CLINICAL PRACTICE GUIDELINES

for the

Management of Patients with Rheumatoid Arthritis

SPANISH SOCIETY OF RHEUMATOLOGY

CLINICAL PRACTICE GUIDELINES

for the

Management of Patients with Rheumatoid Arthritis

These clinical practice guidelines serve to support decision making in healthcare. Adherence to these guidelines is not obligatory and they are not a substitute for the clinical judgement of health professionals.

Publication: 2019

Contents

Foreword **5**

Authors and collaborations **7**

Clinical questions of interest **13**

CPG recommendations **15**

1. Introduction **19**

2. Scope and objetives **23**

3. Method of development **25**

4. Disease burden of RA in Spain **31**

5. Pathogenesis. The development of RA **41**

6. Classification/Diagnosis **45**

6.1. New criteria (2010 ACR/EULAR classification criteria) 45

6.2. Sources of delays in patient care 48

6.3. Primary care: the role of primary care in the detection and referral of patiens with RA 50

7. Treatment **55**

7.1. General principles of the treatment 55

7.2. Drugs used in RA 57

7.3. Pharmacological treatment 69

7.3.1. Initial pharmacological treatment 69

7.3.2. Treatment of patients refractory to conventional DMARDs 76

7.3.3. Treatment with the first biologic or targeted DMARD 84

7.3.4. Treatment of patients in whom the first biologic fails 99

7.4. Other treatments 107

8. Treatment of RA in special situations **113**

8.1. RA as a complex disease 113

8.2. Patients in remission/dose reduction 117

8.3. Cardiovascular risk 121

8.4. Interstitial lung disease 126

8.5. Serious infections 137

8.6. Cancer 141

9. Management of risk in the treatment of RA 147
9.1. Screening 147
9.2. Treatment monitoring 148
9.3. Vaccinations 149
9.4. Pregnancy and breastfeeding 152
10. Treatment adherence 157
11. The role of nursing 161
12. General recommendations on patient management 165
13. The patient perspective 167
14. Diagnostic and therapeutic strategies 183
15. Dissemination and implementation 185
16. Future lines of research 189
Appendices 191
Appendix 1. SIGN Levels of evidence and grades of recommendation 191
Appendix 2. Information for patients 193
Appendix 3. Glossary and abbreviations 244
Appendix 4. Declarations of interest 250
Appendix 5. Drugs for RA. Pregnancy and breastfeeding 253
References 260

Foreword

These clinical practice guidelines (CPGs) have been created under the auspices of the Spanish Society of Rheumatology (SER), a non-profit scientific organisation. Having recognised the need for these guidelines, the SER set up the initial group of researchers to be involved and the timetable for their development. It also signed agreements with the funding bodies safeguarding the editorial independence of the guideline developers regarding the contents of the guidelines.

The SER Research Unit selected the principal investigator and members of the expert panel in accordance with current legislation, developed the methodology to be followed, and coordinated the meetings held and the drafting of the CPGs, including the systematic reviews of the evidence conducted as part of the guideline development process.

The goal of these Clinical Practice Guidelines for the Management of Patients with Rheumatoid Arthritis is to provide practical recommendations for clinicians based on the best available scientific evidence, concerning the most effective treatments and follow-up of this disease.

The content of these CPGs brings the evidence available at the time of writing the previous GUIPCAR (at the start of 2011) up-to-date as of the end of 2017. With advances in knowledge and the appearance of new evidence, it is anticipated that the guidelines should be updated again in 4 years' time.

Authors and collaborations

GUIPCAR working group for the development of Clinical Practice Guidelines for the Management of Patients with Rheumatoid Arthritis

Coordination

Clinical coordinator

Alejandro Balsa Criado. Head of Rheumatology, La Paz University Hospital, Madrid, Spain.

Coordinación metodológica

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

Expertos elaboradores de las recomendaciones

Jose María Álvaro-Gracia Álvaro. Rheumatologist, La Princesa University Hospital, Madrid, Spain.

José Luis Andreu Sánchez. Head of Rheumatology, Puerta de Hierro, Majadahonda University Hospital, Madrid, Spain.

Francisco Javier Blanco García. Rheumatologist, University Hospital Complex in A Coruña, A Coruña, Spain.

Laura Cano García. Rheumatology Nurse Specialist, Regional University Hospital in Málaga, Málaga, Spain.

Esmeralda Delgado Frías. Rheumatologist, Canarias University Hospital, Santa Cruz de Tenerife, Spain.

José Federico Díaz González. Rheumatologist, Canarias University Hospital and Professor in Medicine, University of La Laguna, Santa Cruz de Tenerife, Spain.

Ana Mª Fernández Ortiz. Rheumatologist, Almansa General Hospital, Albacete, Spain.

Blanca García Magallón. Rheumatologist, San Jorge General Hospital, Huesca, Spain.

Luis Gómez Carrera. Pulmonologist, La Paz University Hospital, Madrid, Spain.

Carlos González Juanatey. Cardiologist, Lucus Augusti University Hospital, Lugo, Spain.

M. Vanesa Hernández Hernández. Rheumatologist, Canarias University Hospital, Santa Cruz de Tenerife, Spain.

Antonio Juan Mas. Rheumatologist, Son Llàtzer University Hospital, Palma de Mallorca, Spain.

Francisco Javier Narváez García. Rheumatologist, Bellvitge University Hospital, Barcelona, Spain.

Ana Ortiz García. Rheumatologist, La Princesa University Hospital, Madrid, Spain.

Lucía Silva Fernández. Rheumatologist, University Hospital Complex in Ferrol, A Coruña, Spain.

Alejandro Tejedor Varillas. Family medicine specialist, Dasur Getafe Primary Health Centre, Madrid and coordinator of the National Rheumatology Group of the Spanish Society of Family and Community Medicine (SEMFYC), Spain.

Reviewers of the scientific evidence

Miguel Ángel Abad Hernández. Rheumatologist, Virgen del Puerto Hospital, Plasencia, Cáceres, Spain.

Gloria Candelas Rodríguez. Rheumatologist, San Carlos Clinical University Hospital, Madrid, Spain.

Isabel Castrejón Fernández. Rheumatologist and Associate Professor of Rheumatology, Rush University Medical Center, Chicago, USA.

Eugenio Chamizo Carmona. Rheumatologist, Mérida Hospital, Badajoz, Spain.

Jesús Maese Manzano. Rheumatologist, SER Evidence-based Rheumatology Working Group (RBE), Madrid, Spain.

José de la Mata Llord. Rheumatologist, Instituto Salud Osteoarticular ARI, Madrid, Spain.

María Betina Nishishinya Aquino. Rheumatologist and Sports Medicine Specialist, Clínica Quirón, Barcelona, Spain.

Ana Ortiz García. Rheumatologist, La Princesa University Hospital, Madrid, Spain.

Claudia Pereda Testa. Rheumatologist, HLA Mediterráneo Hospital, Almería, Spain.

Lucía Silva Fernández. Rheumatologist, University Hospital Complex in Ferrol, A Coruña, Spain.

Francisca Sivera Mascaró. Rheumatologist, Elda University General Hospital, Alicante, Spain.

Patient representatives in the working group

Laly Alcaide Cornejo. Patient with rheumatoid arthritis, Madrid, Spain.

Gonzalo López Alonso. Patient with rheumatoid arthritis, Madrid, Spain.

Strategy for literature and database searches

Mercedes Guerra Rodríguez. Documentalist, SER Research Unit, Madrid, Spain.

Estimation of the disease burden

Ricard Gènova Maleras. Demographer, Health Reports and Studies Service, Directorate General for Public Health, Madrid Region, Spain.

Collaborators

Methodological support

Nieves Plana Farras. Preventive Medicine and Public Health Specialist, SER Research Unit, Madrid, Spain.

Daniel Seoane Mato. Preventive Medicine and Public Health Specialist, SER Research Unit, Madrid, Spain.

Qualitative research with patients

Petra Díaz del Campo Fontecha. Sociologist, SER Research Unit, Madrid, Spain.

Design of patient information

Laly Alcaide Cornejo. Patient with rheumatoid arthritis, Madrid, Spain.

Alberto Cantabrana Alútiz. Rheumatologist, Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain.

Petra Díaz del Campo Fontecha. Sociologist, SER Research Unit, Madrid, Spain.

Gonzalo López Alonso. Patient with rheumatoid arthritis, Madrid, Spain.

External review

Mario H. Cardiel. Lecturer in Medical Sciences and Rheumatologist, Centro de Investigación Clínica de Morelia, Michoacán, Mexico.

Enrique R. Soriano. Head of Rheumatology, Department of Clinical Medicine, Hospital Italiano de Buenos Aires, Argentina.

Acknowledgements

Special thanks to **Federico Díaz González**, Director of the SER Research Unit, for helping to maintain the editorial independence of these CPGs.

Collaborating organisations

Spanish Society of Rheumatology (SER)

Spanish Society of Cardiology (SEC)

Spanish Society of Pulmonology and Thoracic Surgery (SEPAR)

Spanish Society of Familiy and Community Medicine (SEMFYC)

Spanish national coordinator of associations for patients with arthritis and their families (ConArtritis)

Members of these organisations have contributed to the authorship of the CPGs.

Declaration of interests

All members of the GUIPCAR working group have made declarations of interest and these are presented in Appendix 4.

Public scrutiny

These guidelines were made available for public scrutiny. Information detailing this process is available from the Clinical Practice Guidelines section (under Research) on the SER website (www.ser.es).

Funding

The development of these CPGs, under the auspices of SER, has been funded by Abbvie, BMS, Lilly, MSD, Pfizer, Roche and UCB. The Spanish Rheumatology Foundation (FER), the body responsible for employing the staff of the SER Research Unit and coordinating payments to panellists and reviewers, acted completely independently. The funders had no direct or indirect influence on the selection of panellists, searching or interpretation of the evidence, or any part of the final draft of the guidelines, agreeing to fund the guideline development process even in the event that the evidence gathered ran against their interests. In this way, it was ensured that the design of the process, and analysis and interpretation of the results have been conducted completely independently of the industrial funders.

These guidelines should be cited as follows

GUIPCAR working group, Clinical Practice Guidelines for the Management of Patients with Rheumatoid Arthritis, Madrid, Spanish Society of Rheumatology (SER), 2019.

Clinical questions of interest

Classification/Diagnosis

1. In patients with early rheumatoid arthritis, what is the clinical utility of the new classification criteria published in 2010 compared to the 1997 criteria?

Initial pharmacological treatment

2. In patients with rheumatoid arthritis, what is the efficacy of initial treatment with glucocorticoids at doses of >10 mg of prednisone, added to any disease-modifying anti-rheumatic drug (DMARD)?
3. In patients with rheumatoid arthritis, what is the efficacy of initial treatment with triple conventional DMARD therapy?

Treatment of patients refractory to conventional DMARDs

4. In patients with rheumatoid arthritis who do not respond to methotrexate monotherapy, is it more effective to add a biologic DMARD or use a combined therapy with conventional DMARDs?
5. In patients with rheumatoid arthritis with a poor response to conventional DMARDs, are biologic or targeted DMARDs more effective?

Treatment with first biologic or targeted DMARD

6. In patients with rheumatoid arthritis, what is the efficacy of the combination of any biologic DMARD with a conventional DMARD other than methotrexate?
7. In patients with rheumatoid arthritis, which dose of methotrexate in combination with a biologic DMARD is associated with the best clinical outcomes, highest drug concentrations and lowest antibody production?
8. In patients with rheumatoid arthritis, are there differences in terms of efficacy between the different biologic DMARDs used as a first-line treatment?
9. In patients with rheumatoid arthritis, what is the efficacy of targeted DMARD monotherapy compared to conventional DMARD or biologic DMARD monotherapy?

Treatment of patients in whom the first biologic fails

10. In patients with rheumatoid arthritis who have had a poor response to a first antibody to tumour necrosis factor (anti-TNF) agent, is another anti-TNF agent or a non-anti-TNF biologic DMARD more effective?

11. In patients with rheumatoid arthritis, after failure of a first anti-TNF, is a second biologic or a targeted DMARD more effective?

Patients in remission/dose reduction

12. In patients with rheumatoid arthritis receiving biologics who have achieved remission of disease activity, what is the rate of recurrence when the dose of biologics is reduced?

Interstitial lung disease

13. In patients with rheumatoid arthritis and interstitial lung disease, which is the safest biologic DMARD?

14. In patients with rheumatoid arthritis and interstitial lung disease, which drugs have shown to be effective for the treatment of the lung disease?

Serious infections

15. In patients with rheumatoid arthritis on biological therapy who have had a serious infection, is it safe to restart biological therapy?

Cancer

16. In patients with rheumatoid arthritis and a history of cancer, what is the safest biological therapy?

Treatment adherence

17. In patients with rheumatoid arthritis, which individual-, disease- and treatment-related factors are associated with poor treatment adherence/persistence?

Role of nursing

18. In patients with rheumatoid arthritis, what is the efficacy of educational intervention programmes run by nurses?

CPG recommendations*

Classification/Diagnosis

In patients with seropositive arthritis, the recommendation is to use the 2010 ACR/EULAR classification criteria to support the clinical impression of the physician **(Grade B recommendation)**.
In patients with seronegative arthritis, the use of these classification criteria is not recommended and the diagnosis should depend on the clinical impression of the rheumatologist **(Grade √ recommendation)**.

Initial pharmacological treatment

In patients with rheumatoid arthritis, the recommendation is to use glucocorticoids at a dose equivalent to prednisone 10-30 mg/day as the initial treatment in combination with one of several conventional DMARDs followed by gradual tapering of the dose **(Grade B recommendation)**.
Although triple therapy is not recommended as the initial treatment for rheumatoid arthritis, it could be considered in patients in whom glucocorticoids are contraindicated **(Grade C recommendation)**.

