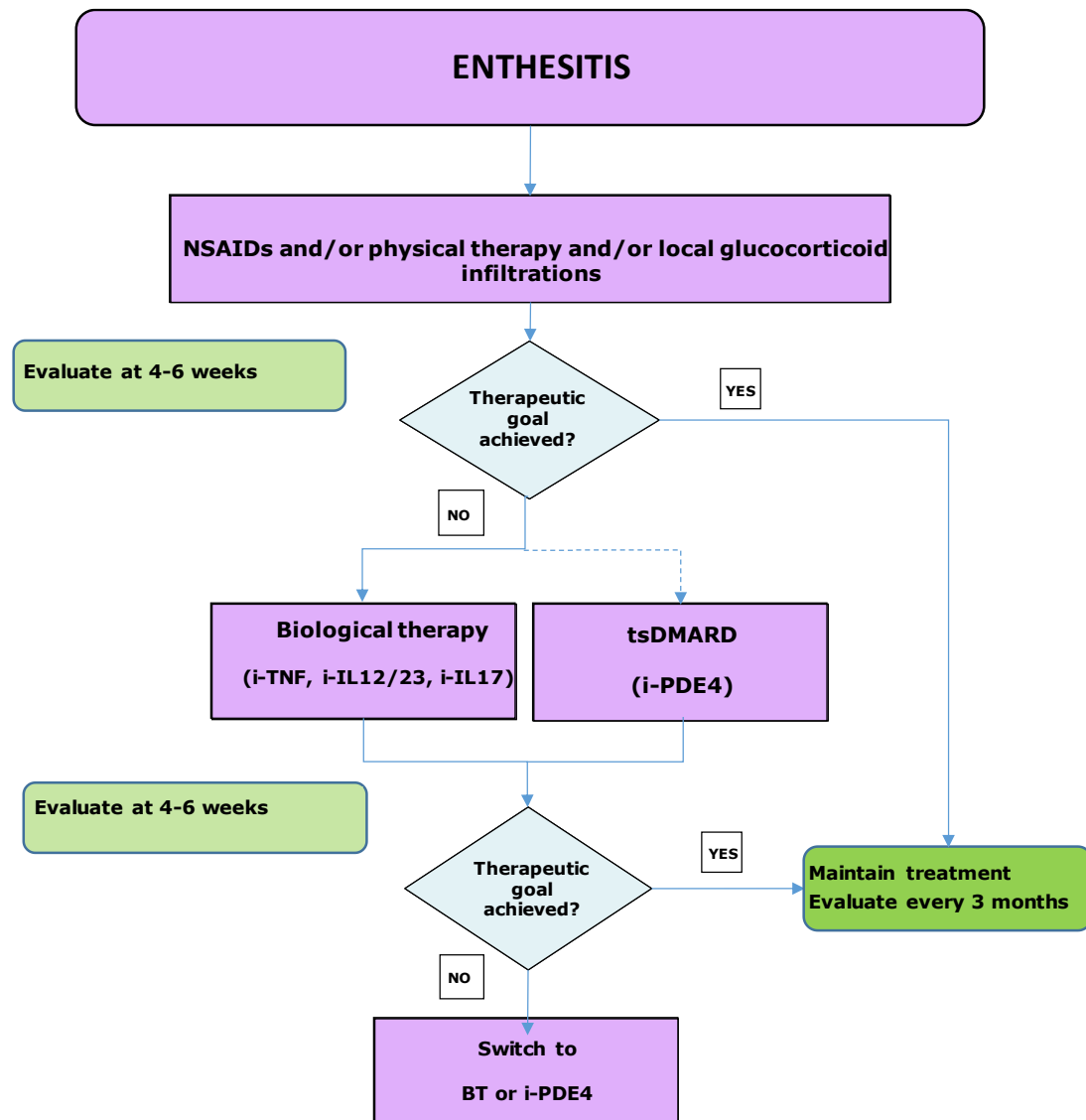


11.2. Algorithm 2: Treatment of peripheral arthritis in PsA

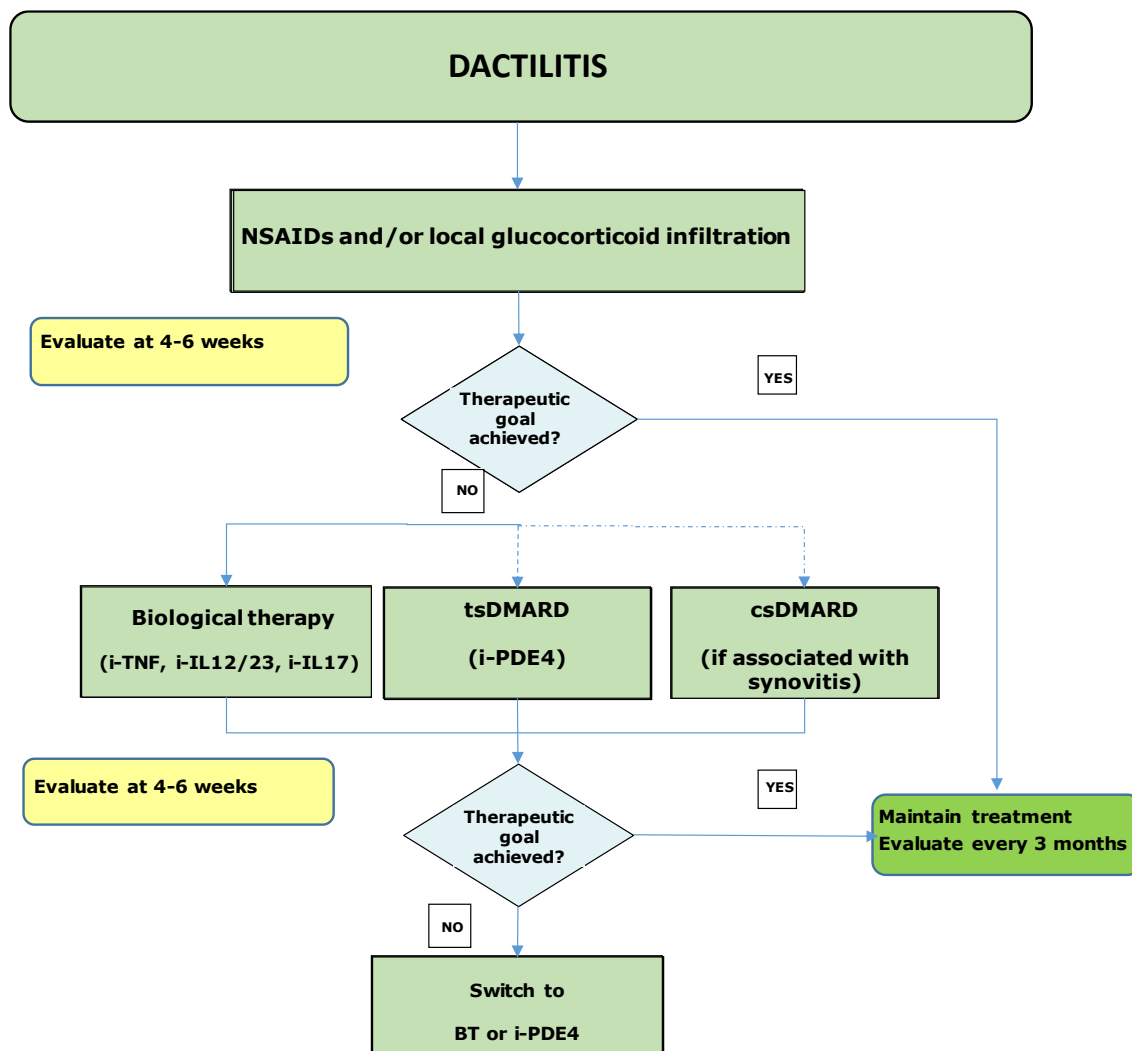


* The use of Apremilast is recommended for the treatment of peripheral arthritis after failure or intolerance to csDMARDs, when it is deemed more convenient than BT given the patient profile.

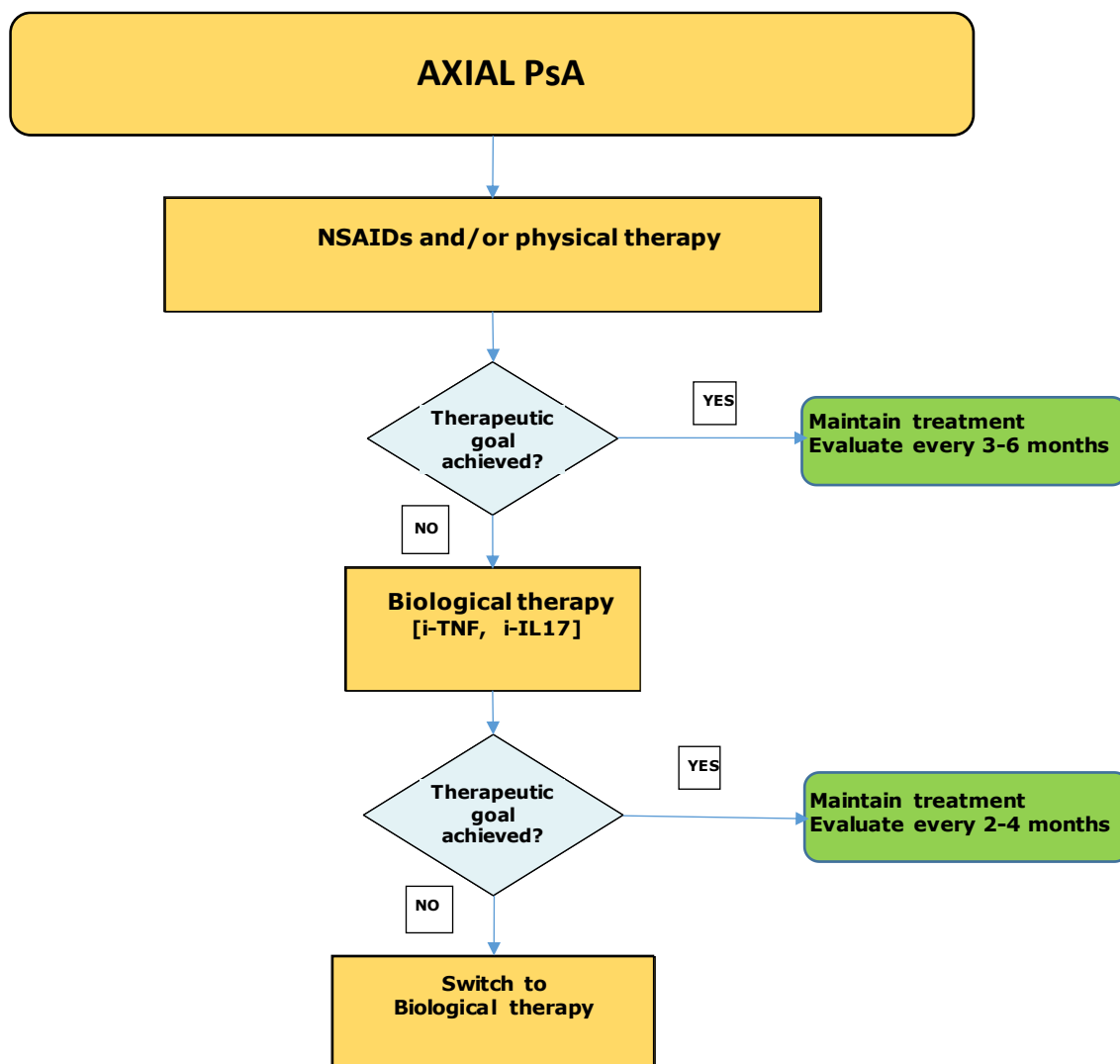
11.3. Algorithm 3. Treatment of enthesitis in PsA