Treatment of patients refractory to conventional DMARDs

In patients with rheumatoid arthritis in whom methotrexate monotherapy fails, either the use of a combination treatment with conventional DMARDs or a biological therapy is recommended, depending on patient characteristics **(Grade B recommendation)**.
In patients with rheumatoid arthritis in whom conventional DMARD therapy fails, the recommendation is to use a combined therapy, with a biologic or targeted therapy, depending on patient characteristics **(Grade C recommendation)**.

Treatment with the first biologic or targeted DMARD

In patients with rheumatoid arthritis requiring biological therapy with contraindications or intolerance to methotrexate, the recommendation is to use leflunomide in combination with a biologic **(Grade B recommendation)**.
In patients with rheumatoid arthritis who receive combination treatment with methotrexate and anti-TNF agents, the recommendation is to use methotrexate at doses of at least 10 mg/week **(Grade B recommendations)**.

* The system used for grading the recommendations is set out in Appendix 1.

In patients with rheumatoid arthritis, it is not possible to recommend a specific biological agent for first-line treatment in association with methotrexate **(Grade B recommendation)**.

As monotherapy, the recommendation is to use an anti-IL6 agent rather than an anti-TNF agent **(Grade B recommendation)**.

In patients with indications for biologic DMARD or targeted DMARD therapy in whom, for any reason, these drugs cannot be used in combination with conventional DMARDs, the guideline development group considers that the use of Janus kinase inhibitor monotherapy is a good alternative treatment **(Grade √ recommendation)**.

Treatment of patients in whom the first biologic fails

In patients with rheumatoid arthritis who have had an inadequate response to a first anti-TNF, it is justifiable to use a second anti-TNF agent or a biologic acting on a different therapeutic target, depending on the type of inefficacy and patient characteristics **(Grade D Recommendation)**.

In patients with rheumatoid arthritis in whom biological therapy has failed, regardless of the number of drugs and their mechanisms of action, either a biologic or a targeted DMARD may be used **(Grade B recommendation)**.

Patients in remission/dose reduction

In patients with rheumatoid arthritis who have achieved remission or low disease activity with biological therapy for at least 6 months, the recommendation is to progressively taper the dose of the biologic, despite the risk of relapse **(Grade B recommendation)**.

Interstitial lung disease

In patients with rheumatoid arthritis and interstitial lung disease who require treatment with a biologic, abatacept is recommended as the safest option **(Grade C recommendation)**.

As an alternative option, rituximab could be used **(Grade D recommendation)**.

Although some retrospective studies have suggested that rituximab and abatacept may be effective for the treatment of interstitial pneumonia, especially in patients with non-usual interstitial pneumonia, the guideline development group considers that the available evidence is insufficient and/or inadequate to be able to make a definitive recommendation in patients with rheumatoid arthritis and interstitial lung disease **(Grade D recommendation)**.

Serious infections

Patients with rheumatoid arthritis who have developed a serious infection while on biological therapy should subsequently be treated with abatacept. If an anti-TNF is preferred, the recommended agent is etanercept **(Grade D recommendation)**.

Cancer

The recommendation is to assess patients with rheumatoid arthritis and a history of cancer who are due to start biological therapy on a case-by-case basis and reach a consensus between the patient, the oncologist and other specialists involved **(Grade C recommendation)**.

There is no evidence for recommending any specific biological therapy.

Treatment adherence

The recommendation is to supervise treatment adherence, especially in women, elderly and comorbid patients **(Grade D recommendation)**.

Patient education programmes should be run and a relationship of trust fostered between patients and clinicians, to improve treatment adherence **(Grade D recommendation)**.

Role of nursing

The recommendation is that specific individual or group educational programmes led by nurses are included in the routine follow-up of patients with rheumatoid arthritis **(Grade D recommendation)**.

Specific educational programmes led by nurses should be ongoing **(Grade √ recommendation)**.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory systemic autoimmune disease. It tends to mainly affect the joints, the synovial membrane being the first structure involved. The disease then spreads to neighbouring structures with changes in cartilage, ligaments, joint capsules and bone. On the other hand, systemic inflammatory changes can lead to the involvement of other organs such as the heart, lungs, kidneys, skin and eyes, as well as the haematopoietic system and the neuropsychiatric sphere. In patients who are not adequately treated, the disease usually leads to joint damage, functional impairment and a higher risk of death[1].

The aetiology of RA remains unknown. It is agreed that environmental or other trigger factors play a role in susceptible individuals. Specifically, there are data on various toxic, sex, environmental, infectious and genetic susceptibility factors that may increase the likelihood of developing RA[2].

To reduce the variability observed in clinical practice and improve the care provided to and quality of life of individuals with RA, the Spanish Society of Rheumatology (SER) has led the development of clinical practice guidelines, with the participation of a multidisciplinary team of health professionals involved in their care. Clinical practice guidelines are defined as a document that gathers a set of recommendations based on a systematic review of the evidence and assessment of the risks and benefits of alternative care options, seeking to optimise the provision of healthcare[3].

The recommendations of the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) have been the most widely used internationally[4]. In Spain, the first Clinical Practice Guidelines for the Management of Rheumatoid Arthritis (GUIPCAR) were developed by the SER in 2001 and these were updated in 2007 and 2011[5]. In recent years, there have been significant advances, some involving how to manage the various extra-articular manifestations of RA such as interstitial lung disease and all aspects of cardiovascular morbidity and mortality. Additionally, there are new therapeutic considerations such as the importance of early treatment, proactively seeking disease remission, the development of new drugs, the various strategies for disease management, both first-line treatments and those used after treatment failure with conventional disease-modifying anti-rheumatic drugs (DMARDs) or the first or subsequent biological therapies, and the presence of comorbidities. Further, the CPGs need to be revised to take into account new classification criteria that have been validated and to underline the key role of primary care (PC) in both the detection and the referral of patients with suspected RA. All these considerations, together with the need for

adequate management of the risk of using biologics with special attention to monitoring treatments, vaccinations, and special situations such as pregnancy and breastfeeding, and taking into account the role of nursing staff and patients themselves, make it necessary to update the content of the guidelines. In this context, we developed the 2017 GUIPCAR, clinical practice guidelines for the management of patients with RA, which seek to guide users concerning all the aforementioned issues.

This document is the result of the work of a considerable number of health professionals involved in the management of patients with RA. The guidelines are organised into chapters that provide an answer to the questions posed at the start of each one. Then, the recommendations are presented and these are followed by a summary of the evidence.

Details of the methods used for developing the CPGs (search strategy for each clinical question, evidence tables, etc.) are provided in an appendix available from the SER website.

As the guideline sponsor, the SER hopes to stimulate effective, safe and coordinated decision making by healthcare professionals, regarding the management of RA centred on patients with the condition.

Epidemiological data and clinical manifestations

Epidemiology and scale of the problem in quantitative terms

The global prevalence of RA is between 0.5 and 1% of the adult population. The estimated annual incidence in Southern and Northern Europe, respectively, is 16.5 and 29 cases per 100,000 people, and the prevalence is highest in women between 50 and 60 years old[6, 7]. We should bear in mind that the consequences of the disease, without adequate treatment, are major, resulting in severe disability in a significant proportion of patients, with a reduction in quality of life. Early initiation of DMARDs and adequate treatment allow the impact of the disease to be reduced and improve the prognosis. RA has been classically associated with high direct and indirect costs: pharmaceutical, healthcare and surgical, as well as related to sick leave and disability, etc.; however, new estimates indicate the efficacy of biological therapies[5].

Clinical manifestations

A detailed description of the clinical manifestations of RA is beyond the scope of this publication. In brief, the cardinal signs and symptoms of RA are pain and inflammation of the joints involved, especially the hands, and they tend to be symmetrical. Additionally, there are other general manifestations such as fatigue, general malaise, morning stiffness, weakness, functional limitation and depression, which together with potential extra-articular involvement of, for example, the skin, cardiovascular system, bone, nervous system, eyes and/or lungs, reduce quality of life and life expectancy[1, 8].

2. Scope and objetives

Scope

These guidelines focus on the care of adults with RA. They seek to provide to users with guidance concerning an ideal systematic approach to using the various therapeutic interventions available for this disease, as well as the general principles of diagnosis and monitoring.

Patients with juvenile idiopathic arthritis are beyond the scope of these guidelines.

They address factors associated with treatment of the disease, including alternative treatment options, and cover general matters concerning the diagnosis, prognostic factors, monitoring and collaboration with other specialities (pulmonologists, cardiologists and general practitioners).

Objetives of the guidelines

Main objetive

To provide rheumatologists and other health professionals with recommendations on the treatment options available for the clinical management of adult patients with RA based on the best available evidence. If the evidence is insufficient or of poor quality, recommendations are based on the consensus reached by the members of the working group.

Specific objetives

- To enhance the clinical skills of health professionals involved in the care of people with RA in order to improve the quality of the care provided
- To reduce variability in clinical practice regarding treatment of the disease
- To assess the efficacy, safety, efficiency and cost-effectiveness of the various pharmacological and non-pharmacological treatment interventions
- To summarise the scientific evidence to increase the knowledge of all health professionals involved in the care process, hoping in this way to improve patient quality of life
- To improve the clinical approach to RA with recommendations focused on the early initiation of treatment to reduce the disability and morbidity associated with this condition

- To encourage collaboration between health professionals of different specialities involved in the treatment of patients with RA
- To produce general informative materials for patients with RA and their families and caregivers, to help them to better understand the process and factors that have an impact on the course of the disease

Target users of the guideline

Seeking to achieve comprehensive patient care, these guidelines are aimed at rheumatologists and other health professionals who may be involved in the care of patients with RA working in primary and specialist care, namely, those from the specialities of cardiology, pulmonology, traumatology, rehabilitation, family medicine, and nursing, as well as other specialists involved in the care for these patients. It is also aimed at patients and family members seen by these health professionals. In the case of patients and families, this is a tool that will help them learn about the potential strategies for RA treatment and what this treatment may achieve, in order to avoid the use of treatment regimens that are not backed by scientific evidence or by strong expert consensus.

3. Method of development

In the development of these CPGs for the management of patients with RA, we followed a series of steps, as described below:

Establishment of the guideline development group (GDG)

A multidisciplinary working group was established composed of health professionals involved in care delivery, technical staff of the SER Research Unit and representatives of patients. All participants are listed in the authorship and collaborations section. The composition of the group is outlined below:

- **Coordinators:** one specialist in rheumatology, as the principal investigator, and one methodological expert, a member of the technical staff of the SER Research Unit, were responsible for the coordination of the clinical and methodological aspects of the CPGs and the support provided to the GDG.
- **Expert panel:** specialists in rheumatology, cardiology, pulmonology, family medicine, and specialised nursing were selected through a call for experts or contacting the various scientific societies in the field. As members of the expert panel, these people were responsible for drafting the recommendations in the CPGs.
- **Reviewers of the scientific evidence:** several rheumatologists, members of the working group of SER reviewers, were responsible for systematically reviewing the available scientific evidence and collecting the evidence on the basis of which the expert panel drafted the recommendations.
- **Patients:** as well as clinical professionals, two patients participated in the GDG itself, from the early stages of the project.

A work plan was established outlining the different stages in the development of the guidelines and deadlines.

Definition of the scope and objectives

An update is warranted, given the time since publication of the previous GUIPCAR and the new evidence that has emerged during that time. The new scope and objectives were defined by consensus based on the clinical experience and knowledge of the participating health professionals.

Drafting of the clinical questions

After establishing the scope and objectives of the guidelines, the members of the GDG set the clinical questions to be answered. First, a list of general clinical questions was drawn up. Then, having selected those potentially related to the objectives of the guidelines, questions were re-drafted using the Patient, Intervention, Comparison and Outcome (PICO) framework. The question related to adherence was not framed in the PICO format, being based on a non-systematic review of the studies published on the topic.

Literature search, evaluation and evidence synthesis

A literature search was carried out in the following databases: Medline (through PubMed), Embase (Elsevier), Cochrane Library (Wiley Online Library) and Cumulative Index to Nursing & Allied Health Literature (CINAHL; EBSCOhost). These databases were selected because they are among the main sources of biomedical information to which we had access. Natural language terms were combined with controlled vocabulary from the thesaurus of each database (MeSH, Emtree and DeCS), seeking to balance the sensitivity and specificity of the searches. No time restriction was applied. Searches were carried out up to the end of 2017. Regarding the question related to treatment optimisation, the 2011 GUPCAR guidelines were used as the reference to establish the time limit for the search; that is, the search started from the start of 2011.

Initially, all the search strategies were designed to retrieve only primary studies from the aforementioned databases; however, when this strategy yielded few or insignificant results, they were supplemented by a manual search of the reference lists in the key documents selected for the review. References proposed by researchers or reviewers consulted and new papers identified in Really Simple Syndication (RSS) feeds were also included. In these ways, studies have also been included that were published in 2018, later than the cut-off date used in the initial search. Searches were restricted to studies in humans published in English, French or Spanish.

The references retrieved were managed using EndNote x7 Reference Manager. The search strategy for the various different databases is explained in the methodological appendix on the SER website. Based on this search strategy, a total of 13,553 publications were identified and their titles and abstracts were reviewed, to select those which might provide answers to the clinical questions posed. From this, 867 papers were selected to be read in full, and among these, 124 original papers and reviews met the inclusion criteria.

Regarding the "Patients' perspective" chapter, we deemed it appropriate to carry out a systematic review of scientific studies of the experience of patients with RA. We used the Setting, Perspective, Intervention, Comparison and Evaluation framework and, as well as the aforementioned sources of information, we consulted the CINAHL database. The search identified 604 publications, among which there were 79 original papers that met the inclusion criteria.

Study inclusion criteria

Studies were included if they had the characteristics described below:

- **Study population:** adults diagnosed with RA.
- **Intervention:** new diagnostic criteria, early treatment, DMARDs, biological therapy, multidisciplinary management involving pulmonologists, cardiologists, family physicians and rheumatologists, health education programmes, treatment discontinuation.
- **Outcome variables:** efficacy in reducing disease activity and structural damage, measured with the usual clinical parameters; functional capacity; quality of life; drug levels; infection; survival; mortality, recurrence, adherence, satisfaction and self-care capacity.
- **Diseño de estudios:** meta-analyses and systematic reviews of randomised controlled trials (RCTs), double-blind phase III and IV RCTs, and observational and descriptive studies with an ideal minimum duration of 6 months and sample size of 50 patients.

Exclusion criteria

The following were excluded: studies in children, adolescents and pregnant women; studies not suited to the PICO framework, in terms of the patient sample, intervention, comparison group(s), outcome(s) or study design; and abstracts, posters, narrative reviews, letters, editorials and any type of unpublished study.

Assessment of study quality

Studies likely to be relevant were selected by applying the aforementioned inclusion and exclusion criteria. Critical reading was performed using the critical appraisal sheets of the Scottish Intercollegiate Guidelines Network (SIGN) and the Osteba critical appraisal tools[9]. After this, the internal and external validity of the studies was assessed. Selected studies were used to construct evidence tables con-

taining the key data, concerning the study method, results and quality. The modified SIGN system was used to assess the level of evidence[10].

Drafting of the recommendations

After the critical reading, the recommendations were drafted based on formal assessment or considered judgement, having summarised the evidence relevant to each of the clinical questions[10]. The following were also taken into account: the quality, quantity and consistency of the scientific evidence and the generalizability of results, as well as their applicability and their clinical impact. The modified SIGN system was also used to grade the strength of the recommendations[10]. Any recommendations that were controversial or lacked evidence were agreed by consensus in a meeting of the GDG.

Preparation of patient information

As well as updating the evidence on treatments for RA, the goals set for these CPGs included the addition of the patients' perspective.

First, we tackled the task of gathering information on the view of patients with RA of their own condition. Various individuals with RA participated voluntarily in qualitative research, using discussion group techniques, to recount their experience and describe their concerns.

Subsequently, following a structure developed by the guideline coordinators based on the recommendations in the complete guidelines and the qualitative information, agreement was reached on a template for the patient version. This information was written in language and formatted in a style tailored to the target audience and covers topics related to the disease which might be most useful for them. For developing this patient-focused material, a specific working subgroup was created, including professionals and patients from the GDG.

External review and publication of the final document

Having completed the aforementioned tasks, an advanced draft of the CPGs was produced and then reviewed by the GDG. Each section was analysed and changes considered necessary, from a comprehensive perspective, were proposed.

After this, the guidelines were externally reviewed by professionals selected for their knowledge of this condition and guideline development methods. The pur-

pose of this step was to increase the external validity of the document and ensure the accuracy of the recommendations.

Public scrutiny

The draft of the complete version of these CPGs passed through a process of public scrutiny by the members of the SER and stakeholders (pharmaceutical industry, other scientific societies and patient´s associations). It was made available on the website of the SER for a period of 17 days, together with a questionnaire to collect comments, seeking to gather data on people's opinion and scientific assessment of the guidelines' methods and/or recommendations. Detailed information concerning this process is provided in an appendix on the SER website: www.ser.es, together with the guidelines themselves in the Clinical Practice Guidelines section (under Research).

Scientific societies and other organisations

The organisations involved in the development of this guideline, represented by members of the GDG, were various scientific societies, the SER, the Spanish Society of Cardiology (SEC), the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), and the Spanish Society of Family and Community Medicine (SemFYC), and also a Spanish national coordinator of associations for patients with arthritis and their families (ConArtritis).

How to use the CPGs

These CPGs are organised into chapters. The chapters concerning PICO format questions contain a statement of the question, a table summarising the evidence and an evaluation of the overall quality of the studies included, as well as box containing a statement of the recommendations and their strength, a brief introduction to the question, the amount of evidence and its consistency across studies, applicability and relevance in our setting.

4. Disease burden of RA in Spain

This section presents the main results of the most recently available estimate concerning the burden of RA in Spain, together with changes therein since 1990. First, we briefly explain the key concepts related to this type of health measure.

Burden of disease indicators. The Global Burden of Disease Study

In countries with a very high life expectancy and undergoing demographic and epidemiological transitions, such as Spain, the traditional mortality measures are insufficient to reflect the health status of the population. A great deal of the observed improvement in survival is achieved by exchanging avoidable deaths for a higher prevalence of people with disability and poor health. Since more years of life does not always mean a better quality of life and a lower prevalence of disease, indicators that include mortal and non-mortal consequences are better for describing the real impact of health problems at the population level. This is especially relevant in diseases which, given their characteristics, seldom lead to death but may have widespread non-lethal effects in the population and/or are very severe for some individuals, such as is the case of diseases involving bone, joints and connective tissue.

Burden of disease studies specifically attempt to gather and synthesise data on these two types of impact of diseases and injuries. Their objective is to estimate and synthesise, in a single indicator, the impact not only in terms of mortality (as do mortality indicators) but also of disability and poor health due to various causes. This allows us to reconsider and appropriately measure the effects on population health of diseases and disorders that, since they do not appear in the statistics as the main cause of death, are not well captured by usual health indicators based on mortality. The overall idea of what burden of disease studies seek to measure has been dealt with in more depth in various different studies[11-14].

The indicator typically used in burden of disease studies is so-called disability-adjusted life years (DALYs). This indicator combines a measure quantifying premature death (years of life lost, YLL) and a measure quantifying health losses (years lived with disability or poor health, YLD). Both are calculated for each age, sex and cause (of death or disease).

The information on the estimated burden of RA and all rheumatic diseases in Spain presented in this document are taken from the 2016 Global Burden of Di-

sease Study (GBD 2016), recently published in The Lancet*, which provides information regarding the methods used and complete results[15-17]. This study also reports retrospective data since 1990, and these have also been used in this section.

The Global Burden of Disease Study includes all the demographic and epidemiological data available in each country in order to obtain the best possible image of the impact of each disease in the population. It uses the national death registers, both exhaustive and non-exhaustive, of all the countries that have one and other sources of information regarding mortality if such registers do not exist (for example, verbal autopsies). Regarding the information on the non-lethal consequences of diseases and injuries, it uses data from registers (primary and hospital care) as well as information from national health and disability surveys and from the so-called demographic and health surveys carried out by countries with no reliable registers. It also processes evidence regarding the incidence, prevalence, stage, severity and sequelae reported in the scientific literature for each disease and injury type. Hundreds of technicians and experts from all over the world participate in this enormous task.

Burden of RA in Spain

Rheumatic diseases (ICD-10 Chapter XIII) represent a significant health problem worldwide. According to GBD 2016[15-17], they account for almost 6% of the total global burden of disease, being associated with more than 140 million DALYs. In Western Europe overall and Spain in particular, they are relatively more important, given that the 13 and 1.2 million DALYs estimated for Western Europe and Spain respectively represent 11.4% and 11.1% of the total burden of disease in these areas in 2016.

RA is a separate subcategory within diseases of the musculoskeletal system and connective tissue (which appear in GBD 2016 as "Musculoskeletal disorders"), which are part of a larger group of non-communicable diseases. In GBD 2016, the AR subcategory includes the following ICD-10 codes:

- **M05-M06.9, M08-M08.9** for mortality
- **M05-M06.9** for disability and morbidity

RA has a greater relative impact on health in the Spanish population than that observed in the European and world populations overall. Specifically, it was associated with 61,506 DALYs in 2016, which represents 0.6% of the total burden of disease

* The complete results of the GBD 2016 can be consulted and downloaded from the Institute of Health Metrics and Evaluation website: https://vizhub.healthdata.org/gbd-compare/

in Spain (compared to 0.5% in Western Europe and 0.2% globally). It accounts for 5% of the total burden of rheumatic diseases in Spain (4.4% of the total burden of disease in Western Europe and 4% globally).

Table 1. Disability-adjusted life years for all causes, rheumatic diseases and rheumatoid arthritis globally, in Western Europe and in Spain in 2016

	Globally	Western Europe	Spain
All causes	2,391,258,033	112,836,724	11,137,595
Rheumatoid disease	140,030,556	12,825,046	1,231,456
Rheumatoid arthritis	5,563,425	558,325	61,506

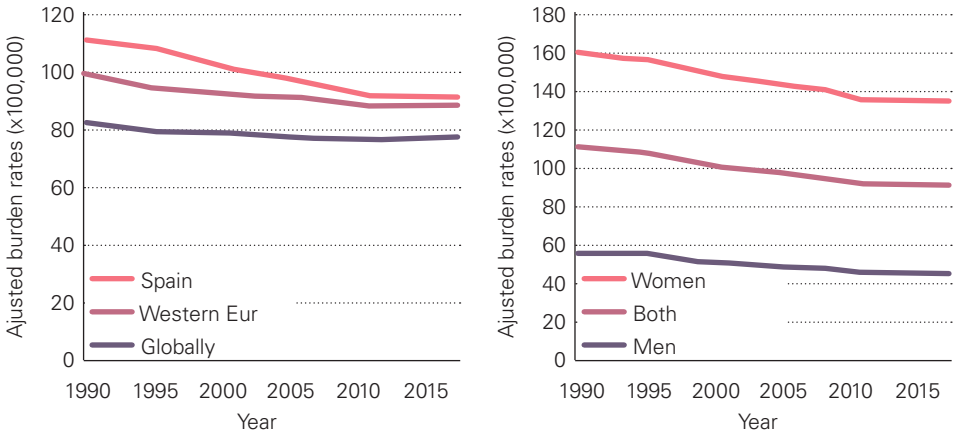
Source: Produced in-house from GBD 2016 data.

Disability-adjusted life years tend to be expressed in absolute terms, measured in life years. Nonetheless, it is advisable to express the indicator in relative terms, taking into account the size of the population (gross rates) and, above all, adjusting it for age in order to avoid the confounding effect caused by the different levels of ageing across populations, which as it is well known, directly affects the measurement of the impact of diseases and causes of death. This is achieved with the so-called adjusted or standardised rates.

The adjusted burden rates for RA in 2016 are higher in Spain (92.0 per 100,000 people) than in Western Europe (89.6) and globally (78.0). They have decreased over time, with a greater improvement in Spain than in Europe, compared to much more stable rates observed globally.

By sex, the adjusted burden rates for RA are 3-fold higher in women (135.2 vs 46.7 per 100,000 men, in 2016). These rates have significantly decreased in the period 1990-2016.

Figure 1. Disability-adjusted life years for rheumatoid arthritis globally, in Western Europe and in Spain, and adjusted for sex. Period 1990-2016. Adjusted rates (per 100,000 people)



	Globally	Western Eur	Spain
1990	82.8	100.7	112.1
1995	80.2	95.7	108.9
2000	80.0	93.6	102.1
2005	77.8	92.1	98.2
2010	77.6	89.4	93.0
2016	78.0	89.6	92.0

Spain	Both	Women	Men
1990	112.1	160.8	56.9
1995	108.9	156.4	55.9
2000	102.1	148.3	51.7
2005	98.2	143.6	49.7
2010	93.0	136.4	47.4
2016	92.0	135.2	46.7

Source: Produced in-house from GBD 2016 data.

Rheumatic diseases have very different weights depending on which of the components of disease burden are considered: only 0.3% of deaths and 0.2% of the YLLs in Spain in 2016 are attributable to these conditions because they cause few deaths, and in general, develop at advanced ages, and hence, the measure of premature death has relatively little weight. In contrast, more than 1 in 5 YLDs (21.3%) in 2016 were caused by rheumatologic diseases, this indicating an enormous negative impact on the health of people in Spain.

The relative weight of RA among all rheumatic diseases has decreased somewhat over time in Spain (from 5.4% in 2000 to 5.0% in 2016). Although this condition is not cited on many death certificates, it should be noted that a third of deaths allocated to ICD 10 Chapter XIII (33.5%) are due to RA, while the non-lethal component accounts for just 4.7% of the total burden of rheumatic diseases.

Table 2. Burden of rheumatic diseases and rheumatoid arthritis in Spain. Deaths, years of life lost, years lived with disability and disability-adjusted life years. Period 2000-2016

Spain. Rheumatic diseases

	Deaths	YLL	YLD	DALYS
2000	1,029	14,322	982,169	996,491
2005	873	12,199	1,047,631	1,059,831
2010	916	12,008	1,135,851	1,147,859
2016	1,064	12,775	1,218,680	1,231,456

Spain. Rheumatoid arthritis

	Deaths	YLL	YLD	DALYS
2000	364	5,622	48,274	53,896
2005	293	4,519	52,086	56,604
2010	289	4,258	54,141	58,398
2016	303	4,276	57,231	61,506

Spain. Rheumatic diseases
(% over total causes)

	Deaths	YLL	YLD	DALYS
2000	0.3%	0.2%	20.5%	9.4%
2005	0.2%	0.2%	20.2%	9.7%
2010	0.2%	0.2%	20.3%	10.3%
2016	0.3%	0.2%	21.3%	11.1%

Spain. Rheumatoid arthritis
(% over Rheumatic diseases)

	Deaths	YLL	YLD	DALYS
2000	35.4%	39.3%	4.9%	5.4%
2005	33.6%	37.0%	5.0%	5.3%
2010	31.6%	35.5%	4.8%	5.1%
2016	28.5%	33.5%	4.7%	5.0%

Source: Produced in-house from GBD 2016 data.