11.4. Algorithm 4: Treatment of dactylitis in PsA



11.5. Algorithm 5: Treatment of the axial disease in SpAs



12. Appendix

Appendix 1. Levels of evidence and recommendations

Oxford Centre for Evidence-Based Medicine – Levels of Evidence (294)

Recommendation Grade	Evidence Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential Diagnosis / Symptom Prevalence Study	Economic and Decision Analyses
A	1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR [†] validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
	1b	Individual RCT (with narrow Confidence Interval)	Individual inception cohort study with > 80% follow-up; CDR [†] validated in a single population	Validating** cohort study with good reference standards ^{†††} ; or CDR [†] tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
	1c	All or none§	All or none case-series	Absolute SpPins and SnNouts ^{††}	All or none case-series	Absolute better-value or worse-value analyses ^{††††}
B	2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
	2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR [†] or validated on split-sample§§§ only	Exploratory** cohort study with good ^{†††} reference standards; CDR [†] after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses

Recommendation Grade	Evidence Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential Diagnosis / Symptom Prevalence Study	Economic and Decision Analyses
	2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
	3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
	3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
C	4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Notes

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because:

1. EITHER a single result with a wide Confidence Interval
2. OR a Systematic Review with troublesome heterogeneity

Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic

	estimation or a diagnostic category.)
‡	See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into “derivation” and “validation” samples.
††	An “Absolute SpPin” is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An “Absolute SnNout” is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards exist independently of the test, and are applied blindly or objectively to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the ‘test’ is included in the ‘reference’, or where the ‘testing’ affects the ‘reference’) implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are ‘significant’.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 – 5 years chronic)

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies <i>or</i> extrapolations* from level 1 studies
C	level 4 studies <i>or</i> extrapolations* from level 2 or 3 studies
D	level 5 evidence <i>or</i> troublingly inconsistent or inconclusive studies of any level

* “Extrapolations” are where data is used in a situation that has potentially clinically important differences than the original study situation.

Appendix 2. Glossary and Abbreviations

Glossary

Disease Burden: Indicator that measures the loss of health in a given population whether or not the consequences of the disease are lethal. Its unit of measure is disability adjusted life years (DALYs).

Cochrane Library: Database provided by the Cochrane Collaboration, which consists of, among other things, original systematic reviews carried out by this organization (Cochrane Database of Systematic Reviews - CDSR). The intention is to summarize meta-analyses and other evidence-based research to aid the medical community in gauging the effectiveness of treatments, medicines, and the like.

Dactylitis: Inflammation of the joints and tendons in the fingers and toes; commonly known as “Sausage Fingers”.

Embase: European database (Dutch) managed by Excerpta Medica that canvases the worldwide literature in the fields of clinical medicine and pharmacology.

Randomized Controlled Trial (RCT): A study design in which subjects are randomly assigned to two groups: an experimental group that receives the treatment being tested, and a comparison (or control group) that receives standard treatment (or sometimes a placebo). Both groups are monitored to observe any differences in the results. In this way the effectiveness of treatment is assessed.

Enthesitis: Inflammatory process in the enthesis that occurs at the point where tendons and ligaments meet bone. The most frequent symptoms are pain, inflammation, and redness in the affected area.

In-depth Interview: Qualitative investigation technique for obtaining information via a conversation between an informant (with previously predetermined characteristics) and an interviewer.

Open Trial: 1. Clinical trial where the researcher knows which treatment is being administered.
2. Clinical trial with an open sequential design.

Blind Trial or Double-Blind Trial: clinical trial where neither the participants (blind) nor medical staff (double-blind) know which treatment is being administered.

Case-Control Study: Study that identifies patients with a disease (cases) - for example lung cancer - and compare various outcomes vis-à-vis a group without the disease (control).

The relationship between one or more factors (for example, tobacco) associated with the disease is examined by comparing exposure frequency with this or other factors among cases and controls.

Cohort Study: A study design consisting of one or more samples (cohorts of individuals) presenting varying degrees of exposure to a risk factor. The study measures disease onset or studied condition(s).

Primary Study: A study that collects original data. Unlike a synopsis or review, it includes results from individual primary research. It also differs from a systematic review, which summarizes results from a group of primary studies.

Cross-Sectional Descriptive Study: A study that describes the frequency of an event or exposure at a given time (single measurement). It examines the relationship between a risk factor (or exposure) and an effect (or result) in a defined population and at a given time (**cut-off value**). Also called a prevalence study.

Discussion Group: Qualitative research technique that seeks to identify attitudes, positions, assessments, and/or perceptions regarding something or somebody from the perspective of a group of individuals.

Clinical Practice Guide: Set of recommendations based on a systematic review of evidence, and an assessment of the risks and benefits of different alternatives, in order to optimize patient health care.

Qualitative Investigation: Methodology that encompasses a plurality of theoretical concepts, methods, and techniques. It differs from other types of investigation in that it examines phenomena in their natural context, in an attempt to identify the significance and interpretation of such phenomena from a patient's perspective. This involves an evaluation of empirical material (interviews, observations, texts, etc.) that can further describe both routine and problematic situations, and what they mean in the lives of the relevant individuals.

Medline: Predominantly clinical database maintained by the U.S. National Library of Medicine that is available online (PubMed) and in CD-ROM format.

Meta-analysis: Statistical technique used to integrate results from different studies (studies on diagnostic tests, clinical trials, cohort studies, etc.) weighing the individual studies according to their size. It is also used when referring to systematic reviews that use meta-analysis.

Morbidity: A disease or how frequently a disease occurs in a population.

Mortality: Fatality rate or number of deaths due to a given disease in a group of patients over a certain period.

NICE: *National Institute for Health and Care Excellence*. Independent body belonging to the NHS (*National Health Service*, in UK). Its role consists of providing clinicians, patients, and the public with the best available scientific evidence, mainly in the form of clinical guidelines, as well as recommendations regarding public health and health technology.

Odds Ratio (OR): It is a measure of treatment effectiveness. If it is equal to 1, the treatment effect is not different from that of the control. If the OR is higher (or lower) than 1, the treatment effect is higher (or lower) than the effect of the control. It should be noted that the effect being measured can be adverse (e.g., death, disability) or desirable (e.g., stop smoking).

PEDro: Physiotherapy Evidence Database. Free database that include randomized control trials, systematic reviews, and guidelines on clinical practice and physiotherapy.

Placebo: Substance given to a control group in a clinical trial, ideally identical in appearance to the experimental treatment that has no known specific effect on the disease. In the context of non-pharmacological interventions, a placebo is habitually referred to as a "sham treatment".

Prevalence: Proportion of patients with a finding or disease in a given population, at a particular time.

Systematic Review (SR): A study in which the evidence on a topic has been systematically identified, evaluated, and summarized according to predetermined criteria. It can include meta-analysis or not.

Case Series: Analysis of a series of patients suffering from the same disease.

SIGN: Scottish Intercollegiate Guidelines Network. Multidisciplinary Scottish Agency that draws up guidelines on clinical practice based on evidence, as well as methodological documents about the design of these guidelines.

Uveitis: Inflammation of the uvea (middle layer of the eye), which is the part of the eye that supplies blood to most of the eyeball.

Abbreviations

ACR: American College of Rheumatology

ADA: Adalimumab

IJA: Idiopathic Juvenile Arthritis

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

PC: Primary Care

PsA: Psoriatic Arthritis

RA: Rheumatoid Arthritis

ASAS: Assessment of Spondyloarthritis International Society

ASDAS: ASAS-endorsed Disease Activity Score

ASQoL: ASAS-Quality of Life Instrument

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

BASFI: Bath Ankylosing Spondylitis Functional Index

BASMI: Bath Ankylosing Spondylitis Metrology Index

BASRI: Bath Ankylosing Spondylitis Radiology Index

CEBM: Centre for Evidence-Based Medicine

DAS: Disease Activity Score

AS: Ankylosing Spondylitis

EASI-QoL: Evaluation of Ankylosing Spondylitis Quality of Life

RCT: Randomized Clinical Trial

EMA: European Medicines Agency

SpA: Spondyloarthritis

AxSpA: Axial Spondyloarthritis

Nr-axSpA: Non-Radiographic Axial Spondyloarthritis

ESSG: European Spondyloarthropathy Study Group

EULAR: European League against Rheumatism

VAS: Visual Analogue Scale

DMARD: Disease-Modifying Antirheumatic Drugs

FDA: Food and Drug Administration

FER: Spanish Foundation of Rheumatology

GC: Glucocorticoids

CPG: Clinical Practice Guideline

GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

HAQ: Health Assessment Questionnaire

HAQ-S: Health Assessment Questionnaire for the Spondyloarthropathies

HLA-B27: Human leukocyte antigen B27

CI: Confidence Interval

PI: Principal investigator

ISEL: Interpersonal Support Evaluation List

LEF: Leflunomide

LSQ: Leeds Satisfaction Questionnaire

mSASSS: Modified Stoke Ankylosing Spondylitis Spinal Score

MTX: Methotrexate

NPJ: Number of Painful Joints

NSJ: Number of Swollen Joints

NRS: Numerical Rating Scale

WHO: World Health Organization

CRP: C-reactive Protein

PICO: Patient/ Intervention/ Comparison/ Outcome

PsARC: Psoriatic Arthritis Response Criteria

QoL: Quality of Life Instrument

MRI: Magnetic resonance imaging

SER: Spanish Society of Rheumatology (Sociedad Española de Reumatología)

SF-36: Short Form Health Survey

RU: Research Unit

ESR: Erythrocyte Sedimentation Rate

GPV: Global Patient Visualization

Appendix 3. Declaration of Interests

The following members of the guideline development group declare that they have no conflicts of interests: Irene Escribano Logroño, Fernando García Pérez, and Santos Yuste Zazo.

Raquel Almodóvar González has received funding from Pfizer, Abbvie and MSD to attend meetings, congresses and courses; fees from Abbvie, MSD, Pfizer, Roche and UCB for presentations; and financial support from Pfizer, Abbvie and Roche for educational programs and courses.

José Manuel Benítez del Castillo Sánchez has received funding from MSD to attend meetings, congresses and courses; and fees from Abbvie for presentations.

Juan D Cañete Crespillo has received funding from Pfizer, Abbvie, UCB and Celgene to attend meetings, congresses and courses; fees from Abbvie, MSD, Pfizer, UCB, Janssen and Celgene for presentations; and financial support from Pfizer, Abbvie, UCB, Janssen and Novartis for consulting services regarding pharmaceutical services or technologies.

Eugenio De Miguel Mendieta has received funding from Abbvie, Pfizer, MSD, BMS, Roche and to attend meetings, congresses and courses; fees from Abbvie, Pfizer, Menarini, BMS, MSD, Schering-Plough, Roche, UCB, Janssen and Astra-Zeneca for presentations; financial support from Abbvie, Pfizer and MSD for taking part in a research; financial support from Abbvie, Pfizer and Janssen for consulting services regarding pharmaceutical services or technologies.