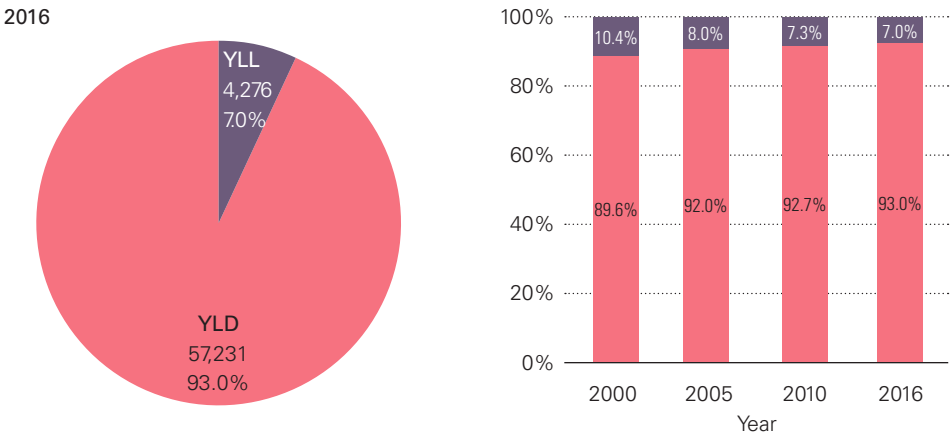
Figure 2. Burden of rheumatoid arthritis in Spain. Deaths, years of life lost, years lived with disability and disability-adjusted life years. Period 2000-2016

Source: Produced in-house from GBD 2016 data.

The number of deaths and YLLs due to RA decreased from 2000 to 2005 and has remained stable since then. In contrast, the impact of disability and poor health (YLDs) has significantly increased, and this has led to a clear upward trend in the overall burden of disease in DALYs. This is fully compatible with the fact that the adjusted rate has decreased: the steady improvement in the life expectancy of the Spanish population and longer survival of people with RA - most of whom die from other causes - leads the years lived with this condition (YLDs) to progressively increase over time and, in turn, to an increase in the overall burden of disease.

Regarding the total burden of RA (61,506 DALYs in 2016), the mortality component (4,276 YLLs, 7%) has a much smaller relative weight than the disability and poor health component (57,231 YLDs, 93%). Further, its weight has tended to decrease over time, and hence, the relative weight of disability in the measurement of the burden of RA has progressively increased.

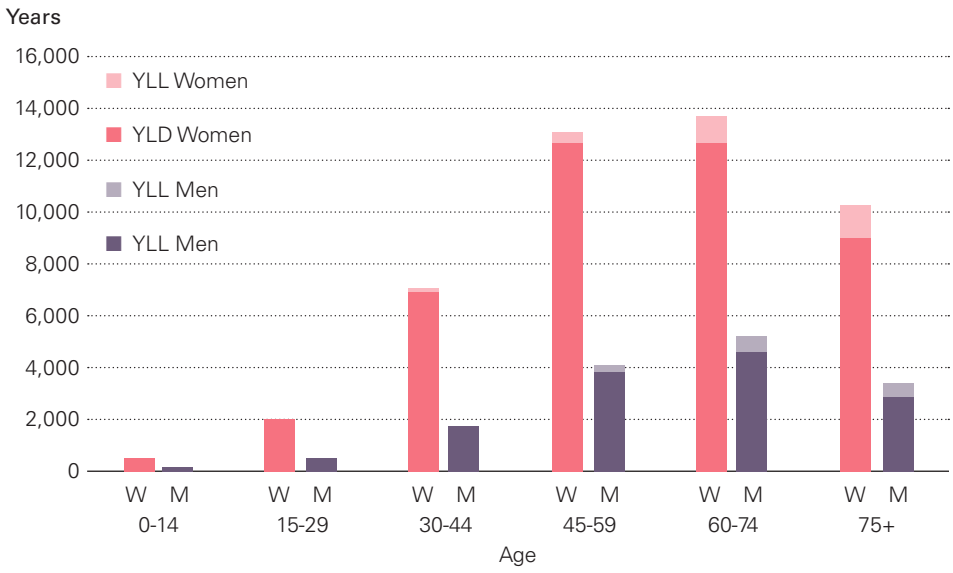
Figure 3. Burden of rheumatoid arthritis in Spain. Proportional distribution of the years of life lost due to death and years of life with disability. Year 2016 and period 2000-2016



Source: Produced in-house from GBD 2016 data.

The burden of RA is not evenly distributed as a function of sex and age. In a given age, it is higher in women than in men, up to 3-fold higher for all ages combined and up to 4-fold higher in the age range between 15 and 44 years old. The burden of RA is greatest among middle-aged (≥45 years old) and elderly people. The modal age group is 60-74 years old. Nonetheless, we should note that the burden of the disease in young women (30-44 years) is considerable, higher than that in men in any age group. The mortality component (YLLs) is negligible in those <45 years of age and is still not very notable at older ages.

Figure 4. Burden of rheumatoid arthritis in Spain. Years of life lost and years lived with disability by sex and age group. Year 2016



Source: Produced in-house from GBD 2016 data.

Table 3. Burden of rheumatoid arthritis in Spain. Years of life lost, years lived with disability and disability-adjusted life years by sex and age group. Year 2016. Years and rates per 100,000 people

Years	Women			Men		
Age	YLD	YLL	DALYS	YLD	YLL	DALYS
0-14	319	12	331	88	11	68
15-29	1,950	26	1,976	485	17	503
30-44	6,884	102	6,986	1,748	49	1,797
45-59	12,710	411	13,121	3,910	232	4,141
60-74	12,642	1,083	13,725	4,617	555	5,172
75+	9,009	1,275	10,284	2,869	503	3,372
Total	43,514	2,910	46,423	13,717	1,366	15,083

Rates (x100 mil)	Women			Men		
Age	YLD	YLL	DALYS	YLD	YLL	DALYS
0-14	9.3	0.3	9.7	2.4	0.3	2.7
15-29	58.1	0.8	58.9	14.0	0.5	14.5
30-44	127.9	1.9	129.8	31.8	0.9	32.7
45-59	245.0	7.9	253.0	75.7	4.5	80.2
60-74	346.0	29.6	375.7	138.7	16.7	155.3
75+	338.1	47.9	386.0	166.9	29.2	196.1
Total	**183.8**	**12.3**	**196.1**	**60.1**	**6.0**	**66.1**

Source: Produced in-house from GBD 2016 data.

In conclusion, the burden of RA is higher in Spain than in Europe as a whole and globally, and much higher in women than in men, and despite a downward trend in burden rates, the number of DALYs is increasing considerably, above all due to population ageing. While it is not commonly the main cause of death, the impact of RA on health is associated with non-lethal effects, measured as the amount of time lived with this disease (YLDs). We should take into account that, given that it is a chronic condition, cases developing at an early age make a large contribution to the total burden, and that the increase in life expectancy, thanks to the decrease in deaths due to other causes, means that a growing number of people have to live with RA for longer and longer. This represents a major future health challenge for the Spanish population.

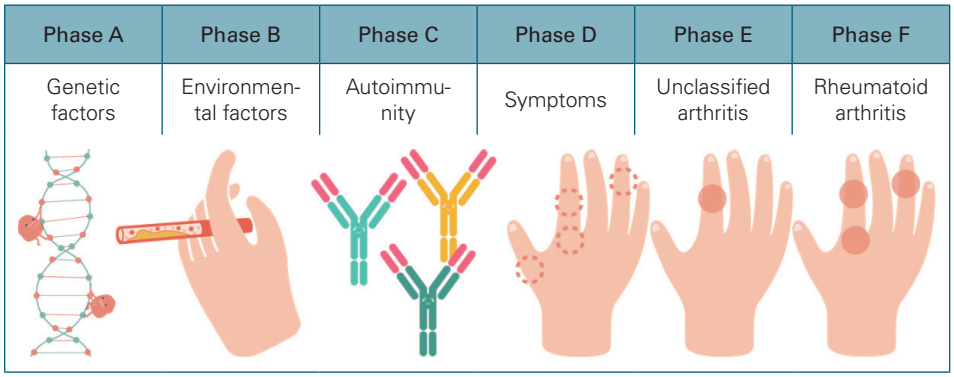
Various studies report specific analysis of the burden of RA and rheumatic diseases from the results of the global estimates for 2010, 2013 and 2015[18-20], though not yet for 2016, for which the data have only recently become available.

5. Pathogenesis. The development of RA

Currently, it is accepted that there are several phases in the development of RA (Figure 1) that the European League Against Rheumatism (EULAR) study group for risk factors for RA attempted to define and classify in 2012[21]. The report published defines the following phases in the development of the disease in a patient:

- Phase A: genetic risk factors for RA
- Phase B: environmental risk factors for RA
- Phase C: systemic autoimmunity associated with RA
- Phase D: symptoms, without clinical arthritis
- Phase E: unclassified or undifferentiated arthritis, when arthritis is detected, but there is insufficient evidence to confirm the diagnosis of RA
- Phase F: RA

Figure 1. Development phases of rheumatoid arthritis.



Source: Produced in-house.

The first three phases are preclinical stages of the disease; in the fourth phase, there are symptoms, but no inflammation is detected clinically; in the fifth (Phase E), there is evidence of inflammation; and in the sixth (Phase F), RA can be diagnosed.

Regarding the role of genetics, twin studies have suggested that, among all risk factors identified to date, genetic variation is important in the development of RA[22]. Most of the genetic associations are found in patients with the disease who are anti-citrullinated protein antibody (ACPA) positive, and such associations are weaker or lacking in ACPA-negative patients. The genetic factor most frequently associated with the development of RA and which accounts for around 30% of the risk is the locus that codes for human leukocyte antigen (HLA) class II molecules, specifically the shared epitope, the sequence of amino acids in positions

70-74 of the third allelic hypervariable region of the DRB1 chain present in various HLA-DRB1 molecules. This association is particularly strong in ACPA-positive individuals. Other non-HLA genes, including PTPN22 or STAT4, have also been associated with a susceptibility to develop RA.

Regarding environmental factors, smoking is the environmental risk factor most consistently associated with the development of RA. As with genetic risk factors, this association is stronger in ACPA-positive patients and it increases when tobacco exposure is combined with the predisposing genetic factors in the same individual[23]. Several other environmental factors have also been associated with the development of RA and these include periodontal disease, occupational silica exposure, consumption of salt and alcohol (the latter having a protective effect) and hormonal levels[24].

The presence of both rheumatoid factor (RF) and ACPA has been detected some years before the development of RA. The risk of developing RA is higher in ACPA-positive than RF-positive individuals and higher the longer the time horizon[25, 26].

A further step in the development of the disease is the onset of signs and symptoms with no clinically detectable inflammation. Various articles have been published analysing the progression towards RA in patients with systemic autoimmunity (Phase C) or with symptoms, but no clinical inflammation (phase D). At this point, the characteristics of the symptoms are very important. One study explored progression towards arthritis in patients with joint pain, this occurring in 20% of cases when the definition of the symptoms was limited to non-trauma joint pain, without more detailed criteria, and up to 60% of cases when the symptoms were defined as inflammatory joint pain with symmetric involvement of small joints in hands and feet[27]. Seeking to standardise patient care in phase D of the disease, a description of the clinical characteristics of patients with joint pain associated with the highest risk of developing RA has recently been published[28].

Continuing along the progression of the pathological process, we have patients with clinical inflammation who cannot be diagnosed with RA, at least not yet. This phase is what we call undifferentiated arthritis. It has also been widely studied, especially concerning predictors of the onset of RA, such factors having been reviewed in the literature[29].

Finally, after more or less these phases, based on criteria whose strengths and weaknesses are discussed in another chapter, we are able to establish a diagnosis of RA and the process has reached the disease phase[30]. Understanding the phases of the pathogenesis of the disease should facilitate early treatment, which has

shown to be one of the most important factors in the long term[31] in the context of the concept of a window of opportunity[32]. Advancing our knowledge of the phases in which the disease has not yet produced clinical manifestations raises the possibility of providing treatment before disease onset, which might enable disease prevention, understood as preventing its onset in high-risk individuals.

The treatment of patients in this preclinical phase requires clarifying some controversial issues such as what type of treatment is appropriate, how we identify individuals who are going to develop RA and how we decide which patients to treat. In relation to this, persistent disease has been associated with the following: being female, smoking, a long duration of symptoms, a large number of painful or inflamed joints, symptoms affecting the hands, high levels of acute phase reactants, the presence of RF and ACPA, and meeting the 1987 American College of Rheumatology (ACR) criteria or radiological damage. Nonetheless, given that none of these factors is sufficient in itself, using a combination of predictors is likely to be the best approach to predicting disease persistence.

In any case and despite some outstanding issues, advances in the knowledge and management of increasingly early phases of RA, together with the establishment of strategies for the treatment and clinical follow-up of patients and expansion of the therapeutic arsenal in recent years, have led to a revolution in our conception of the disease and its prognosis.

6. Classification/Diagnosis

6.1. New criteria (2010 ACR/EULAR classification criteria)

Clinical question 1

In patients with early rheumatoid arthritis, what is the clinical utility of the new classification criteria published in 2010 compared to the 1997 criteria?

Summary of the evidence

In patients with early rheumatoid arthritis, the 2010 ACR/EULAR criteria show higher sensitivity but lower specificity than the 1987 ARA criteria, when a clinical experts' opinion or requiring DMARD therapy* are used as the gold standard for the diagnosis[33-41].	1+, 2+, 2-
In patients with early rheumatoid arthritis, it has been suggested that the 2010 ACR/EULAR criteria may be more sensitive and less specific than the 1987 ARA criteria when persistent arthritis is used as the gold standard[40, 42].	2+, 2-
The 2010 ACR/EULAR criteria were found to be less sensitive than the 1987 ARA criteria for the diagnosis of patients with seronegative rheumatoid arthritis[39, 43].	2-
In patients with early arthritis, use of the 2010 ACR/EULAR criteria would allow an earlier diagnosis of rheumatoid arthritis than the 1987 ARA criteria[33, 37, 41, 43, 44].	1+, 2+, 2-

* Studies that use requiring DMARD therapy as a gold standard set varying follow-up periods

Recommendations

In patients with seropositive arthritis, the recommendation is to use the 2010 ACR/EULAR classification criteria to support the clinical impression of the physician **(Grade B recommendation)**.

In patients with seronegative arthritis, the use of these classification criteria is not recommended and the diagnosis should depend on the clinical impression of the rheumatologist **(Grade √ recommendation)**.

Research on patients with RA requires an appropriate and reliable classification of the disease. In recent decades, there has been an emphasis on early treatment of RA, since numerous studies have demonstrated that achieving a state of remission or low disease activity early is beneficial for the long-term prognosis of the disease. For this, the identification of early disease is key to be able to start early treatment. In relation to this, the 1987 ACR criteria[45] are not suitable for the diagnosis of RA in

early stages of the disease. These criteria were developed in order to define homogeneous groups of patients with the disease for research purposes and were based on patients with a mean disease duration of 7 years. In order to identify patients with early RA for clinical trials and other studies, a joint working group from the ACR and EULAR developed new classification criteria for RA, published in 2010[30]. The primary objective of these criteria was to increase the sensitivity and specificity in the diagnosis of RA in patients at earlier stages of the disease, the population in which they have been developed and validated. The new criteria differ from the old ones in various respects. In the new classification system, there is no need for the presence of joint damage (indeed, these criteria should not be used if there are radiological findings of RA), and nor does it consider the presence of rheumatoid nodules, given that these are signs of RA having progressed and the current goal of treatment is to avoid these consequences. Morning stiffness was removed given its lack of specificity, while acute phase reactant and antibody levels were included in the new classification. Further, there was a change in the evaluation of joint symptoms, although there is still a focus on small joints. The new 2010 ACR/EULAR criteria should only be applied in patients with swelling in at least one joint and for whom there is no alternative diagnosis that better explains the symptoms. In candidate patients, the assessment of joint involvement, serology (autoantibodies), acute phase reactants and symptom duration yields a score between 0 and 10. Patients with a score ≥ 6 are classified as having RA.

Since the publication of the 2010 ACR/EULAR criteria, numerous studies have compared their diagnostic performance with that of the 1987 ACR criteria. For this, various different gold standards for the diagnosis of RA have been used, including the opinion of experts, the use of methotrexate (MTX) or any other DMARD, persistent arthritis or the presence of erosions.

A secondary analysis of the SAVE study[33] compared the diagnostic performance of the two sets of criteria in 303 patients with early arthritis taking as the gold standard expert diagnosis or starting DMARD treatment by 52 weeks of follow-up. The 2010 criteria had a greater sensitivity than those of 1987 for both starting DMARDs (80% vs 55%) and expert diagnosis (85% vs 65%); however, they had a lower specificity for both gold standards (61% vs 76% for starting DMARDs treatment; 64% vs 80% for expert diagnosis) (Level of evidence 1+). The prospective study of Berglin and Dahlqvist[34] in 313 patients with a less than 1-year history of arthritis obtained similar results using the same gold standards, also after 1 year of follow-up (Level of evidence 2+). In the study by Reneses *et al.*[35], the two sets of criteria were compared in 201 patients with a less than 1-year history of arthritis considering three gold standards: use of MTX, use of another DMARD and expert diagnosis by 1 year

of follow-up. The 2010 criteria had a higher sensitivity for all three gold standards and had a greater specificity for the use of MTX. Overall, the diagnostic accuracy of the 2010 criteria was higher than that of the 1987 criteria (77% vs 59%); 75% vs 58%; and 84% vs 75% respectively) (Level of evidence 2+). Zhao *et al.*[40] comparing the performance of the two sets of criteria considering the use of MTX after 1 year of follow-up and persistent disease as gold standards in 414 patients found that the 2010 criteria have a greater sensitivity than those of 1987 with no loss in specificity (Level of evidence 2-). Another study by the same authors[46] found that the 2010 criteria had a much higher sensitivity (83% vs 38%) but lower specificity (55% vs 99%) than those of 1987. Britsemmer *et al.*[36] also found the 2010 criteria had a higher sensitivity and lower specificity than those of 1987 for expert diagnosis and use of MTX after 1 year of follow-up, in 455 patients with a less than 2-year history of arthritis. In contrast, when joint erosion after 3 years was used as the reference, both sets of criteria were found to be highly sensitive but have a low specificity (2010 criteria: sensitivity 91%, specificity 21%); 1987 criteria: sensitivity 97%, specificity 17%) (Level of evidence 2+). In relation to this, a study by Mäkinen *et al.*[47] that used joint erosion after 10 years of follow-up as the gold standard, the authors also concluded that neither of the sets of criteria is good for predicting joint erosion (Level of evidence 2).

In two studies in which patients had a very short history of arthritis (less than 33[7] and 63[8] months since the start of symptoms), the 2010 criteria showed higher sensitivity and lower specificity in the classification of RA when use of DMARDs and clinical diagnosis were used as the references (Level of evidence 2+). A study with 2,258 patients carried out in the *Leiden Early Arthritis Clinic*[42] considered persistent arthritis, as well as the start of MTX or another DMARD, as the gold standards. Comparing the criteria led to similar results for the three reference diagnoses, and again, the 2010 criteria were found to have a higher sensitivity and lower specificity than those of 1987 in all the comparisons (Level of evidence 2+).

Other studies have not found significant differences between the two sets of criteria. A French cohort with 270 patients with a less than 1-year history of arthritis that used the combination of the clinical diagnosis of RA and the use of DMARDs after 2 years as the reference[48] did not find differences in diagnostic performance, similar areas under the curve being found for both sets of criteria. The same research group[49] compared the criteria again using the same cohort but considering the diagnosis of RA by a physician after 10 years of follow-up as the reference, and concluded that the two sets of criteria have a similar sensitivity but that the 2010 criteria have a higher specificity (Level of evidence 2-). A population-based study carried out in the *Nurses Health Study I and II cohorts*[50], which contained 128 wo-

men between 25 and 55 years of age, the authors concluded that both sets of criteria are suitable for diagnosing RA with no great differences between them. On the other hand, a short duration of symptoms was not used as an inclusion criterion, given its nature as a population-based cohort, and nor did the authors report the mean disease duration in the sample. Therefore, it is not possible to draw conclusions for populations with early arthritis (Level of evidence 2-).

Although, as mentioned above, several studies have endorsed a greater sensitivity and speed in diagnosis with the 2010 ACR/EULAR criteria, it has been shown that the sensitivity is notably lower in patients seronegative for RF and anti-cyclic citrullinated peptide (anti-CCP) antibodies[39, 43, 51]. The 2010 ACR/EULAR criteria fail to identify some seronegative patients who were identified using the 1987 ACR criteria[51]. In contrast, with the new 2010 ACR/EULAR criteria, it is possible to classify as having RA patients with few swollen joints, but who are RF positive and have a slightly elevated erythrocyte sedimentation rate (ESR), which may imply an overdiagnosis of RA in patients with self-limiting disease who would not have needed treatment with DMARDs[33, 37, 41, 43, 44, 52].

In summary, it has been shown that in patients with seropositive arthritis, the new 2010 ACR/EULAR are superior to the 1987 ACR criteria. In contrast, in patients with seronegative arthritis, the opinion of experts seems to be more useful than the new criteria.

6.2. Sources of delays in patient care

Delays in the start of treatment with the first DMARD after the onset of RA worsen the prognosis of the disease. It is currently accepted that the optimal treatment of RA requires early diagnosis and treatment with DMARDs, ideally within 12 weeks after the start of symptoms[53-58]. Unfortunately, the reality of rheumatologic care in Spain is that patients wait on average more than 6 months to receive their first treatment with DMARDs after starting to have symptoms, although it is difficult to accurately determine the date of onset of symptoms in cases that end up being diagnosed as RA[59]. According to the EMAR study, the delay between the start of the symptoms and the start of DMARDs has reduced in recent decades, although it is still far from ideal[60].

Although treatment delays have multiple underlying factors and are generalized in our social and cultural environment[61], one factor that is likely to be key in both diagnostic and treatment delays is the perception by patients that the process is not severe and that joint pain is a minor symptom for which they do not need to seek healthcare[62]. In brief, the factors that may potentially lead to these delays

are the time until patients consider they have a health problem until they seek an appointment with their general practitioner (GP), and until their GP refers them to a rheumatologist, as well as waiting lists in rheumatology departments and for tests, and delays in appointments for receiving results and starting treatment.

There are important delays in patient care not only at the time of diagnosis, but also when the treatment is being adjusted to achieve a state of remission, or at least, of low inflammatory activity. The treatment-to-target approach is currently generally accepted[54, 56, 63] and this type of strategy requires patients to be reviewed every 1 to 3 months while seeking remission.

Addressing each of these factors needs specific measures, some of which depend on the organisation of health systems, but others clearly involve health education for the general public. Regarding the specific measures to be implemented, experts agree on the following:

Delays until seeking an appointment with a GP

Raise awareness in the general population about the initial symptoms of RA, through campaigns in schools and colleges, if targeting young people, or in the media, if targeting the general population.

Delays until referral to a rheumatologist

Strengthen collaboration between primary care physicians and rheumatology departments through continuous medical education initiatives (compression tests of metacarpophalangeal and metatarsophalangeal joints; x-rays of hands and feet; requests for anti-citrullinated protein antibody and RF tests).

Waiting lists for specialists

Allocate appropriate human resources and systems for facilitating communication between primary care and rheumatology and for prioritising appointments. The use of tele-consultations, remote interprofessional consultations[64] and/or rheumatologist consultations in local health centres may also be useful.

Delays until appointments for receiving test results and starting treatment

Implement protocols in early arthritis units and agreements with imaging departments and laboratories for prioritising tests if RA is suspected.

Difficulties in monitoring treatment response every 1 to 3 months

Allocate appropriate human resources and facilitate self-management of prioritised successive appointments by rheumatology departments themselves. In rela-

tion to this, the intervals between appointments could be adapted in accordance with the healthcare quality standards of the SER and the Rheumatology Society of the Autonomous Region of Madrid (SORCOM)[65-67].

6.3. Primary care: the role of primary care in the detection and referral of patients with RA

The role of primary care in the early suspicion and detection of RA

In accordance with the numerous studies that recommend a systematic and well-planned approach for the proper and rapid suspicion and early diagnosis of RA, the role of the GPs is key in avoiding delays in the treatment of RA. The earlier adequate treatment is started, the greater the likelihood of controlling the inflammatory process and reducing structural damage; that is, the higher the chance of taking action within the window of opportunity for treatment. The diagnosis of RA in early stages of the disease is one of the cornerstones of disease control; hence, in the event of dealing with a case of possible recent-onset arthritis in primary care, experts recommend acting fast following a protocol[31, 32, 59, 61, 68-72].

Clinical assessment of a patient with suspected arthritis

In accordance with current written recommendations for the early diagnosis of RA, an initial assessment of a patient with recent-onset arthritis in primary care should be based on a thorough clinical history and a complete physical examination, together with a number of relevant tests[70-72].

The *clinical history* should cover both personal and family clinical history, including any history of smoking, as well as sociodemographic data, the history of the disease and any recent changes therein, and treatments given, both in the past and ongoing.

In the *physical examination*, as well as the usual examination by organs and systems, it is particularly important to carry out a detailed assessment of the musculoskeletal system and detect promptly any inflammatory patterns in the case of the involvement of few or several joints and whether there is also systemic involvement[28, 73-76].

Regarding *tests*, various different reviews and sets of recommendations advocate performing a blood test that includes a complete blood count, assessment of the ESR, RF level, ACPA status (whenever available), biochemical parameters, and liver and kidney function, and basic urianalysis[71-73, 77]. For the initial assessment of structural damage, X-rays should be taken of hands and feet. Imaging such as ultrasound and magnetic resonance imaging (MRI) scans would be indicated only

in certain selected cases in which there is a high level of suspicion but arthritis is not evident clinically[72, 78-83].

In patients with signs and symptoms suggesting early arthritis, various different studies have shown that assessment of RF levels and ACPA status, a complete blood test and imaging tests support the suspicion of RA[71, 72, 83].

Initial treatment and referral to a rheumatologist in patients with suspected early arthritis

Initial treatment: analgesics, nonsteroidal anti-inflammatory drugs and glucocorticoids

Various studies also conclude that, in the cases of suspected early arthritis, if an initial treatment in primary care is required, this should be aimed at controlling symptoms with analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs). Symptomatic treatment should be started in parallel with referral to a rheumatologist, to avoid delays in analysing the aetiology of such cases and be able to establish a definitive diagnosis as early as possible[31, 32, 68]. At this stage, oral glucocorticoids should be avoided or used at very low doses, of less than 7.5 mg/day, and for a limited period. In cases of suspected early arthritis, a glucocorticoid should only be prescribed by a rheumatologist and always in combination with a DMARD and on the basis of its effect[5].

Referral to a rheumatologist

GPs promptly referring cases of suspected early arthritis to a rheumatologist helps minimise delays in diagnosis and treatment, thereby making it possible to take advantage of the window of opportunity[31, 61, 68, 69]. Table 4 summarises the rheumatology referral criteria from the SERAP Project, developed by the SER in collaboration with primary care physicians, and the referral criteria for RA established by Emery[84]. Current recommendations advocate referral when at least one of the three symptoms listed (in the table) is present for at least 4 weeks, regardless of the suspected diagnosis; except cases of suspected septic arthritis, which should be referred immediately, without delay.