Jordi Gratacós Masmitjà has received funding from UCB, MSD, Pfizer, Abbvie, Janssen, Celgene and Novartis to attend meetings, congresses and courses as well as for presentations; fees from MSD, Pfizer and Abbvie for educational programs and investigations; financial support from UCB, Pfizer, ABBVIE, Janssen, Celgene, Novartis for consulting services regarding pharmaceutical services or technologies.

M^a José León Cabezas has received funding from Abbvie and Roche to attend meetings, congresses and courses; financial support from Merck, Abbvie, Gebro Pharma and Lilly for presentations; and financial support from Abbvie and Merck for educational programs and courses.

Luis Francisco Linares Ferrando has received funding from Abbvie, Pfizer and MSD to attend meetings, congresses and courses; fees from Abbvie, Pfizer, Grünenthal and MSD for presentations; funding from Colegio de Médicos de Murcia for educational programs and courses; funding from Abbvie and Novartis to take part in an investigation; and financial support from MSD for consulting services regarding pharmaceutical services or technologies.

Carlos Montilla Morales has received funding from Abbvie and MSD to attend meetings, congresses and courses.

María Victoria Navarro Compán has received funding from Abbvie and Pfizer to attend meetings, congresses and courses; fees from Abbvie, BMS and Roche for presentations; and funding from Abbvie for participating in research.

Ruben Queiro Silva has received funding from Abbvie, Celgene, Pfizer, MSD, Janssen and UCB to attend meetings, congresses, courses and presentations; and financial support from Janssen, Abbvie, UCB and Pfizer for consulting services regarding pharmaceutical services or technologies.

Julio Ramírez García has received funding from MSD, Abbvie, Pfizer, Bristol and Roche to attend meetings, congresses and courses and for presentations.

Juan Carlos Torre Alonso has received funding from Pfizer, MSD and Abbvie to attend meetings, congresses and courses; fees from Pfizer, MSD, Amgen and Glaxo SmithKline for presentations and financial support from UCB for consulting services regarding pharmaceutical services or technologies.

Ricardo Valverde Garrido has received funding from Abbvie, Janssen-Cilag, Leo-Pharma and Pfizer to attend meetings, congresses and courses; fees from Abbvie and Janssen-Cilag for presentations; and funding from MSD and Pfizer for taking part in research.

Bibliography

1. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis and rheumatism*. 1984;27(4):361-8.
2. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Annals of the rheumatic diseases*. 2009;68(6):777-83.
3. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Annals of the rheumatic diseases*. 2009;68 Suppl 2:ii1-44.
4. Sociedad Española de Reumatología. ESPOGUÍA: guía de práctica clínica sobre el manejo de los pacientes con Espondiloartritis. [[monografía en internet]]. Madrid: Sociedad Española de Reumatología; 2009 [updated [20 septiembre 2013]].
5. Catanoso M, Pipitone N, Salvarani C. Epidemiology of psoriatic arthritis. *Reumatismo*. 2012;64(2):66-70.
6. Guías de Práctica Clínica. Guíasalud.es. Fecha de consulta: 2015 Marzo 10. Disponible en: <http://www.guiasalud.es/web/guest/guias-practica-clinica> [
7. Grupo de trabajo sobre actualización de GPC. Actualización de Guías de Práctica Clínica en el Sistema Nacional de Salud. Manual Metodológico. Plan de Calidad para el Sistema Nacional de Salud del Ministerio de Sanidad y Política Social. Instituto Aragonés de Ciencias de la Salud: Guías de Práctica Clínica en el SNS: I+CS Nº 2007/02-01; 2009.
8. Akkoc N, Khan MA. Ankylosing Spondylitis and the Spondyloarthropathies. In: Weissman R, Heijden vd, eds, editor. *Epidemiology of Ankylosing Spondylitis and related Spondyloarthropathies*: Philadelphia Mosby Elsevier; 2006. p. 117-31.
9. Munoz-Fernandez S, de Miguel E, Cobo-Ibanez T, Carmona L, Steiner M, Descalzo MA, et al. Early spondyloarthritis: results from the pilot registry ESPIDEP. *Clinical and experimental rheumatology*. 2010;28(4):498-503.
10. Stolwijk C, Boonen A, van Tubergen A, Reveille JD. Epidemiology of spondyloarthritis. *Rheumatic diseases clinics of North America*. 2012;38(3):441-76.
11. Collantes E, Veroz R, Escudero A, Munoz E, Munoz MC, Ciscal A, et al. Can some cases of 'possible' spondyloarthropathy be classified as 'definite' or 'undifferentiated' spondyloarthropathy? Value of criteria for spondyloarthropathies. Spanish Spondyloarthropathy Study Group. *Joint, bone, spine : revue du rhumatisme*. 2000;67(6):516-20.
12. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. *Rheumatology (Oxford, England)*. 2014;53(4):650-7.
13. Fernandez Sueiro JL, Juanola Roura X, Canete Crespillo Jde D, Torre Alonso JC, Garcia de Vicuna R, Queiro Silva R, et al. Documento SER de consenso sobre el uso de terapias biológicas en la artritis psoriásica. *Reumatología clínica*. 2011;7(3):179-88.
14. Juanola Roura X, Zarco Montejó P, Sanz Sanz J, Munoz Fernandez S, Mulero Mendoza J, Linares Ferrando LF, et al. [Consensus Statement of the Spanish Society of Rheumatology on the management of biologic therapies in spondyloarthritis except for psoriatic arthritis]. *Reumatología clínica*. 2011;7(2):113-23.
15. Braun J, Bollow M, Remlinger G, Eggens U, Rudwaleit M, Distler A, et al. Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum*. 1998;41(1):58-67.

16. Carmona L, Ballina J, Gabriel R, Laffon A. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. *Annals of the rheumatic diseases*. 2001;60(11):1040-5.
17. O'Neill T, Silman AJ. Psoriatic arthritis. Historical background and epidemiology. *Baillieres Clin Rheumatol*. 1994;8(2):245-61.
18. Gonzalez-Alvaro I, Martinez-Fernandez C, Dorantes-Calderon B, Garcia-Vicuna R, Hernandez-Cruz B, Herrero-Ambrosio A, et al. Spanish Rheumatology Society and Hospital Pharmacy Society Consensus on recommendations for biologics optimization in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. *Rheumatology (Oxford, England)*. 2014.
19. Braun J, Pincus T. Mortality, course of disease and prognosis of patients with ankylosing spondylitis. *Clin Exp Rheumatol*. 2002;20(6 Suppl 28):S16-22.
20. Carmona L, Gonzalez-Alvaro I, Balsa A, Angel Belmonte M, Tena X, Sanmarti R. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. *Annals of the rheumatic diseases*. 2003;62(9):897-900.
21. Gladman DD, Farewell VT, Wong K, Husted J. Mortality studies in psoriatic arthritis: results from a single outpatient center. II. Prognostic indicators for death. *Arthritis Rheum*. 1998;41(6):1103-10.
22. Lehtinen K. Mortality and causes of death in 398 patients admitted to hospital with ankylosing spondylitis. *Annals of the rheumatic diseases*. 1993;52(3):174-6.
23. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol*. 2008;26(5 Suppl 51):S35-61.
24. Wong K, Gladman DD, Husted J, Long JA, Farewell VT. Mortality studies in psoriatic arthritis: results from a single outpatient clinic. I. Causes and risk of death. *Arthritis Rheum*. 1997;40(10):1868-72.
25. Bakland G, Gran JT, Nossent JC. Increased mortality in ankylosing spondylitis is related to disease activity. *Annals of the rheumatic diseases*. 2011;70(11):1921-5.
26. Estrategia en enfermedades reumáticas y musculoesqueléticas del Sistema Nacional de Salud. Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad; 2013.
27. Abasolo Alcázar L, Gratacós Masmitjá J, Hidalgo Vega A, Jover Jover J, Lizán Tudela L, Paz Ruiz S, et al. Costes y cargas de las enfermedades reumáticas. *Science Communications*. Springer SBM Spain, S.A.U. Madrid.
28. Gratacos J, Dauden E, Gomez-Reino J, Moreno JC, Casado MA, Rodriguez-Valverde V. Health-related quality of life in psoriatic arthritis patients in Spain. *Reumatologia clinica*. 2014;10(1):25-31.
29. Loza E, Abasolo L, Jover JA, Carmona L. Burden of disease across chronic diseases: a health survey that measured prevalence, function, and quality of life. *The Journal of rheumatology*. 2008;35(1):159-65.
30. Pereira J, Cañón J, Álvarez E, Gènova R. La medida de los problemas de salud en el ámbito internacional: los estudios de carga de enfermedad. *Rev Admin Sanitaria*. 2001;V(19):441-66.
31. Ariza-Ariza R, Hernandez-Cruz B, Collantes E, Batlle E, Fernandez-Sueiro JL, Gratacos J, et al. Work disability in patients with ankylosing spondylitis. *J Rheumatol*. 2009;36(11):2512-6.
32. Lajas C, Abasolo L, Bellajdel B, Hernandez-Garcia C, Carmona L, Vargas E, et al. Costs and predictors of costs in rheumatoid arthritis: a prevalence-based study. *Arthritis Rheum*. 2003;49(1):64-70.
33. Boonen A. A review of work-participation, cost-of-illness and cost-effectiveness studies in ankylosing spondylitis. *Nature clinical practice Rheumatology*. 2006;2(10):546-53.

34. Lázaro P, Parody E, Méndez Rubio J, Alfaro N. También está en tu mano. Impacto de las enfermedades reumáticas en España. Un análisis de técnicas avanzadas de investigación en Servicios de Salud (TAISS) para la Fundación Abbot. 2009.
35. Petrikova A, Dolezal T, Klimes J, Vocelka M, Sedova L, Kolar J. The economic burden of the ankylosing spondylitis in the Czech Republic: comparison between 2005 and 2008. *Rheumatology international*. 2013;33(7):1813-9.
36. Pentek M, Poor G, Wiland P, Olejarova M, Brzosko M, Codreanu C, et al. Biological therapy in inflammatory rheumatic diseases: issues in Central and Eastern European countries. *The European journal of health economics : HEPAC : health economics in prevention and care*. 2014;15 Suppl 1:S35-43.
37. Palla I, Trieste L, Tani C, Talarico R, Cortesi PA, Mosca M, et al. A systematic literature review of the economic impact of ankylosing spondylitis. *Clin Exp Rheumatol*. 2012;30 (4 Suppl. 73):S136-S41.
38. Huscher D, Merkesdal S, Thiele K, Zeidler H, Schneider M, Zink A. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. *Annals of the rheumatic diseases*. 2006;65(9):1175-83.
39. Brodsky V, Balint P, Geher P, Hodinka L, Horvath G, Koo E, et al. Disease burden of psoriatic arthritis compared to rheumatoid arthritis, Hungarian experiment. *Rheumatology international*. 2009;30(2):199-205.
40. Kobelt G, Sobocki P, Mulero J, Gratacos J, Pocovi A, Collantes-Estevez E. The burden of ankylosing spondylitis in Spain. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2008;11(3):408-15.
41. Collantes E. Espondiloartropatías. Concepto, Clasificación y Características Generales. In: Pascual E, Rodríguez V, Carbonell J, Gómez-Reino J, editors. *Tratado de reumatología: ARAN Ediciones Madrid (España)*; 1998.
42. van der Linden S; van der Heijde D. Classification of spondyloarthropathies. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt M, Weissman MH, editors. *Rheumatology: Edinburgh: Mosby (Elsevier)*; 2003. p. 1149-51.
43. Braun J, Sieper J. Ankylosing spondylitis. *Lancet*. 2007;369(9570):1379-90.
44. Khan MA. Thoughts concerning the early diagnosis of ankylosing spondylitis and related diseases. *Clinical and experimental rheumatology*. 2002;20(6 Suppl 28):S6-10.
45. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Annals of the rheumatic diseases*. 2015;74(1):65-73.
46. van der Horst-Bruinsma IE, Nurmohamed MT, Landewe RB. Comorbidities in patients with spondyloarthritis. *Rheumatic diseases clinics of North America*. 2012;38(3):523-38.
47. Mercieca C, van der Horst-Bruinsma IE, Borg AA. Pulmonary, renal and neurological comorbidities in patients with ankylosing spondylitis; implications for clinical practice. *Current rheumatology reports*. 2014;16(8):434.
48. Cauli A, Mathieu A. Psoriatic arthritis: genetics and pathogenesis. *Reumatismo*. 2012;64(2):71-8.
49. Gladman DD, Farewell VT. HLA studies in psoriatic arthritis: current situation and future needs. *The Journal of rheumatology*. 2003;30(1):4-6.
50. Wilson FC, Icen M, Crowson CS, McEvoy MT, Gabriel SE, Kremers HM. Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. *Arthritis and rheumatism*. 2009;61(2):233-9.
51. Eder L, Zisman D, Barzilai M, Laor A, Rahat M, Rozenbaum M, et al. Subclinical atherosclerosis in psoriatic arthritis: a case-control study. *The Journal of rheumatology*. 2008;35(5):877-82.

52. Tam LS, Shang Q, Li EK, Tomlinson B, Chu TT, Li M, et al. Subclinical carotid atherosclerosis in patients with psoriatic arthritis. *Arthritis and rheumatism*. 2008;59(9):1322-31.
53. Jones SM, Harris CP, Lloyd J, Stirling CA, Reckless JP, McHugh NJ. Lipoproteins and their subfractions in psoriatic arthritis: identification of an atherogenic profile with active joint disease. *Annals of the rheumatic diseases*. 2000;59(11):904-9.
54. Tam LS, Tomlinson B, Chu TT, Li M, Leung YY, Kwok LW, et al. Cardiovascular risk profile of patients with psoriatic arthritis compared to controls--the role of inflammation. *Rheumatology (Oxford, England)*. 2008;47(5):718-23.
55. Sommer DM, Jenisch S, Suchan M, Christophers E, Weichenthal M. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. *Archives of dermatological research*. 2006;298(7):321-8.
56. Cinar M, Dinc A, Simsek I, Erdem H, Koc B, Pay S, et al. Evaluation of the short-term efficacy of NSAIDs on patients with active ankylosing spondylitis in daily practice: a 3-month, longitudinal, observational study. *Rheumatology international*. 2010;30(3):331-40.
57. Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis and rheumatism*. 2008;58(7):1981-91.
58. Lord PA, Farragher TM, Lunt M, Watson KD, Symmons DP, Hyrich KL. Predictors of response to anti-TNF therapy in ankylosing spondylitis: results from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford, England)*. 2010;49(3):563-70.
59. Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. *Annals of the rheumatic diseases*. 2004;63(6):665-70.
60. Rudwaleit M, Schwarzlose S, Hilgert ES, Listing J, Braun J, Sieper J. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. *Annals of the rheumatic diseases*. 2008;67(9):1276-81.
61. Weiss A, Song IH, Haibel H, Listing J, Sieper J. Good correlation between changes in objective and subjective signs of inflammation in patients with short- but not long duration of axial spondyloarthritis treated with tumor necrosis factor-blockers. *Arthritis research & therapy*. 2014;16(1):R35.
62. Barkham N, Keen HI, Coates LC, O'Connor P, Hensor E, Fraser AD, et al. Clinical and imaging efficacy of infliximab in HLA-B27-Positive patients with magnetic resonance imaging-determined early sacroiliitis. *Arthritis and rheumatism*. 2009;60(4):946-54.
63. Sieper J, Lenaerts J, Wollenhaupt J, Rudwaleit M, Mazurov VI, Myasoutova L, et al. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1. *Annals of the rheumatic diseases*. 2014;73(1):101-7.
64. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. *Arthritis and rheumatism*. 2006;55(6):864-72.
65. Kyburz D, Gabay C, Michel BA, Finckh A. The long-term impact of early treatment of rheumatoid arthritis on radiographic progression: a population-based cohort study. *Rheumatology (Oxford, England)*. 2011;50(6):1106-10.
66. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford, England)*. 2004;43(7):906-14.

67. van der Linden MP, le Cessie S, Raza K, van der Woude D, Knevel R, Huizinga TW, et al. Long-term impact of delay in assessment of patients with early arthritis. *Arthritis and rheumatism*. 2010;62(12):3537-46.
68. van Nies JA, Tsonaka R, Gaujoux-Viala C, Fautrel B, van der Helm-van Mil AH. Evaluating relationships between symptom duration and persistence of rheumatoid arthritis: does a window of opportunity exist? Results on the Leiden Early Arthritis Clinic and ESPOIR cohorts. *Annals of the rheumatic diseases*. 2015;74(5):806-12.
69. Collantes E, Zarco P, Munoz E, Juanola X, Mulero J, Fernandez-Sueiro JL, et al. Disease pattern of spondyloarthropathies in Spain: description of the first national registry (REGISPONSER) extended report. *Rheumatology (Oxford, England)*. 2007;46(8):1309-15.
70. Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Annals of the rheumatic diseases*. 2013;72(6):815-22.
71. Juanola Roura X, Collantes Estevez E, Leon Vazquez F, Torres Villamor A, Garcia Yebenes MJ, Queiro Silva R, et al. Recommendations for the detection, study and referral of inflammatory low-back pain in primary care. *Reumatologia clinica*. 2015;11(2):90-8.
72. Ash ZR, Barkham N, McGonagle D, Hensor E, Emery P, Marzo-Ortega H. Long term results of a remission induction approach to early axial spondyloarthritis: Still looking for the window of opportunity. *Arthritis and Rheumatism*. 2011;63(10).
73. Baraliakos X, Koenig A, Jones H, Szumski A, Collier D, Bananis E. AB0861 Relationship between disease duration and treatment response in patients with ankylosing spondylitis (AS). *Annals of the Rheumatic Diseases*. 2013;71(Suppl 3):687.
74. Ash Z, Gaujoux-Viala C, Gossec L, Hensor EM, FitzGerald O, Winthrop K, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. *Annals of the rheumatic diseases*. 2012;71(3):319-26.
75. Callhoff J, Sieper J, Weiss A, Zink A, Listing J. Efficacy of TNFalpha blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. *Annals of the rheumatic diseases*. 2014.
76. Dougados M, Van Der Heijde D, Sieper J, Braun J, Maksymowych WP, Citera G, et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: A multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis and Rheumatology*. 2014;66(8):2091-102.
77. Landewe R, Braun J, Deodhar A, Dougados M, Maksymowych WP, Mease PJ, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. *Annals of the rheumatic diseases*. 2014;73(1):39-47.
78. Sieper J, van der Heijde D, Dougados M, Maksymowych WP, Scott BB, Boice JA, et al. A Randomized, Double-blind, Placebo-controlled, 16-Week Study of Subcutaneous Golimumab in Patients With Active Non-radiographic Axial Spondyloarthritis. *Arthritis & rheumatology*. 2015;67(10):2702-12.
79. Lekpa FK, Poulain C, Wendling D, Soubrier M, De Bandt M, Berthelot JM, et al. Is IL-6 an appropriate target to treat spondyloarthritis patients refractory to anti-TNF therapy? A multicentre retrospective observational study. *Arthritis research & therapy*. 2012;14(2):R53.
80. Rudwaleit M, Landewe R, van der Heijde D, Listing J, Brandt J, Braun J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Annals of the rheumatic diseases*. 2009;68(6):770-6.

81. Dougados M, d'Agostino MA, Benessiano J, Berenbaum F, Breban M, Claudepierre P, et al. The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. *Joint, bone, spine : revue du rhumatisme*. 2011;78(6):598-603.
82. Kiltz U, Baraliakos X, Karakostas P, Igelmann M, Kalthoff L, Klink C, et al. Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis? *Arthritis care & research*. 2012;64(9):1415-22.
83. Rudwaleit M, Haibel H, Baraliakos X, Listing J, Marker-Hermann E, Zeidler H, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis and rheumatism*. 2009;60(3):717-27.
84. Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis and rheumatism*. 2005;52(4):1000-8.
85. van den Berg R, de Hooge M, van Gaalen F, Reijnierse M, Huizinga T, van der Heijde D. Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology (Oxford, England)*. 2013;52(8):1492-9.
86. van der Heijde D, Sieper J, Maksymowych WP, Dougados M, Burgos-Vargas R, Landewe R, et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Annals of the rheumatic diseases*. 2011;70(6):905-8.
87. Escalas C, Trijau S, Dougados M. Evaluation of the treatment effect of NSAIDs/TNF blockers according to different domains in ankylosing spondylitis: results of a meta-analysis. *Rheumatology (Oxford, England)*. 2010;49(7):1317-25.
88. Machado MA, Barbosa MM, Almeida AM, de Araujo VE, Kakehasi AM, Andrade EI, et al. Treatment of ankylosing spondylitis with TNF blockers: a meta-analysis. *Rheumatology international*. 2013;33(9):2199-213.
89. Baraliakos X, Haibel H, Listing J, Sieper J, Braun J. Continuous long-term anti-TNF therapy does not lead to an increase in the rate of new bone formation over 8 years in patients with ankylosing spondylitis. *Annals of the rheumatic diseases*. 2014;73(4):710-5.
90. Haroon N, Inman RD, Learch TJ, Weisman MH, Lee M, Rahbar MH, et al. The impact of tumor necrosis factor alpha inhibitors on radiographic progression in ankylosing spondylitis. *Arthritis and rheumatism*. 2013;65(10):2645-54.
91. Baeten D, Baraliakos X, Braun J, Sieper J, Emery P, van der Heijde D, et al. Anti-interleukin-17A monoclonal antibody secukinumab in treatment of ankylosing spondylitis: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2013;382(9906):1705-13.
92. Poddubnyy D, Hermann KG, Callhoff J, Listing J, Sieper J. Ustekinumab for the treatment of patients with active ankylosing spondylitis: results of a 28-week, prospective, open-label, proof-of-concept study (TOPAS). *Annals of the rheumatic diseases*. 2014;73(5):817-23.
93. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis and rheumatism*. 1991;34(10):1218-27.
94. De La Mata J, Maese J, Martinez JA, Rosario P, Loza E. Current evidence of the management of undifferentiated spondyloarthritis: a systematic literature review. *Seminars in arthritis and rheumatism*. 2011;40(5):421-9, 9.e1-3.
95. Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. *Jama*. 1977;237(24):2613-4.
96. Sieper J, Landewe R, Rudwaleit M, van der Heijde D, Dougados M, Mease PJ, et al. Effect of certolizumab pegol over ninety-six weeks in patients with axial spondyloarthritis:

results from a phase III randomized trial. *Arthritis & rheumatology* (Hoboken, NJ). 2015;67(3):668-77.