Table 4. Criteria for referral from primary care to a rheumatologist

Criteria for arthritis referral from the SERAP Project At least a 4-week history of any of the following:
1. Swelling of two or more joints 2. Pain on squeezing of metacarpophalangeal joints and/or carpal bones 3. Morning stiffness > 30 minutes
Specific criteria for referral for rheumatoid arthritis established by Emery
1. Three or more swollen joints 2. Metacarpophalangeal or metatarsophalangeal involvement (squeeze test positive) 3. Morning stiffness of ≥30 minutes

Interaction between primary care and rheumatology

Identification of early arthritis by GPs

The 2016 EULAR recommendations for the diagnosis, prognosis and classification of early arthritis are based on the systematic review of Hua *et al.*[72]. One of the objectives of the review was to assess which tools, if used by primary care physicians in patients with suspected early arthritis, might help to differentiate between inflammatory arthritis and other clinical conditions. Only two studies[85, 86] were found that described simple questionnaires with questions about pain, swelling and stiffness. Although both questionnaires were found to have a high sensitivity (94 and 86%) and specificity (93% and 93%), their usefulness is limited by the fact that they have only been applied to small samples and have yet to be validated[87, 88]. The systematic review concluded that there was insufficient evidence to be able to provide clear recommendations on this issue. Nonetheless, this same systematic review[72] emphasised the importance of early referral of patients with suspected early arthritis to a rheumatologist, ideally within the first 12 weeks after the start of symptoms, and confirmed that testing RF levels and especially ACPA status as well as identifying radiological changes can help to achieve an early diagnosis and improve the prognosis of patients with early arthritis.

Proposals for improving the referral process

In order that patients with suspected RA start treatment as early as possible, thereby delaying the impact of the disease and minimizing the damage due to its progression, in turn, improving patient quality of life and the prognosis of the disease, the consensus among experts is to carry out the following:

a. Develop and reach a consensus with primary care physicians on protocols for identifying patients with early arthritis.

b. Establish referral pathways, in accordance with the protocols defined in each autonomous or healthcare region in Spain, which would result in real reductions in the current delays in referral and in improvements in the management of cases of suspected early arthritis, while committing to conduct regular reviews of their efficacy, the extent to which they are used and whether they are appropriate or need improvement.

The ability of primary care physicians to diagnose RA would be strengthened if first there were to be a direct and smooth relationship with rheumatology departments, and with early arthritis units (where they exist), or with an assigned rheumatologist, especially if the referral protocols are developed between both parties with well-defined criteria.

Communication and coordination

Finally, experts also consider that there is a series of strategies that could facilitate and improve the level of communication and interaction between primary care and rheumatology including:

- Promoting and strengthening the role of the assigned rheumatologist, already established in some autonomous regions
- Holding regular joint meetings, face-to-face or remotely, to discuss or present cases and the latest innovations in diagnosis and treatment, considering what is feasible and the resources available
- Making available contact telephone numbers, email addresses, or fax numbers (for both settings) or systems for remote interprofessional consultations, to facilitate communication in cases that must not be delayed, such as patients with suspected early arthritis, and to address one-off problems potentially avoiding unnecessary appointments
- Improving the quality of interprofessional consultation reports concerning patients referred to rheumatology departments, in terms of the provision of appropriate information both in the referral by the primary care physician and in the response by the rheumatologist. If all the information available were provided, this would facilitate the prompt diagnosis of patients with suspected RA and their follow-up and monitoring by their GP, until their next specialist appointment

Coordination requires the development of new working models, with a focus on working as a network or the "management of shared care", which would allow an appropriate level of communication and development of relationships, thereby facilitating the exchange of information, as well as interaction and participation in the decision-making process.

7. Treatment

7.1. General principles of the treatment

The goals of RA treatment should be to control all the manifestations and consequences of the disease, including inflammation, structural sequelae and associated comorbidities. To achieve these goals, the therapeutic approach has undergone major changes since the beginning of the 21st century. The traditional approach was based on a somewhat late introduction of DMARDs due to excessive concern about their adverse effects, and a tendency to settle with a level of improvement known to be achievable, motivated by a perception that the existing drugs were limited in terms of number and efficacy. This mindset has changed significantly, both in terms of the development of a new treatment strategy and the availability of new, more effective drugs. These advances have resulted in the development of new recommendations for a better therapeutic approach to RA[54, 56], some of the key aspects of which are outlined below.

Treatment strategy in RA

Regarding treatment strategy, there are two key factors: the importance of early treatment with DMARDs and the need to be more ambitious in the treatment goal, seeking to achieve disease remission as soon as possible and performing regular assessments. This strategy of treating with a goal is also called treat-to-target (T2T).

Various studies have convincingly demonstrated the importance of early treatment with DMARDs[89-91]. This is also related to the concept of a "window of opportunity", defined as the period of time in which the disease is most susceptible to treatment. In fact, very early treatment is associated with a higher probability of achieving disease remission, even treatment-free remission, and moreover, it has been found, though with less certainty, that the approximate limit in this window of opportunity is 15 to 20 weeks after the appearance of symptoms[68]. Extending this idea, it has been recommended that early treatment with DMARDs is started even in some patients with undifferentiated arthritis when progression to RA is strongly suspected[71]. In line with this, the classification criteria for RA have been changed seeking to make them more applicable for patients with earlier RA[30].

The key elements in a T2T strategy are to reach a treatment target, preferably sustained remission or, if not, a state of low disease activity, using a validated tool for disease monitoring and with regular check-ups until this target is reached[63]. The importance of achieving remission is reflected in the fact that patients in clini-

cal remission show no structural or functional progression[92, 93]. A key question is what is the best way to measure disease remission. In relation to this, we prefer the use of so-called Boolean, Simple Disease Activity Index (SDAI) or Clinical Disease Activity Index (CDAI) remission rather than that based on 28-joint Disease Activity Score (DAS28), since this index may indicate remission in patients who have not really reached this state[94].

Another debated issue is the role of techniques for assessing subclinical synovitis such as ultrasound and MRI. Despite the greater sensitivity of these techniques, they may be not necessary for defining remission given the good correlation between clinical and imaging remission[95, 96]. Further, recent studies have found that strategies based on imaging remission were not superior to considering the clinical remission of RA[97, 98]. This in no way rules out the use of ultrasound or MRI in certain situations in the management of patients with RA.

Novel drugs

The progress in our understanding of the pathophysiological mechanisms of RA and the development of molecular engineering have given rise to so-called biological therapies, based on complex molecules that inhibit targets that are key in the pathogenesis of the disease. More recently small molecules have been developed, for intracellular targets (targeted therapies) that widen the treatment options, as well as increasing the complexity of strategies for the management of RA. These novel drugs are analysed in another section of these guidelines.

Final considerations

We should not overlook the importance of a series of general principles in the management of RA. The treatment should be based on a joint decision between rheumatologists and patients, in which an adequate explanation of the disease, the treatment options and the treatment targets play an essential role[54, 56]. Given the complexity of RA and the numerous treatments available, rheumatologists are the specialists who should be responsible for managing the disease[99, 100], though patient care should be delivered through a multidisciplinary approach that involves nurses and other specialists. Finally, recommendations such as smoking cessation, achieving a good level of physical activity, avoiding obesity and controlling periodontal disease should be part of the overall therapeutic approach for RA.

7.2. Drugs used in RA

Non-steroidal anti-inflammatory drugs

NSAIDs are a family of compounds with a very varied chemical structure characterised by interfering in the production of eicosanoids and having moderate analgesic and anti-inflammatory effects. There are currently more than 20 different NSAIDs available for use in humans in numerous pharmaceutical formulations.

Most NSAIDs used clinically inhibit, to different extents, the two isoforms of cyclooxygenase (COX): COX-1 and COX-2. There is no evidence that combinations of NSAIDs are more effective than any of them alone and no randomised clinical trial with a sufficiently large sample size has compared the efficacy of different NSAIDs.

The main adverse effects of NSAIDs are: 1) gastrointestinal, with nausea, pyrosis, dyspepsia, gastritis, stomach pain, diarrhoea or constipation, and in more severe cases, although infrequent, gastroduodenal ulcers and gastrointestinal bleeding and perforation[101]; 2) renal, involving the retention of sodium and water, this being responsible for the development of distal oedema, but also for triggering or worsening heart failure or hypertension; or 3) cardiovascular, with a higher incidence of cardiovascular events[102], a drug class effect that seems to be most clear with the long-term use of COX-2 inhibitors.

In rheumatology, NSAIDs are mainly used for their analgesic and anti-inflammatory effects (Table 5). Recommendations for their use are as follows: 1) The decision to use a traditional NSAID or COX-2 inhibitor should mainly depend on patient gastrointestinal risk factors, and proton pump inhibitors (PPIs) should be prescribed together with NSAIDs in patients with gastrointestinal risk factors, while the occasional use of NSAIDs in young patients does not justify gastro-protection with PPIs. 2) Although both traditional NSAIDs and COX-2 inhibitors are associated with higher cardiovascular risk, these adverse effects generally tend to be more closely associated with COX-2 inhibitors, and there is some evidence suggesting that naproxen is the best NSAID regarding its effect on the cardiovascular system. 3) NSAIDs must be avoided in patients with chronic kidney disease or inflammatory bowel disease. 4) We should recognise that the treatment response to NSAIDs is somewhat idiosyncratic, and hence, when prescribing them, we should take into account patients' prior experience with these drugs, in terms of effectiveness and tolerability. And 5) with the exception of acetylsalicylic acid (ASA) at antiplatelet doses, no more than one NSAID should be used in a given patient.

In RA, NSAIDs are mainly used to reduce morning stiffness.

Table 5. Usual doses of non-steroidal anti-inflammatory drugs

Drug	Total dose (mg/24 h)	Dosing interval (h)
Acetylsalicylic acid	3,000-6,000	6-8
Ibuprofen	1,200-2,400	8
Flurbiprofen Slow release flurbiprofen	200-300 200	12 24
Mefenamic acid	750-1,500	8
Meclofenamate Sodium	200-400	8
Diflunisal	500-1,000	12
Naproxen	500-1,000	12
Ketoprofen Slow release ketoprofen	200 200	8-12 24
Aceclofenac	200	12
Diclofenac Slow release diclofenaco	150-200 100	8-12 24
Phenylbutazone	200-400	12-24
Indomethacin	75-150	8
Sulindac	200-400	12
Tenoxicam	20	24
Meloxicam	7.5-15	24
Nabumetone	1,000-2,000	12-24
Celecoxib	200-400	12-24
Etoricoxib	90	24

Glucocorticoids

Glucocorticoids are among the anti-inflammatory and immunosuppressive agents most used in RA (Table 6). In countries neighbouring Spain, patients with active RA often use glucocorticoids concomitantly with conventional DMARDs, with use rates of 38%[103] to 55%[104]. In the "AREXCELLENCE" study[105] [conducted in Spain], 58% of patients with RA were treated with prednisone at doses of less than 10 mg/day (unpublished data). The rationale for the use of glucocorticoids in the treatment of active RA was initially just to rapidly alleviate the symptoms through inflammation inhibition. Nonetheless, research in the last decade has demonstrated that glucocorticoid treatment delays both the start and progres-

sion of radiological joint damage, and hence, they are now considered a standard component of therapy with conventional DMARDs.

The low profile of adverse effects attributable to these drugs at low doses (< 7.5 mg/day of prednisone or equivalent)[106-108], and the diversity of agents, routes of administration and regimens available, together with their low cost, make glucocorticoids in combination with conventional DMARDs a very attractive therapy for the management of patients with RA. Nonetheless, there are still misconceptions regarding the benefit/risk ratio of glucocorticoid therapy in patients with RA that may be limiting their use. EULAR drew up recommendations on the follow-up of patients on low doses of glucocorticoids based on the opinion of experts and patients. These recommendations concluded that, in daily clinical practice, there is no need to carry out special check-ups for patients treated with low-dose glucocorticoids, except for screening for osteoporosis and pretreatment assessment of fasting blood glucose levels, risk factors for glaucoma and potential ankle oedema[109].

To date, there is no evidence of significant differences in terms of efficacy or adverse effects between the use of the most commonly used formulations (prednisone, prednisolone, methylprednisolone and deflazacort) when used at equivalent doses. Whenever possible, we should prescribe a single daily dose to be taken in the morning, and the dose should be tapered (moving first from divided doses to a single dose and then reducing the dose) until the complete withdrawal of the medication if the clinical response is adequate.

Table 6. Classification of glucocorticoids by their duration of action

Duration of action	Glucocorticoid
Short	hydrocortisone, prednisone and prednisolone
Intermediate	methylprednisolone, paramethasone, triamcinolone and deflazacort
Long	betamethasone and dexamethasone

Intraarticular glucocorticoids may be used for the treatment of RA, with good outcomes. Nonetheless, their independent effects on radiological progression have not been studied. Their clinical application is limited to local control in the joints where they have been injected.

Disease-modifying antirheumatic drugs

DMARDs are a heterogeneous group of agents, with different mechanisms of action and toxicity, used in RA patients to reduce inflammation and generally prevent negative outcomes of the disease (Table 7). MTX is the most widely used DMARD

in the treatment of this condition. Classically, the use of DMARDs for controlling signs and symptoms of RA has been based on an empirical approach, in many cases, without the mechanisms of action being clearly known. The development and approval of biological and synthetic drugs for specific targets has increased the family of DMARDs to include agents that act on extra- and intracellular therapeutic targets, selectively or with high specificity.

DMARDs are currently divided into two groups:

- Synthetic DMARDs (sDMARDs): drugs which were synthesised and then found to have an anti-rheumatic activity.
- Biologic DMARDs (bDMARDs): drugs developed to target specific molecules, such as a soluble protein or a cell surface receptor, this group including original biological compounds and biosimilar drugs.

Although by definition all DMARDs modify rheumatic disease processes, there is a fundamental difference in the mechanism of action between the two types. All the biological compounds currently used in rheumatology are receptor fusion proteins or monoclonal antibodies, designed to target a specific extracellular molecule that has a role in disease activity. In contrast, the synthetic chemical compounds are low molecular weight molecules that work by interfering in intracellular processes.