97. Rudwaleit M, van der Heijde D, Landewe R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Annals of the rheumatic diseases*. 2011;70(1):25-31.

98. Gratacos J, Diaz Del Campo Fontecha P, Fernandez-Carballido C, Juanola Roura X, Linares Ferrando LF, de Miguel Mendieta E, et al. Recommendations by the Spanish Society of Rheumatology on the Use of Biological Therapies in Axial Spondyloarthritis. *Reumatologia clinica*. 2017.

99. Arends S, Brouwer E, van der Veer E, Groen H, Leijnsma MK, Houtman PM, et al. Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. *Arthritis research & therapy*. 2011;13(3):R94.

100. Fagerli KM, Lie E, Heiberg MS, Van Der Heijde DMFM, Kalstad S, Mikkelsen K, et al. Predictors of ASDAS major improvement in patients with ankylosing spondylitis receiving their first TNF inhibitor. Results from a longitudinal observational study. *Arthritis and Rheumatism*. 2011;63(10).

101. Grintborg B, Ostergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. *Annals of the rheumatic diseases*. 2010;69(11):2002-8.

102. Maneiro JR, Souto A, Salgado E, Mera A, Gomez-Reino JJ. Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis. *RMD open*. 2015;1(1):e000017.

103. Gremese E, Bernardi S, Bonazza S, Nowik M, Peluso G, Massara A, et al. Body weight, gender and response to TNF-alpha blockers in axial spondyloarthritis. *Rheumatology* (Oxford, England). 2014;53(5):875-81.

104. Grintborg B, Hojgaard P, Lund Hetland M, Steen Krogh N, Kollerup G, Jensen J, et al. Impact of tobacco smoking on response to tumour necrosis factor-alpha inhibitor treatment in patients with ankylosing spondylitis: results from the Danish nationwide DANBIO registry. *Rheumatology* (Oxford, England). 2015.

105. Sieper J, van der Heijde D, Dougados M, Brown LS, Lavie F, Pangan AL. Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis. *Annals of the rheumatic diseases*. 2012;71(5):700-6.

106. Baraliakos X, Borah B, Braun J, Baeten D, Laurent D, Sieper J, et al. Long-term effects of secukinumab on MRI findings in relation to clinical efficacy in subjects with active ankylosing spondylitis: an observational study. *Annals of the rheumatic diseases*. 2016;75(2):408-12.

107. Maksymowych WP, Salonen D, Inman RD, Rahman P, Lambert RG. Low-dose infliximab (3 mg/kg) significantly reduces spinal inflammation on magnetic resonance imaging in patients with ankylosing spondylitis: a randomized placebo-controlled study. *The Journal of rheumatology*. 2010;37(8):1728-34.

108. Song IH, Hermann K, Haibel H, Althoff CE, Listing J, Burmester G, et al. Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. *Annals of the rheumatic diseases*. 2011;70(4):590-6.

109. Baraliakos X, Haibel H, Listing J, Sieper J, Braun J. Radiographic progression in ankylosing spondylitis results after up to 8 years of infliximab treatment. *Arthritis and Rheumatism*. 2011;63(10).

110. Maksymowych WP, Chiowchanwisawakit P, Clare T, Pedersen SJ, Ostergaard M, Lambert RG. Inflammatory lesions of the spine on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis: evidence of a relationship between inflammation and new bone formation. *Arthritis and rheumatism*. 2009;60(1):93-102.
111. Poddubnyy D, Haibel H, Listing J, Marker-Hermann E, Zeidler H, Braun J, et al. Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondylarthritis. *Arthritis and rheumatism*. 2012;64(5):1388-98.
112. Ramiro S, van der Heijde D, van Tubergen A, Stolwijk C, Dougados M, van den Bosch F, et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. *Annals of the rheumatic diseases*. 2014;73(8):1455-61.
113. Song IH, Hermann KG, Haibel H, Althoff CE, Poddubnyy D, Listing J, et al. Prevention of new osteitis on magnetic resonance imaging in patients with early axial spondyloarthritis during 3 years of continuous treatment with etanercept: data of the ESTHER trial. *Rheumatology (Oxford, England)*. 2015;54(2):257-61.
114. van der Heijde D, Landewe R, Baraliakos X, Houben H, van Tubergen A, Williamson P, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. *Arthritis and rheumatism*. 2008;58(10):3063-70.
115. van der Heijde D, Landewe R, Einstein S, Ory P, Vosse D, Ni L, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. *Arthritis and rheumatism*. 2008;58(5):1324-31.
116. van der Heijde D, Salonen D, Weissman BN, Landewe R, Maksymowych WP, Kupper H, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. *Arthritis research & therapy*. 2009;11(4):R127.
117. Baraliakos X, Heldmann F, Callhoff J, Listing J, Appelboom T, Brandt J, et al. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. *Annals of the rheumatic diseases*. 2014;73(10):1819-25.
118. Braun J, Baraliakos X, Deodhar A. Effect of secukinumab on clinical and radiographic outcomes in ankylosing spondylitis: 2-year results from the randomised phase III MEASURE 1 study. *Ann Rheum Dis*. 2016.
119. Haroon N, Shen H, Carty A, Anton A, Cook RJ, Inman RD. Continuance of non-steroidal anti-inflammatory drugs may reduce radiographic progression in ankylosing spondylitis patients on biological therapy. *Arthritis and Rheumatism*. 2011;63(10).
120. Dadoun S, Geri G, Paternotte S, Dougados M, Gossec L. Switching between tumour necrosis factor blockers in spondyloarthritis: a retrospective monocentre study of 222 patients. *Clinical and experimental rheumatology*. 2011;29(6):1010-3.
121. Glinborg B, Ostergaard M, Krogh NS, Tarp U, Manilo N, Loft AG, et al. Clinical response, drug survival and predictors thereof in 432 ankylosing spondylitis patients after switching tumour necrosis factor alpha inhibitor therapy: results from the Danish nationwide DANBIO registry. *Annals of the rheumatic diseases*. 2013;72(7):1149-55.
122. Gulyas K, Bodnar N, Nagy Z, Szamosi S, Horvath A, Vancsa A, et al. Real-life experience with switching TNF-alpha inhibitors in ankylosing spondylitis. *The European journal of health economics : HEPAC : health economics in prevention and care*. 2014;15 Suppl 1:S93-100.
123. Lie E, van der Heijde D, Uhlig T, Mikkelsen K, Rodevand E, Koldingsnes W, et al. Effectiveness of switching between TNF inhibitors in ankylosing spondylitis: data from the NOR-DMARD register. *Annals of the rheumatic diseases*. 2011;70(1):157-63.

124. Pavelka K, Fojtíková M, Hejduk K. Efficacy of the first and subsequent courses of anti-TNF therapy in patients with ankylosing spondylitis - Results from the Czech National Register ATTRA. *Reumatologia*. 2012;50(4):294-306.
125. Rudwaleit M, Van den Bosch F, Kron M, Kary S, Kupper H. Effectiveness and safety of adalimumab in patients with ankylosing spondylitis or psoriatic arthritis and history of anti-tumor necrosis factor therapy. *Arthritis research & therapy*. 2010;12(3):R117.
126. Braun J, Baraliakos X, Kiltz U. Secukinumab (AIN457) in the treatment of ankylosing spondylitis. *Expert Opin Biol Ther*. 2016;16(5):711-22.
127. Braun J, Sieper J, Aelion J, Emery P, Deodhar A, Porter B, et al. Secukinumab improves multiple parameters of disease activity in subjects with active ankylosing spondylitis through 52 weeks of subcutaneous therapy: Data from the phase 3 measure 2 study. *Annals of the Rheumatic Diseases*. 2015;74:1147.
128. Song IH, Heldmann F, Rudwaleit M, Listing J, Appel H, Braun J, et al. Different response to rituximab in tumor necrosis factor blocker-naïve patients with active ankylosing spondylitis and in patients in whom tumor necrosis factor blockers have failed: a twenty-four-week clinical trial. *Arthritis and rheumatism*. 2010;62(5):1290-7.
129. Baraliakos X, Listing J, Brandt J, Zink A, Alten R, Burmester G, et al. Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. *Arthritis research & therapy*. 2005;7(3):R439-44.
130. Brandt J, Khariouzov A, Listing J, Haibel H, Sorensen H, Grassnickel L, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis and rheumatism*. 2003;48(6):1667-75.
131. Deng X, Zhang J, Zhang J, Huang F. Thalidomide reduces recurrence of ankylosing spondylitis in patients following discontinuation of etanercept. *Rheumatology international*. 2013;33(6):1409-13.
132. Haibel H, Heldmann F, Braun J, Listing J, Kupper H, Sieper J. Long-term efficacy of adalimumab after drug withdrawal and retreatment in patients with active non-radiographically evident axial spondyloarthritis who experience a flare. *Arthritis and rheumatism*. 2013;65(8):2211-3.
133. Song IH, Althoff CE, Haibel H, Hermann KG, Poddubnyy D, Listing J, et al. Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial. *Annals of the rheumatic diseases* [Internet]. 2012; 71(7):[1212-5 pp.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/794/CN-00880794/frame.html>.
134. Borrás-Blasco J, Gracia-Perez A, Rosique-Robles JD, Castera ME, Abad FJ. Clinical and economic impact of the use of etanercept 25 mg once weekly in rheumatoid arthritis, psoriatic arthropathy and ankylosing spondylitis patients. *Expert Opinion on Biological Therapy*. 2014;14(2):145-50.
135. Cantini F, Niccoli L, Cassara E, Kaloudi O, Nannini C. Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis: A randomized, prospective, long-term, follow-up study. *Biologics: Targets and Therapy* [Internet]. 2013; 7(1):[1-6 pp.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/769/CN-00912769/frame.html>.
136. De Stefano R, Frati E, De Quattro D, Menza L, Manganelli S. Low doses of etanercept can be effective to maintain remission in ankylosing spondylitis patients. *Clinical Rheumatology*. 2014;33(5):707-11.
137. Lee J, Noh JW, Hwang JW, Oh JM, Kim H, Ahn JK, et al. Extended dosing of etanercept 25 mg can be effective in patients with ankylosing spondylitis: a retrospective analysis. *Clinical rheumatology*. 2010;29(10):1149-54.

138. Morck B, Pullerits R, Geijer M, Bremell T, Forsblad-D'Elia H. Infliximab dose reduction sustains the clinical treatment effect in active HLAB27 positive ankylosing spondylitis: A two-year pilot study. *Mediators of Inflammation*. 2013;2013.
139. Navarro-Compan V, Moreira V, Ariza-Ariza R, Hernandez-Cruz B, Vargas-Lebron C, Navarro-Sarabia F. Low doses of etanercept can be effective in ankylosing spondylitis patients who achieve remission of the disease. *Clinical rheumatology*. 2011;30(7):993-6.
140. Paccou J, Bacle-Boutry MA, Solau-Gervais E, Bele-Philippe P, Flipo RM. Dosage adjustment of anti-tumor necrosis factor-alpha inhibitor in ankylosing spondylitis is effective in maintaining remission in clinical practice. *The Journal of rheumatology*. 2012;39(7):1418-23.
141. Zavada J, Uher M, Sisol K, Forejtova S, Jarosova K, Mann H, et al. A tailored approach to reduce dose of anti-TNF drugs may be equally effective, but substantially less costly than standard dosing in patients with ankylosing spondylitis over 1 year: A propensity score-matched cohort study. *Annals of the Rheumatic Diseases*. 2014.
142. Lee SH, Lee YA, Hong SJ, Yang HI. Etanercept 25 mg/week is effective enough to maintain remission for ankylosing spondylitis among Korean patients. *Clinical rheumatology*. 2008;27(2):179-81.
143. Yates M, Hamilton LE, Elender F, Dean L, Doll H, MacGregor AJ, et al. Is Etanercept 25 mg Once Weekly as Effective as 50 mg at Maintaining Response in Patients with Ankylosing Spondylitis? A Randomized Control Trial. *The Journal of rheumatology*. 2015;42(7):1177-85.
144. Almirall M, Salman-Monte TC, Lisbona MP, Maymo J. Dose reduction of biological treatment in patients with axial spondyloarthritis in clinical remission: Are there any differences between patients who relapsed and to those who remained in low disease activity? *Rheumatology international*. 2015;35(9):1565-8.
145. Arends S, van der Veer E, Kamps FB, Houtman PM, Bos R, Bootsma H, et al. Patient-tailored dose reduction of TNF-alpha blocking agents in ankylosing spondylitis patients with stable low disease activity in daily clinical practice. *Clinical and experimental rheumatology*. 2015;33(2):174-80.
146. Plasencia C, Kneepkens EL, Wolbink G, Krieckaert CL, Turk S, Navarro-Compan V, et al. Comparing Tapering Strategy to Standard Dosing Regimen of Tumor Necrosis Factor Inhibitors in Patients with Spondyloarthritis in Low Disease Activity. *The Journal of rheumatology*. 2015;42(9):1638-46.
147. Boonen A, Sieper J, van der Heijde D, Dougados M, Bukowski JF, Valluri S, et al. The burden of non-radiographic axial spondyloarthritis. *Seminars in arthritis and rheumatism*. 2015;44(5):556-62.
148. Braun J, van der Horst-Bruinsma IE, Huang F, Burgos-Vargas R, Vlahos B, Koenig AS, et al. Clinical efficacy and safety of etanercept versus sulfasalazine in patients with ankylosing spondylitis: a randomized, double-blind trial. *Arthritis and rheumatism*. 2011;63(6):1543-51.
149. Sieper J, Koenig A, Baumgartner S, Wishneski C, Foehl J, Vlahos B, et al. Analysis of uveitis rates across all etanercept ankylosing spondylitis clinical trials. *Annals of the rheumatic diseases*. 2010;69(1):226-9.
150. Zochling J, Maxwell L, Beardmore J, Boonen A. TNF-alpha inhibitors for ankylosing spondylitis. *Cochrane Database of Systematic Reviews* [Internet]. 2005; (3). Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005468/abstract>.
151. O'Dwyer T, O'Shea F, Wilson F. Exercise therapy for spondyloarthritis: a systematic review. *Rheumatology international*. 2014;34(7):887-902.
152. Giannotti E, Trainito S, Arioli G, Rucco V, Masiero S. Effects of physical therapy for the management of patients with ankylosing spondylitis in the biological era. *Clinical Rheumatology*. 2014;33(9):1217-30.
153. Laskowski ER, Lexell J. Exercise and sports for health promotion, disease, and disability. *Physical Medicine & Rehabilitation*

2012;4(11):795-6.

154. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Annals of the rheumatic diseases*. 2011;70(6):896-904.
155. Chodsko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, Salem GJ, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. *Medicine and science in sports and exercise*. 2009;41(7):1510-30.
156. Dagfinrud H, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. *The Cochrane database of systematic reviews*. 2008(1):Cd002822.
157. Uhrin Z, Kuzis S, Ward MM. Exercise and changes in health status in patients with ankylosing spondylitis. *Archives of internal medicine*. 2000;160(19):2969-75.
158. Cooksey R, Brophy S, Husain MJ, Irvine E, Davies H, Siebert S. The information needs of people living with ankylosing spondylitis: a questionnaire survey. *BMC musculoskeletal disorders*. 2012;13:243.
159. Papagoras C, Markatseli TE, Saougou I, Alamanos Y, Zikou AK, Voulgari PV, et al. Cardiovascular risk profile in patients with spondyloarthritis. *Joint, bone, spine : revue du rhumatisme*. 2014;81(1):57-63.
160. Passalent LA, Soever LJ, O'Shea FD, Inman RD. Exercise in ankylosing spondylitis: discrepancies between recommendations and reality. *The Journal of rheumatology*. 2010;37(4):835-41.
161. Chung HY, Machado P, van der Heijde D, D'Agostino MA, Dougados M. Smokers in early axial spondyloarthritis have earlier disease onset, more disease activity, inflammation and damage, and poorer function and health-related quality of life: results from the DESIR cohort. *Annals of the rheumatic diseases*. 2012;71(6):809-16.
162. Matthey DL, Dawson SR, Healey EL, Packham JC. Relationship between smoking and patient-reported measures of disease outcome in ankylosing spondylitis. *The Journal of rheumatology*. 2011;38(12):2608-15.
163. Ward MM. Predictors of the progression of functional disability in patients with ankylosing spondylitis. *The Journal of rheumatology*. 2002;29(7):1420-5.
164. Kaan U, Ferda O. Evaluation of clinical activity and functional impairment in smokers with ankylosing spondylitis. *Rheumatology international*. 2005;25(5):357-60.
165. Reed MD, Dharmage S, Boers A, Martin BJ, Buchanan RR, Schachna L. Ankylosing spondylitis: an Australian experience. *Internal medicine journal*. 2008;38(5):321-7.
166. Ward MM, Weisman MH, Davis JC, Jr., Reveille JD. Risk factors for functional limitations in patients with long-standing ankylosing spondylitis. *Arthritis and rheumatism*. 2005;53(5):710-7.
167. Aaverns HL, Oxtoby J, Taylor HG, Jones PW, Dziedzic K, Dawes PT. Smoking and outcome in ankylosing spondylitis. *Scandinavian journal of rheumatology*. 1996;25(3):138-42.
168. Fallahi S, Jamshidi AR, Gharibdoost F, Mahmoudi M, Ahmadzadeh N, Nicknam MH. The correlation between pack-years of smoking and disease activity, quality of life, spinal mobility, and sacroiliitis grading in patients with ankylosing spondylitis. *Turkish Journal of Rheumatology*. 2013;28(3):181-8.
169. Bodur H, Ataman S, Rezvani A, Bugdayci DS, Cevik R, Birtane M, et al. Quality of life and related variables in patients with ankylosing spondylitis. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2011;20(4):543-9.
170. Ward MM, Hendrey MR, Malley JD, Learch TJ, Davis JC, Jr., Reveille JD, et al. Clinical and immunogenetic prognostic factors for radiographic severity in ankylosing spondylitis. *Arthritis and rheumatism*. 2009;61(7):859-66.

171. Chen CH, Chen HA, Lu CL, Liao HT, Liu CH, Tsai CY, et al. Association of cigarette smoking with Chinese ankylosing spondylitis patients in Taiwan: a poor disease outcome in systemic inflammation, functional ability, and physical mobility. *Clinical rheumatology*. 2013;32(5):659-63.
172. Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet*. 2015.
173. Gladman DD, Thavaneswaran A, Chandran V, Cook RJ. Do patients with psoriatic arthritis who present early fare better than those presenting later in the disease? *Annals of the rheumatic diseases*. 2011;70(12):2152-4.
174. Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. *Annals of the rheumatic diseases*. 2015;74(6):1045-50.
175. Kirkham B, de Vlam K, Li W, Boggs R, Mallbris L, Nab HW, et al. Early treatment of psoriatic arthritis is associated with improved patient-reported outcomes: findings from the etanercept PRESTA trial. *Clinical and experimental rheumatology*. 2015;33(1):11-9.
176. Scarpa R, Atteno M, Lubrano E, Provenzano G, D'Angelo S, Spadaro A, et al. The effectiveness and safety of TNF-alpha blockers in the treatment of early psoriatic arthritis: an Italian multicentre longitudinal observational pilot study. *Clinical rheumatology*. 2011;30(8):1063-7.
177. Scarpa R, Peluso R, Atteno M, Manguso F, Spano A, Iervolino S, et al. The effectiveness of a traditional therapeutical approach in early psoriatic arthritis: results of a pilot randomised 6-month trial with methotrexate. *Clinical rheumatology*. 2008;27(7):823-6.
178. Sterry W, Ortonne JP, Kirkham B, Brocq O, Robertson D, Pedersen RD, et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. *BMJ (Clinical research ed)*. 2010;340:c147.
179. Theander E, Husmark T, Alenius GM, Larsson PT, Teleman A, Geijer M, et al. Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). *Annals of the rheumatic diseases*. 2014;73(2):407-13.
180. Helliwell P, Coates L, Chandran V, Gladman D, de Wit M, FitzGerald O, et al. Qualifying unmet needs and improving standards of care in psoriatic arthritis. *Arthritis care & research*. 2014;66(12):1759-66.
181. McHugh NJ, Balachrishnan C, Jones SM. Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. *Rheumatology (Oxford, England)*. 2003;42(6):778-83.
182. Kavanaugh A, Ritchlin C, Rahman P, Puig L, Gottlieb AB, Li S, et al. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. *Annals of the rheumatic diseases*. 2014;73(6):1000-6.
183. Kavanaugh A, van der Heijde D, McInnes IB, Mease P, Krueger GG, Gladman DD, et al. Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial. *Arthritis and rheumatism*. 2012;64(8):2504-17.
184. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet*. 2013;382(9894):780-9.
185. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic

- arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Annals of the rheumatic diseases*. 2014;73(6):990-9.
186. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, van der Heijde D, et al. Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis. *The New England journal of medicine*. 2015;373(14):1329-39.
 187. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015.
 188. Kavanaugh A, Puig L, Gottlieb AB, Ritchlin C, You Y, Li S, et al. Efficacy and safety of ustekinumab in psoriatic arthritis patients with peripheral arthritis and physician-reported spondylitis: post-hoc analyses from two phase III, multicentre, double-blind, placebo-controlled studies (PSUMMIT-1/PSUMMIT-2). *Annals of the rheumatic diseases*. 2016;75(11):1984-8.
 189. Goulabchand R, Mouterde G, Barnetche T, Lukas C, Morel J, Combe B. Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials. *Annals of the rheumatic diseases*. 2014;73(2):414-9.
 190. Kavanaugh A, McInnes IB, Mease P, Krueger GG, Gladman D, van der Heijde D, et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study). *Annals of the rheumatic diseases*. 2014;73(9):1689-94.
 191. Mease P, Maldonado M, Wollenhaupt J, Deodhar A, Gladman D, Stach C, et al. Effect of certolizumab pegol over 48 weeks on signs and symptoms in patients with psoriatic arthritis with and without prior tumor necrosis factor inhibitor exposure. *Journal of rheumatology* [Internet]. 2014; 41(7):[1447-8 pp.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/983/CN-01056983/frame.html>.
 192. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *The Journal of rheumatology*. 2006;33(4):712-21.
 193. van der Heijde D, Landewe RB, Mease PJ, McInnes IB, Conaghan PG, Pricop L, et al. Brief Report: Secukinumab Provides Significant and Sustained Inhibition of Joint Structural Damage in a Phase III Study of Active Psoriatic Arthritis. *Arthritis & rheumatology (Hoboken, NJ)*. 2016;68(8):1914-21.
 194. Acosta Felquer ML, Coates LC, Soriano ER, Ranza R, Espinoza LR, Helliwell PS, et al. Drug therapies for peripheral joint disease in psoriatic arthritis: a systematic review. *The Journal of rheumatology*. 2014;41(11):2277-85.
 195. Kingsley GH, Kowalczyk A, Taylor H, Ibrahim F, Packham JC, McHugh NJ, et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatology (Oxford, England)* [Internet]. 2012; 51(8):[1368-77 pp.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/669/CN-00842669/frame.html>.
 196. Chandran V, Schentag CT, Gladman DD. Reappraisal of the effectiveness of methotrexate in psoriatic arthritis: results from a longitudinal observational cohort. *The Journal of rheumatology*. 2008;35(3):469-71.
 197. Behrens F, Finkenwirth C, Pavelka K, Stolfa J, Sipek-Dolnicar A, Thaci D, et al. Leflunomide in psoriatic arthritis: results from a large European prospective observational study. *Arthritis care & research*. 2013;65(3):464-70.