The new synthetic DMARDS that recognise specific targets have been grouped into:

a. conventional synthetic DMARDs (csDMARDs): antirheumatic drugs designed in the traditional way, such as MTX and sulfasalazine (SSZ).

b. targeted synthetic DMARDs (tsDMARDs): oral synthetic drugs such as tofacitinib (TOFA) and baricitinib (BARI), developed to interact with specific molecules.

Table 7. Disease-modifying drugs: doses and trade names

Drug	Treatment regimen	Nombres comerciales

ABATACEPT[a]	• The dose is adjusted to body weight:
	  • <60 kg: 500 mg
	  • de 60 a 100 kg: 750 mg
	  • >100 kg: 1.000 mg
	• Intravenous infusion for 30 minutes. Subsequently, two additional doses 2 and 4 weeks after the first infusion, then one dose every 4 weeks
	• The subcutaneous formulation is administered at 125 mg weekly
	• It can be used alone or combined with another DMARD
		ORENCIA®
		• Vial of containing 250 mg of lyophilized powder for reconstitution
		• 125 mg in a volume of 1 ml in a prefilled syringe for weekly administration
		• Prefilled pen containing 125 mg in a volume of 1 ml for weekly administration

Table 7. Disease-modifying drugs: doses and trade names

Drug	Treatment regimen	Nombres comerciales
ADALIMUMAB[a]	• 40 mg/14 days subcutaneously • In some patients, the dosing interval should be shortened to 7-10 days instead of the recommended 14 days • In some patients, the dosing interval should be shortened to 7-10 days instead of the recommended 14 days • It can also be used alone or combined with another DMARD	HUMIRA® • Prefilled syringe containing 40 mg • Prefilled pen containing 40 mg
ANAKINRA[a]	• 100 mg/day, subcutaneously	KINERET® • Prefilled syringe containing 100 mg
AZATHIOPRINE[bd]	• 1.5 – 2.5 mg/kg/day, orally • Start at low doses of 1 mg/kg/day and gradually increase to a maintenance dose of 100-150 mg/day over 4-6 weeks	IMUREL® • 50-mg coated tablet • Vial of concentrate for solution for infusion containing 50 mg
CERTOLIZUMAB PEGOL[a]	• 400 mg at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every other week • During treatment with Cimzia®, treatment with MTX should be continued as appropriate	CIMZIA® • Prefilled syringe containing 200 mg • Prefilled pen containing 200 mg
CYCLOPHOSPHAMIDE[bd]	• 1.5-2.5 mg/kg/day, orally. Start at 50 mg/day and increase the dose every 4-6 weeks until response, up to a maximum of 2.5 mg/kg/day. • 3 to 6 mg/kg of body weight per day (equivalent to 120 to 240 mg/m2 of body surface), under intravenous infusion	GENOXAL® • 50-mg tablet • 1000-mg IV vial • 200-mg IV vial
CHLOROQUINE[bd]	• 250 mg/day, orally • Do not exceed 4 mg/kg/day	RESOCHIN® • 250-mg tablet
CICLOSPORIN[bd]	• 2.5-5.0 mg/kg/day, orally • The dose can be increased by 0.5 mg/kg/day every other week up to 5 mg/kg/day	SANDIMMUN NEORAL® • 25-, 50-, and 100-mg tablets • Oral solution 100 mg/ml
ETANERCEPT (ETN)[a]	• 50 mg, once a week • In children, 25 mg a weeks • Combined or alone	ENBREL® BENEPALI® ERELZY® • Prefilled syringe and pen containing 50 mg

Table 7. Disease-modifying drugs: doses and trade names

Drug	Treatment regimen	Nombres comerciales
GOLIMUMAB[a]	• 50 mg, once a month, on the same day each month • Must be taken together with MTX	SIMPONI® • Prefilled syringe containing 50 mg • Prefilled pen containing 50 mg
HYDROXICHLOROQUINE (HCQ)[b]	• 200 mg/day, orally • Do not exceed 6.5 mg/kg/day	DOLQUINE® • 200-mg tablet
INFLIXIMAB (IFX)[a]	• 3 mg/kg by intravenous infusion for 2 hours • Then, additional infusions of 3 mg/kg doses, 2 and 6 weeks after the first one, and then once every 8 weeks. The dose can be increased to 5 mg/kg if not effective or if there is relapse. In some patients, it may be necessary to shorten the infusion interval to 4-6 weeks, instead of the 8 weeks recommended for maintenance • IFX must be used in combination with MTX or other immunomodulators (such as leflunomide or azathioprine)	REMICADE® INFLECTRA® REMSIMA® FLIXABI® • Vial of concentrate for solution for infusion containing 100 mg
LEFLUNOMIDE (LEF)[b]	• 20 mg/day, orally	ARAVA® • 10- and 20-mg tablets

Table 7. Disease-modifying drugs: doses and trade names

Drug	Treatment regimen	Nombres comerciales
METHOTREXATE (MTX)[b]	• 15 mg/week, orally or subcutaneously for 4-6 weeks and then, if not effective, increase to 20-25 mg/week • Folic or folinic acid (5-15 mg/week) must be given 24 hours after MTX	METOTREXATO ALMIRALL® • Injectable solution, 50 mg/2 ml vial METOTREXATO LEDERLE® • 2.5-mg tablet • Injectable solution 25 mg/ml METOJECT® • Prefilled syringes (7.5; 10; 12.5; 15; 17.5; 20; 22.5; 25; 27.5; 30 mg) QUINUX® • Prefilled syringes (7.5; 10; 15; 20; 25 mg) NORDIMET® • Prefilled pens (7.5; 10; 12.5; 15; 17.5; 20; 22.5; 25 mg) IMETH® • Prefilled pens (7.5; 10; 12.5, 15; 17.5; 20; 22.5, 25 mg) Bertanel® • Prefilled pens (7.5; 10; 15, 20, 25, 30 mg) Glofer® • Prefilled pens (7,5; 10; 15; 20; 25 mg)
BARICITINIB[c]	• 4 mg once per day • 2 mg once per day is appropriate for patients ≥ 75 years old with a history of chronic or recurrent infections and patients with kidney failure (ClCr 30-60 ml/min) • Not recommended in patients with a creatinine clearance < 30 l/h • We could also consider giving 2 mg once daily in patients who have achieved sustained low disease activity on 4 mg once daily • Can be used alone or combined with MTX	OLUMIANT® • 2- and 4-mg tablets
RITUXIMAB[a]	• Two 1,000-mg IV infusions, 2 weeks apart, in combination with MTX • Methylprednisolone 100 mg IV (or equivalent) should be given before the infusion to reduce the incidence and severity of adverse reactions	MABTHERA® • 100- and 500-mg vials TRUXIMA® • 100- and 500-mg vials

Table 7. Disease-modifying drugs: doses and trade names

Drug	Treatment regimen	Nombres comerciales
SARILUMAB[a]	• 200 mg once every other week, subcutaneously • If neutropenia, thrombocytopenia and/or elevated liver enzymes appear, the dose should be reduced to 150 mg every other week	KEVZARA® • Prefilled syringes and pens (150 mg and 200 mg)
SULFASALAZINE (SSZ)[b]	• 2-3 g/day, orally	SALAZOPYRINA® • 500-mg tablet
TOCILIZUMAB[a]	• 8 mg/kg of body weight once every 4 week. • In individuals weighing over 100 kg, we should not exceed a dose of 800 mg • If neutropenia, thrombocytopenia and/or elevated liver enzymes appear, the dose should be reduced to 4 mg/kg • 162 mg weekly, subcutaneously	ROACTEMRA® • 80-, 200- and 400-ml vials • Prefilled syringe 162 mg/sc/week
TOFACITINIB[c]	• 5 mg, twice daily • Alone or in combination with MTX	XELJANZ® • 5-mg tablet

a: biologic DMARD; b: conventional synthetic DMARD; c: targeted synthetic DMARD; d: for occasional use, e: for exceptional use.

Small molecules or targeted DMARDs

Cytokines play a key role in the control of cell growth and immune response. Many of them work by binding to type I and II cytokine receptors. In turn, these receptors activate another group of proteins including Janus kinases (JAKs), which participate in the signalling pathways associated with the regulation of gene expression. Their name comes from the two-faced Roman god Janus, reflecting the two similar domains in this family of kinases. These two domains are found bound intracellularly to hormone receptors located in the plasma membrane, although some JAKs are also found in the cytoplasm.

After a cytokine has bound to its receptor, members of the JAK family self- and trans- phosphorylate, resulting in the phosphorylation of STAT that migrates to the cell nucleus to modulate the transcription of effector genes. In this way, the intracellular JAK/STAT signal transduction interacts with interferons (IFNs), most interleukins (ILs), as well as a variety of cytokines and endocrine factors such as

erythropoietin, thrombopoietin, growth hormone, oncostatin M, leukaemia inhibitory factor, ciliary neurotrophic factor, granulocyte-macrophage colony-stimulating factor (GM-CSF) and prolactin[110].

Janus kinase inhibitors or Jakinibs block the activity of Janus kinase family enzymes, by interfering in the JAK-STAT signalling pathway. There four types of JAK (JAK1, JAK2, JAK3 and tyrosine kinase 2 [TYK2]) and these work in pairs, each with different biological effects. The inhibitors of these four types of JAK are useful in the treatment of cancer and inflammatory diseases such as RA and psoriatic arthritis:

- *JAK1* is one of the targets in the field of immune and inflammatory diseases. It interacts with the other JAKs to transduce the proinflammatory signalling triggered by cytokines. Hence, the inhibition of JAK1 is expected to have a beneficial effect in a range of inflammatory conditions, as well as other diseases triggered by JAK mediated by signalling transduction.
- *JAK2* is involved in a series of differentiation pathways in haematopoiesis, by modulating mainly proteins such as erythropoietin, thrombopoietin and GM-CSF. The activity of JAK2 is responsible for proliferative diseases such as chronic myeloid leukaemia, polycythaemia vera and essential thrombocythemia. All these diseases are caused by point mutations in the JAK2 gene (for example, V617F) or JAK2 fusions, leading to an overactivation of the JAK2/STAT pathways[111, 112]; for this reason, JAK2 is considered to be a clear target in cancer.
- *JAK3* expression is limited to lymphoid lineage cells. The loss of JAK3 function leads to severe combined immunodeficiency and, for this reason, it is has been considered a key target for immunosuppression. JAK3 inhibitors were first successfully used in clinical practice to treat rejection in organ transplantation[113], later also being used in immunoinflammatory diseases.
- *TYK2* is a potential target for immunoinflammatory diseases, having been validated by various genetic studies in humans and knockout mice[114].

Given the wide range of cytokines and signalling hormones that can be modulated through the JAK/STAT pathway, numerous diseases may be therapeutically modulated through JAK inhibition[115, 116] (see Table 8).

Table 8. Biology and diseases mediated by different receptors associated with Janus kinases

Receptor	Janus kinase	Related biology	Impact of the disease
Type I IFN (α, β)	JAK1 TYK2	• Antiviral response • Immunoregulation	• Systemic erythematous lupus/connective tissue disease • Granuloma development (sarcoidosis)
Type II IFN (γ)	JAK1 JAK2	• Antiviral response • Immunoregulationn • T cell-mediated macrophage activation	• Systemic erythematous lupus/connective tissue disease • Granuloma development (sarcoidosis)
GP130 (IL-6, IL-11, ciliary neurotrophic factor, cardiotrophin-1, GM-CSF, leukaemia inhibitory factor , oncostatin M) receptors	JAK1 JAK2 TYK2	• Lymphoid and myeloid cell development • Bone resorption, etc.	• RA • Psoriasis
Common beta chain (IL-3, 5, GM - CSF)	JAK2	• Lymphoid and myeloid cell development	• Eosinophilia • Myelofibrosis
Common gamma chain (IL-2, 7, 9, 15)	JAK1 JAK3	• Lymphoid activation	• Organ transplant • Psoriasis
Homodimeric receptors (erythropoietin, thrombopoietin, prolactin, growth hormone)	JAK2	• Erythropoiesis • Thrombopoiesis • Breastfeeding, Sexual function • Metabolism	• Polycythaemia • Thrombocythaemia • Hyperprolactinaemia • Acromegaly

Some JAK inhibitors (TOFA and BARI) are currently available for patients with RA, while others are still at the development stage (filgotinib, ruxolitinib and upadacitinib).

Tofacitinib

TOFA inhibits JAK1 and JAK3, modulating the expression of IFN I and various cytokines including IL-2, 4, 6, 7, 9, 15 and 21[117-122]. In Spain, it is currently indicated for oral use in combination with MTX for the treatment of active moderate-to-severe RA in adult patients with a poor response or intolerance to one or more DMARDs. It can also be given alone in cases of intolerance to MTX or when MTX is not indicated. The recommended dose is 5 mg, twice daily.

Baricitinib

BARI is a selective inhibitor of JAK1 and JAK2. The BARI-mediated inhibition of these two enzymes modulates the expression of several cytokines including IL-6, GM-CSF, IL-5, IL-3 and INFs[123].

In Spain, it is currently indicated for oral use for the treatment of active moderate-to-severe RA in adult patients with a poor response or intolerance to one or more DMARDs. It can be used in combination with MTX or alone in cases of intolerance to MTX, or when MTX is not indicated. The recommended dose is 4 mg, once daily.

Biosimilars

A biosimilar is a biological drug that is similar, but not identical to the original product. The World Health Organization defines a biosimilar as a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product[124]. Regulation of these agents differs between countries and regions across the world[125].