198. Asaduzzaman ATM, Sikder A, Mahmud MM, Paul HK, Islam MN. Efficacy and safety of leflunomide in psoriatic arthritis. *Journal of Pakistan Association of Dermatologists* [Internet]. 2014; 24(1):[51-6 pp.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/967/CN-00988967/frame.html>.
199. Asiri A, Thavaneswaran A, Kalman-Lamb G, Chandran V, Gladman DD. The effectiveness of leflunomide in psoriatic arthritis. *Clinical and experimental rheumatology*. 2014;32(5):728-31.
200. Schett G, Wollenhaupt J, Papp K, Joos R, Rodrigues JF, Vessey AR, et al. Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis and rheumatism*. 2012;64(10):3156-67.
201. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Annals of the rheumatic diseases*. 2014;73(6):1020-6.
202. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. *Journal of Rheumatology*. 2015;42(3):479-88.
203. Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Annals of the rheumatic diseases*. 2012;71(1):4-12.
204. Ceponis A, Kavanaugh A. Use of methotrexate in patients with psoriatic arthritis. *Clinical and experimental rheumatology*. 2010;28(5 Suppl 61):S132-7.
205. Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JY, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *Journal of the American Academy of Dermatology*. 2008;58(5):851-64.
206. Luelmo J, Gratacos J, Moreno Martinez-Losa M, Ribera M, Romani J, Calvet J, et al. A report of 4 years of experience of a multidisciplinary unit of psoriasis and psoriatic arthritis. *Reumatologia clinica*. 2014;10(3):141-6.
207. Mease P. Methotrexate in psoriatic arthritis. *Bulletin of the Hospital for Joint Disease* (2013). 2013;71 Suppl 1:S41-5.
208. Fernandez Sueiro JL, Juanola Roura X, Canete Crespillo Jde D, Torre Alonso JC, Garcia de Vicuna R, Queiro Silva R, et al. [Consensus statement of the Spanish Society of Rheumatology on the management of biologic therapies in psoriatic arthritis]. *Reumatologia clinica*. 2011;7(3):179-88.
209. Pereda CA, Nishishinya MB, Martinez Lopez JA, Carmona L. Efficacy and safety of DMARDs in psoriatic arthritis: a systematic review. *Clinical and experimental rheumatology*. 2012;30(2):282-9.
210. Ravindran V, Scott DL, Choy EH. A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. *Annals of the rheumatic diseases*. 2008;67(6):855-9.
211. Schett G, Sloan VS, Stevens RM, Schafer P. Apremilast: a novel PDE4 inhibitor in the treatment of autoimmune and inflammatory diseases. *Therapeutic advances in musculoskeletal disease*. 2010;2(5):271-8.
212. Crowley J, Thaci D, Joly P, Peris K, Papp KA, Goncalves J, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥ 156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *Journal of the American Academy of Dermatology*. 2017.
213. Schmutz JL. [Apremilast: Beware of suicidal ideation and behaviour]. *Annales de dermatologie et de venerologie*. 2017;144(3):243-4.

214. Pathan E, Abraham S, Van Rossen E, Withrington R, Keat A, Charles PJ, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis. *Annals of the rheumatic diseases*. 2013;72(9):1475-80.
215. Bakewell CJ, Olivieri I, Aydin SZ, DeJaco C, Ikeda K, Gutierrez M, et al. Ultrasound and magnetic resonance imaging in the evaluation of psoriatic dactylitis: status and perspectives. *The Journal of rheumatology*. 2013;40(12):1951-7.
216. Rose S, Toloza S, Bautista-Molano W, Helliwell PS. Comprehensive treatment of dactylitis in psoriatic arthritis. *The Journal of rheumatology*. 2014;41(11):2295-300.
217. Behrens F, Canete JD, Olivieri I, van Kuijk AW, McHugh N, Combe B. Tumour necrosis factor inhibitor monotherapy vs combination with MTX in the treatment of PsA: a systematic review of the literature. *Rheumatology (Oxford, England)*. 2015;54(5):915-26.
218. Kavanaugh A, McInnes IB, Mease P, Krueger GG, Gladman D, Van Der Heijde D, et al. Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: Results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study). *Annals of the Rheumatic Diseases*. 2014;73(9):1689-94.
219. Kavanaugh A, McInnes IB, Mease PJ, Krueger GG, Gladman DD, Van Der Heijde D, et al. Clinical efficacy, radiographic and safety findings through 2 years of golimumab treatment in patients with active psoriatic arthritis: Results from a long-term extension of the randomised, placebo-controlled GO-REVEAL study. *Annals of the Rheumatic Diseases*. 2013;72(11):1777-85.
220. Fagerli KM, Lie E, van der Heijde D, Heiberg MS, Lexberg AS, Rodevand E, et al. The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study. *Annals of the rheumatic diseases*. 2014;73(1):132-7.
221. Grintborg B, Ostergaard M, Dreyer L, Krogh NS, Tarp U, Hansen MS, et al. Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor alpha therapy: results from the nationwide Danish DANBIO registry. *Arthritis and rheumatism*. 2011;63(2):382-90.
222. Kristensen LE, Gulfe A, Saxne T, Geborek P. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. *Annals of the rheumatic diseases*. 2008;67(3):364-9.
223. Lopez-Ferrer A, Laiz-Alonso A. Psoriatic arthritis: an update. *Actas dermo-sifiliograficas*. 2014;105(10):913-22.
224. Gottlieb AB, Langley RG, Strober BE, Papp KA, Klekotka P, Creamer K, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. *The British journal of dermatology*. 2012;167(3):649-57.
225. Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). *Annals of the rheumatic diseases*. 2009;68(5):702-9.
226. Sanmarti R, Garcia-Rodriguez S, Alvaro-Gracia JM, Andreu JL, Balsa A, Caliz R, et al. 2014 update of the Consensus Statement of the Spanish Society of Rheumatology on the use of biological therapies in rheumatoid arthritis. *Reumatologia clinica*. 2015;11(5):279-94.
227. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis and rheumatism*. 2005;52(10):3279-89.

228. Gladman DD, Mease PJ, Ritchlin CT, Choy EH, Sharp JT, Ory PA, et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis and rheumatism*. 2007;56(2):476-88.
229. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis and rheumatism*. 2004;50(7):2264-72.
230. Combe B, Kerkmann U, Brock F, Gallo G. R. Response to etanercept with or without methotrexate combination therapy in patients with psoriatic arthritis [abstract]. *Arthritis Rheum* 2013;65(Suppl 10):S154.
231. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis and rheumatism*. 2005;52(4):1227-36.
232. Antoni CE, Kavanaugh A, van der Heijde D, Beutler A, Keenan G, Zhou B, et al. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *J Rheumatol*. 2008;35(5):869-76.
233. Kavanaugh A, Krueger GG, Beutler A, Guzzo C, Zhou B, Dooley LT, et al. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. *Annals of the rheumatic diseases*. 2007;66(4):498-505.
234. van der Heijde D, Kavanaugh A, Gladman DD, Antoni C, Krueger GG, Guzzo C, et al. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2. *Arthritis and rheumatism*. 2007;56(8):2698-707.
235. Heiberg MS, Koldingsnes W, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P, et al. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. *Arthritis and rheumatism*. 2008;59(2):234-40.
236. Hoa S CD, Bessette L et al. Comparing adalimumab and etanercept as first line agents in patients with psoriatic arthritis: data from the Rheumadata_ clinical database and registry [abstract]. *ArthritisRheum* 2013; 65(Suppl 10):S145.
237. Genovese MC, Mease PJ, Greenwald MW, Ritchlin CT, Beaulieu AD, Deodhar A, et al. Efficacy and safety of brodalumab over one year in patients with psoriatic arthritis with and without prior exposure to a biologic. *Annals of the Rheumatic Diseases*. 2014;73.
238. Gladman DD, Sampalis JS, Illouz O, Guerette B. Responses to adalimumab in patients with active psoriatic arthritis who have not adequately responded to prior therapy: effectiveness and safety results from an open-label study. *The Journal of rheumatology*. 2010;37(9):1898-906.
239. Mease P, Genovese MC, Gladstein G, Kivitz AJ, Ritchlin C, Tak PP, et al. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Arthritis and rheumatism*. 2011;63(4):939-48.
240. Coates LC, Cawkwell LS, Ng NW, Bennett AN, Bryer DJ, Fraser AD, et al. Sustained response to long-term biologics and switching in psoriatic arthritis: results from real life experience. *Annals of the rheumatic diseases*. 2008;67(5):717-9.
241. Fagerli KM, Lie E, van der Heijde D, Heiberg MS, Kalstad S, Rodevand E, et al. Switching between TNF inhibitors in psoriatic arthritis: data from the NOR-DMARD study. *Annals of the rheumatic diseases*. 2013;72(11):1840-4.
242. Ruwaard J, Kneepkens E, Marsman A, Vogelzang E, Van Der Horst-Bruinsma IE, Rispens T, et al. Efficacy of switching tumor necrosis factor α inhibitor to a second tumor necrosis

- factor α inhibitor and the influence of drug levels and anti-drug antibodies in patients with ankylosing spondylitis and psoriatic arthritis. *Annals of the Rheumatic Diseases*. 2015;74:271.
243. Soubrier AS, Bele-Philippe P, Cortet B, Ramdane-Sebbane N, Bacle-Boutry MA, Lemeunier L, et al. Treatment response, drug survival and safety of anti-tumour necrosis factor alpha therapy in 193 patients with psoriatic arthritis: a twelve-year "real life" experience. *Joint, bone, spine : revue du rhumatisme*. 2015;82(1):31-7.
244. Armstrong AW, Brezinski EA, Follansbee MR, Armstrong EJ. Effects of biologic agents and other disease-modifying antirheumatic drugs on cardiovascular outcomes in psoriasis and psoriatic arthritis: a systematic review. *Current pharmaceutical design*. 2014;20(4):500-12.
245. Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Annals of the rheumatic diseases*. 2015;74(3):480-9.
246. Gonzalez-Juanatey C, Llorca J, Amigo-Diaz E, Dierssen T, Martin J, Gonzalez-Gay MA. High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. *Arthritis and rheumatism*. 2007;57(6):1074-80.
247. Jamnitski A, Symmons D, Peters MJ, Sattar N, McInnes I, Nurmohamed MT. Cardiovascular comorbidities in patients with psoriatic arthritis: a systematic review. *Annals of the rheumatic diseases*. 2013;72(2):211-6.
248. Velez NF, Wei-Passanese EX, Husni ME, Mody EA, Qureshi AA. Management of psoriasis and psoriatic arthritis in a combined dermatology and rheumatology clinic. *Archives of dermatological research*. 2012;304(1):7-13.
249. Perez-Barrio S, Galindez E, Alzaga JMC, Garcia-Vivar ML, Urigoitia P, Belloso RI. Psoriasis and psoriatic arthropathy multidisciplinary clinic at Basurto University Hospital: 2 years of experience. *Journal of the American Academy of Dermatology*. 2014;70(5):AB180.
250. Foulkes A, Chinoy H, Warren RB. High degree of patient satisfaction and exceptional feedback in a specialist combined dermatology and rheumatology clinic. *British Journal of Dermatology*. 2012;167:38.
251. Van de Kerhof P. Psoriasis. In: Bologna JL, Jorizzo JL, RP R, editors. *Dermatología*. Madrid: Mosby Elsevier (España); 2004. p. 125-49.
252. Grønning K, Skomsvoll JF, Rannestad T, Steinsbekk A. The effect of an educational programme consisting of group and individual arthritis education for patients with polyarthritis—A randomised controlled trial. *Patient Education & Counseling*. 2012;88(1):113-20.
253. Grønning K, Rannestad T, Skomsvoll JF, Rygg LØ, Steinsbekk A. Long-term effects of a nurse-led group and individual patient education programme for patients with chronic inflammatory polyarthritis - a randomised controlled trial. *Journal of Clinical Nursing*. 2014;23(7/8):1005-17.
254. Koksvik HS, Hagen KB, Rodevand E, Mowinckel P, Kvien TK, Zangi HA. Patient satisfaction with nursing consultations in a rheumatology outpatient clinic: A 21-month randomised controlled trial in patients with inflammatory arthritides. *Annals of the Rheumatic Diseases* [Internet]. 2013; 72(6):[836-43 pp.]. Available from: <http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/943/CN-00906943/frame.html>.
255. Naranjo A, Bilbao A, Erausquin C, Ojeda S, Francisco FM, Rua-Figueroa I, et al. Results of a specific smoking cessation program for patients with arthritis in a rheumatology clinic. *Rheumatology International*. 2014;34(1):93-9.

256. Garcia-Diaz S, Girabent-Farres M, Roig-Vilaseca D, Reina D, Cerda D, Gonzalez M, et al. [Preference for etanercept pen versus syringe in patients with chronic arthritis. Nurse education workshop]. *Enfermería clínica*. 2013;23(4):164-9.
257. Hennell S, Spark E, Wood B, George E. An evaluation of nurse-led rheumatology telephone clinics. *Musculoskeletal Care*. 2005;3(4):233-40.
258. Rudd RE, Blanch DC, Gall V, Chibnik LB, Wright EA, Reichmann W, et al. A randomized controlled trial of an intervention to reduce low literacy barriers in inflammatory arthritis management. *Patient education and counseling*. 2009;75(3):334-9.
259. Homer D, Nightingale P, Jobanputra P. Providing patients with information about disease-modifying anti-rheumatic drugs: Individually or in groups? A pilot randomized controlled trial comparing adherence and satisfaction. *Musculoskeletal Care*. 2009;7(2):78-92.
260. Alonso Ruiz A, Vidal Fuentes J, Tornero Molina J, Carbonell Abello J, Lazaro P, Mercado D, et al. [Asistance quality standards in rheumatology.]. *Reumatología clínica*. 2007;3(5):218-25.
261. Gomez Reino J, Loza E, Andreu JL, Balsa A, Batlle E, Canete JD, et al. [Consensus statement of the Spanish Society of Rheumatology on risk management of biologic therapy in rheumatic patients]. *Reumatología clínica*. 2011;7(5):284-98.
262. Kalyoncu U, Nakas D, Hayran M, Gossec L, Karadag O, Akdogan A, et al. Nurse-guided completion of the BASDAI questionnaire in ankylosing spondylitis patients with low literacy. *Journal for Nurse Practitioners*. 2010;6(3):201-5.
263. van Eijk-Hustings Y, van Tubergen A, Bostrom C, Braychenko E, Buss B, Felix J, et al. EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis. *Annals of the rheumatic diseases*. 2012;71(1):13-9.
264. Schipper LG, van Hulst LT, Grol R, van Riel PL, Hulscher ME, Fransen J. Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. *Rheumatology (Oxford, England)*. 2010;49(11):2154-64.
265. Katchamart W, Bombardier C. Systematic monitoring of disease activity using an outcome measure improves outcomes in rheumatoid arthritis. *The Journal of rheumatology*. 2010;37(7):1411-5.
266. de la Torre J, Escandón Peláez S, Fernández Ogando E, García Alonso J, Lozano Mateos M, Perez Ayuso P. Documento de consenso sobre el manejo, administración y monitorización a pacientes en tratamiento con Infliximab®. *Metas de Enfermería*. 2007;. 10: 50-5.
267. Almodovar R, Fernandez Nebro A, Gracia Perez LA, Román Ivorra JA, Rodríguez Cros JR, del Pino Montes J, et al. AB1165 Effectiveness of Nursing Consultations in Rheumatology: Results from the Score Study. *Annals of the Rheumatic Diseases*. 2015;74(Suppl 2):1292.
268. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Annals of the rheumatic diseases*. 2010;69(4):631-7.
269. Larsson I, Arvidsson S, Bergman S, Arvidsson B. Patients' perceptions of drug information given by a rheumatology nurse: a phenomenographic study. *Musculoskeletal Care*. 2010;8(1):36-45.
270. Alfaro N, Lazaro P, Gabriele G, Garcia-Vicuna R, Jover JA, Sevilla J. Perceptions, attitudes and experiences of family caregivers of patients with musculoskeletal diseases: a qualitative approach. *Reumatología clínica*. 2013;9(6):334-9.
271. Backman CL, Smith Ldel F, Smith S, Montie PL, Suto M. Experiences of mothers living with inflammatory arthritis. *Arthritis and rheumatism*. 2007;57(3):381-8.
272. Betteridge N, Boehncke WH, Bundy C, Gossec L, Gratacos J, Augustin M. Promoting patient-centred care in psoriatic arthritis: a multidisciplinary European perspective on improving the patient experience. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2015.

273. Madsen M, Jensen KV, Esbensen BA. Men's experiences of living with ankylosing spondylitis: a qualitative study. *Musculoskeletal Care*. 2015;13(1):31-41.
274. Martindale J, Goodacre L. The journey to diagnosis in AS/axial SpA: the impact of delay. *Musculoskeletal Care*. 2014;12(4):221-31.
275. Pelaez-Ballestas I, Perez-Taylor R, Aceves-Avila JF, Burgos-Vargas R. 'Not-belonging': illness narratives of Mexican patients with ankylosing spondylitis. *Medical anthropology*. 2013;32(5):487-500.
276. Pelaez-Ballestas I, Romero-Mendoza M, Burgos-Vargas R. If three of my brothers have ankylosing spondylitis, why does the doctor say it is not necessarily hereditary? The meaning of risk in multiplex case families with ankylosing spondylitis. *Chronic illness*. 2015.
277. Davies H, Brophy S, Dennis M, Cooksey R, Irvine E, Siebert S. Patient perspectives of managing fatigue in Ankylosing Spondylitis, and views on potential interventions: a qualitative study. *BMC musculoskeletal disorders*. 2013;14:163.
278. Eilertsen G, Ormstad H, Kirkevold M, Mengshoel AM, Soderberg S, Olsson M. Similarities and differences in the experience of fatigue among people living with fibromyalgia, multiple sclerosis, ankylosing spondylitis and stroke. *Journal of clinical nursing*. 2015;24(13-14):2023-34.
279. Lacaille D, White MA, Backman CL, Gignac MA. Problems faced at work due to inflammatory arthritis: new insights gained from understanding patients' perspective. *Arthritis and rheumatism*. 2007;57(7):1269-79.
280. Mortada M, Abdul-Sattar A, Gossec L. Fatigue in Egyptian patients with rheumatic diseases: a qualitative study. *Health and quality of life outcomes*. 2015;13:134.
281. Naegeli AN, Flood E, Tucker J, Devlen J, Edson-Heredia E. The patient experience with fatigue and content validity of a measure to assess fatigue severity: qualitative research in patients with ankylosing spondylitis (AS). *Health and quality of life outcomes*. 2013;11:192.
282. Stamm T, Hieblinger R, Bostrom C, Mihai C, Birrell F, Thorstensson C, et al. Similar problem in the activities of daily living but different experience: a qualitative analysis in six rheumatic conditions and eight European countries. *Musculoskeletal Care*. 2014;12(1):22-33.
283. Uttjek M, Nygren L, Stenberg B, Dufaker M. Marked by visibility of psoriasis in everyday life. *Qualitative health research*. 2007;17(3):364-72.
284. Globe D, Bayliss MS, Harrison DJ. The impact of itch symptoms in psoriasis: results from physician interviews and patient focus groups. *Health and quality of life outcomes*. 2009;7:62.
285. McArthur MA, Birt L, Goodacre L. "Better but not best": a qualitative exploration of the experiences of occupational gain for people with inflammatory arthritis receiving anti-TNFalpha treatment. *Disability and rehabilitation*. 2015;37(10):854-63.
286. Pasma A, van 't Spijker A, Luime JJ, Walter MJ, Busschbach JJ, Hazes JM. Facilitators and barriers to adherence in the initiation phase of Disease-modifying Antirheumatic Drug (DMARD) use in patients with arthritis who recently started their first DMARD treatment. *The Journal of rheumatology*. 2015;42(3):379-85.
287. Mengshoel AM. Living with a fluctuating illness of ankylosing spondylitis: a qualitative study. *Arthritis and rheumatism*. 2008;59(10):1439-44.
288. Moverley AR, Vinall-Collier KA, Helliwell PS. It's not just the joints, it's the whole thing: qualitative analysis of patients' experience of flare in psoriatic arthritis. *Rheumatology (Oxford, England)*. 2015;54(8):1448-53.
289. Gronning K, Lomundal B, Koksvik HS, Steinsbekk A. Coping with arthritis is experienced as a dynamic balancing process. A qualitative study. *Clinical rheumatology*. 2011;30(11):1425-32.

290. Barlow JH, Cullen LA, Foster NE, Harrison K, Wade M. Does arthritis influence perceived ability to fulfill a parenting role? Perceptions of mothers, fathers and grandparents. *Patient education and counseling*. 1999;37(2):141-51.
291. Aguiar R, Ambrosio C, Cunha I, Barcelos A. Sexuality in spondyloarthritis--the impact of the disease. *Acta reumatologica portuguesa*. 2014;39(2):152-7.
292. Cakar E, Dincer U, Kiralp MZ, Taskaynatan MA, Yasar E, Bayman EO, et al. Sexual problems in male ankylosing spondylitis patients: relationship with functionality, disease activity, quality of life, and emotional status. *Clinical rheumatology*. 2007;26(10):1607-13.
293. Haugli L, Strand E, Finset A. How do patients with rheumatic disease experience their relationship with their doctors? A qualitative study of experiences of stress and support in the doctor-patient relationship. *Patient education and counseling*. 2004;52(2):169-74.
294. (CEBM) OCfE-bM. Centre for Evidence Based Medicine - Levels of Evidence (March 2009). Disponible en: <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>.