In the last 10 years, the experience with biosimilars has demonstrated that complex proteins can be successfully copied. A biosimilar has the same primary sequence of amino acids as the reference product and has been subject to rigorous clinical tests and analysis in head-to-head comparisons with the reference product[126]. Biosimilars are currently being marketed or under development for various biological agents, including various different tumour necrosis factor (TNF) inhibitors - infliximab (IFX), etanercept (ETN) and adalimumab (ADA)- and rituximab (RTX) for use in rheumatic diseases. A recent systematic review included the results of 19 observational and clinical trials comparing TNF-α inhibitors with their reference biological products, including IFX, ETN and ADA. Eight of these were phase I clinical trials, seven in healthy volunteers and one in patients with ankylosing spondylitis; five were phase III randomised clinical trials, including patients with RA; and six were observational studies that recruited patients with RA or inflammatory bowel disease. This review found that the efficacy and safety of these agents were indistinguishable from those of the original products they copied[127]. The pharmacokinetic measurements for the corresponding biosimilars and their reference products were within the predefined margins of equivalence, and the clinical response and adverse effects were similar. Two studies documented immunological cross-reactivity between products and four cohort studies in which patients were switched from the reference product to a biosimilar found similar efficacy and safety[127].

Most biologics are used long term. This has led to intense discussion about the safety of switching a reference product for a biosimilar, immunogenicity being the main concern. Evidence from clinical trials such as PLANETAS[128] and PLANETRA[129] and usual practice studies such as NOR-Switch[130] suggests that switching between comparable versions of the same active ingredient, as approved by EU legislation, is not expected to result in an increase in immunogenicity. On the other hand, the analysis of patient data included in registries suggests that switching a biologic for its biosimilar may be associated with a shorter duration of treatment response[131], a finding that needs to be confirmed in future research.

The biosimilars currently available include:

1) Infliximab biosimilars: the CT-P13 IFX biosimilar is a chimeric human-murine monoclonal IgG1 antibody, developed as a monoclonal antibody against TNS-α, a biosimilar to the original IFX. It has an identical sequence of amino acids, is produced in the same cell lineage, and shows *in vitro* and *in vivo* pharmacokinetics, specificity and binding affinity and other biological and pharmacological characteristics very similar to the original IFX[128, 129]. It has been shown to have equivalent clinical efficacy and safety to the original IFX in a small set of randomised phase III clinical trials in patients with RA in combination with MTX[129] and in patients with ankylosing spondylitis[128]. The global availability of this IFX biosimilar is growing and it is currently available in more than 70 countries[125].

Another IFX biosimilar, SB2, has recently come onto the market. In phase III comparison clinical trials with the original IFX in patients with RA with a poor response to MTX, SB2 was well tolerated and was associated with similar efficacy, safety, immunogenicity and radiological progression to that observed with IFX after 1 year of follow-up[132, 133].

In Europe, these agents are approved for the treatment of RA, ankylosing spondylitis, psoriatic arthritis and psoriasis, Crohn's disease and ulcerative colitis[134-137].

2) Etanercept biosimilars: SB4 is an ETN biosimilar, manufactured by recombinant DNA technology. It has been demonstrated that SB4 has similar structural, physicochemical and biological properties and therapeutic equivalence to ETN, though they differ by a single amino acid[138]. The clinical benefit and safety of SB4 were assessed in a randomised clinical trial in patients with RA that was active despite being treated with MTX, and at week 24, treatment with SB4 was associated with a similar percentage of patients meeting the ACR20, 50 and 70 criteria to that obtained with the reference original[138]. The incidence of adverse effects related to the treatment was also similar, although SB4 was associated with a lower rate of adverse site reactions, both drugs being well tolerated.

Another biosimilar of ETN, GP2015, was shown to be clinically bioequivalent to the reference drug in the EGALITY study, in patients with moderate-to-severe psoriasis on monotherapy[139]. This study included three treatment switches between the reference drug and the biosimilar. From the start until week 52 of treatment, both in the intermittent and continuous treatments, there were no significant differences in the Psoriasis Area and Severity Index (PASI) scores obtained when on GP2015 or the reference drug. The main objective of achieving equivalence in PASI 75 response rates in week 12 was met. Additionally, these drugs were comparable in terms of safety after 52 weeks, with fewer adverse site reactions and the immunogenicity was low, as expected with treatment with ETN. Another study on RA has been reported, but the publication of results is still pending. By extrapolation, GP2015 is currently marketed for the treatment of RA, psoriatic arthritis, juvenile idiopathic arthritis and non-radiographic ankylosing spondylitis in Spain.

3) Rituximab biosimilar: CT-P10 is a biosimilar of the original RTX; a biological therapy used to treat patients with RA who have had a poor response to at least one antibody to tumour necrosis factor (anti-TNF) -alpha agent. In a multicentre double-blind study, patients with RA were randomly allocated to receiving 1 g of CT-P10 or RTX in weeks 0 and 2, and a second cycle between weeks 24 and 48, depending on disease activity[140]. The safety and efficacy profiles were comparable to those of RTX and pharmacokinetic and pharmacodynamic properties were similar. The percentages of patients positive for anti-drug antibodies at week 24 were 20.0% and 21.7% in the CT-P10 and RTX groups, respectively. To conclude, in patients with RA followed up for 72 weeks, safety and other clinical parameters were comparable with CT-P10 and RTX after up to two courses of treatment.

7.3. Pharmacological treatment

7.3.1. Initial pharmacological treatment

Clinical question 2

In patients with rheumatoid arthritis, what is the efficacy of initial treatment with glucocorticoids at doses of >10 mg of prednisone, added to any DMARD?

Summary of the evidence

Initial combination therapy for rheumatoid arthritis with methotrexate, sulfasalazine and prednisolone 60 mg/day is superior to the use of sulfasalazine alone in terms of the control of disease activity and long-term radiological damage[141, 142].	1+

Methotrexate, sulfasalazine and prednisolone 60 mg/day in the initial treatment of rheumatoid arthritis is similarly effective to the combination of methotrexate and infliximab in terms of the improvement in functional capacity and prevention of radiological damage[143].	1+
The addition of prednisolone 15 mg/day to triple therapy (methotrexate, sulfasalazine and hydroxychloroquine) in the initial treatment of rheumatoid arthritis is similarly effective to the addition of a single dose of IM corticosteroids (methylprednisolone 120 mg or triamcinolone 80 mg) in terms of Disease Activity Score, Health Assessment Questionnaire (HAQ) score, modified Sharp/van der Heijde score and Rheumatoid Arthritis Disease Activity Index[144].	1+
Initial combination therapy regimens for rheumatoid arthritis that include prednisone 30 mg/day or equivalent have demonstrated to be as effective as regimens that include doses of 60 mg/day at the 1-year of follow-up[145-148].	1+
The addition of prednisone 30 mg/day to methotrexate in the initial treatment of low-risk patients with rheumatoid arthritis was associated with a non-statistically significant improvement in rates of remission, response according to EULAR criteria and improvement in HAQ score at 1-year of follow-up[147].	1+
In the initial treatment of rheumatoid arthritis in high-risk patients, there are no differences in rates of remission, good EULAR response or improvement in HAQ score between the addition of methotrexate 30 mg/day or prednisone 60 mg/day[147].	1+
In the initial treatment of rheumatoid arthritis, the addition of prednisone 10 mg/day at stable doses for 2 years to methotrexate reduces the need for long-term biological therapy (6 years), as well as the rate of erosions[149].	2++

Recommendations

In patients with rheumatoid arthritis, the recommendation is to use glucocorticoids at a dose equivalent to prednisone 10-30 mg/day as the initial treatment in combination with one or several conventional DMARDs followed by gradual tapering of the dose **(Grade B recommendation)**.

The use of high doses of glucocorticoids in the initial treatment of RA is controversial. Treatment regimens that include initially high doses of prednisolone, known as COBRA (60 mg/day) or COBRA Light (30 mg/day), have shown to be efficacious, safe and cost-effective in both the short and long term[141-143, 145-148, 150-152]. Despite this, the prescription of high doses of glucocorticoids initially remains uncommon, due partly to concerns regarding potential adverse effects and partly to a perception that it is a complex regimen to administer[153].

Quality of the evidence

The efficacy of the initial treatment of RA with regimens that include high doses of glucocorticoids has been assessed by various authors, although few studies have directly compared them with low doses or no corticosteroids. Since the publication of the COBRA study[141] comparing combination therapy with MTX, SSZ and prednisolone (at initial doses of 60 mg/day tapered to 7.5 mg/day over 6 weeks) with SSZ alone, various clinical studies have used the COBRA regimen in one of the treatment arms. The initial results of COBRA and follow-up at 5[150] and 11[142] years have demonstrated that initial combination therapy with MTX, SSZ and prednisolone 60 mg/day is superior to SSZ alone in terms of control of disease activity and long-term radiological damage (Level of evidence 1+). Unfortunately, it is not possible to determine how much of this benefit is due to MTX or the combination with DMARDs and how much is due to the high doses of prednisolone.

More recently, various different studies have demonstrated that the COBRA Light regimen (prednisolone 30 mg) is not inferior to the COBRA Classic regimen (prednisolone 60 mg) in terms of efficacy at 1-year of follow-up[145-148] (Level of evidence 1+).

The BeST study compared four different strategies for the initial treatment of RA: sequential monotherapy, step-up combination therapy, COBRA Classic combined therapy and combined therapy with MTX and IFX. The COBRA regimen was found to be as effective in terms of improvement in functional capacity and prevention of radiological damage as the combined therapy with IFX[143] (Level of evidence 1+). They were both superior to the sequential monotherapy and step-up combination therapy.

The tREACH trial compared the efficacy of triple therapy (MTX, SSZ and hydroxychloroquine, HCQ) plus initial intramuscular administration of a single dose of glucocorticoids (methylprednisolone 120 mg or triamcinolone 80 mg) with that of triple therapy plus tapered oral glucocorticoids (15 mg/day tapered to 2.5 mg/day over 10 weeks). At the 1-year follow-up, no significant differences were found between these two triple-therapy-plus-glucocorticoid regimens in Disease Activity Score (DAS), Health Assessment Questionnaire (HAQ) score, Sharp/van der Heijde score, Rheumatoid Arthritis Disease Activity Index or adverse events (Level of evidence 1+). This trial also included a treatment arm with initial MTX combined with tapered oral glucocorticoids like in one of triple therapy arms (described above). At the 3-month follow-up, the DAS was lower in patients who received triple therapy than those who received MTX

alone (0.39; 95% CI 0.67 to 0.11). Nonetheless, this difference gradually reduced over time and results were similar at 12 months (0.08; 95% CI -0.34 to 0.19)[144] (Level of evidence 1+).

Results have been recently published from the CareRA trial in which 90 patients classified as low risk (based on an algorithm that included the presence of erosions, RF or anti-CCP positivity, and DAS28-C-reactive protein [CRP]) were randomly allocated to treatment with MTX alone or in combination with the COBRA Slim corticosteroid regimen, consisting of prednisone 30 mg/day initially tapered to 5 mg/day over 6 weeks. Although the patients who received corticosteroids obtained better results in terms of remission, EULAR response and HAQ score at 1-year of follow-up, these differences were not statistically significant[147] (Level of evidence 1+). This trial also randomly allocated 289 high-risk patients to receive the COBRA Classic (MTX, SSZ and prednisolone 60 mg), COBRA Slim or COBRA Avant Garde (MTX, LEF + prednisolone 30 mg) regimens. No differences were found between groups in remission rate, EULAR response or improvement in HAQ score[147] (Level of evidence 1+).

The CARDERA trial randomised 467 patients with early RA into one of four treatment groups: MTX alone, MTX + ciclosporin A, MTX + prednisolone 60 mg/day or MTX + ciclosporin A + prednisolone 60 mg/day. Prednisolone was tapered to 7.5 mg/day by 6 weeks and finally withdrawn at 34 weeks. At 2 years of follow-up, the patients who received MTX + prednisolone showed greater improvement in DAS28 and HAQ scores, achieved a higher rate of remission (DAS28), had fewer erosions and obtained a lower Larsen score than patients receiving MTX alone. No direct comparisons were made between the group given MTX + ciclosporin A and that given MTX + ciclosporin A + prednisolone[154] (Level of evidence 1+).

The CAMERA-II trial randomised 236 DMARD-naïve patients with RA to MTX plus a stable dose of prednisone 10 mg for 2 years or MTX plus placebo. Once the trial had finished, gradual withdrawal of prednisone was attempted. Results have recently been published concerning the long-term follow-up (median of 6.7 years) of 218 patients from the initial trial[149]. The percentage of patients who required initiation of a bDMARD was lower among those who received prednisone initially (31% vs 50% among those on MTX plus placebo; p=0.003). Further, at the 2-year post-trial follow-up, patients who had received prednisone obtained lower Sharp/van der Heijde scores for erosions. No differences were observed in glucocorticoid-related comorbidities at any point during the post-trial follow-up[155] (Level of evidence 2++).

Currently, there are no data available directly comparing oral glucocorticoids at doses greater than or equal to prednisone 30 mg/day or equivalent with these drugs at low doses (less than 10 mg/day) in the initial treatment of RA. The comparison between 30 and 60 mg/day doses indicates that both regimens are similarly effective. For this reason, the 30 mg/day dose is recommended as it is associated with fewer adverse events. What is more, given the adverse effects of prolonged treatment with glucocorticoids, the dose should be tapered and if possible, these drugs should be withdrawn, as in clinical trials.

Clinical trials that have used the COBRA Classic regimen in some of the treatment arms have produced consistent results and these support the use of high-dose corticosteroids together with various combinations of DMARDs. The various studies that have compared high-dose (60 mg) with moderate-dose (30 mg) regimens have not shown differences in the follow-up[145-148]. Out of the two studies that directly compared the use of glucocorticoids at doses >10 mg/day to placebo, only one[154] found clear benefits of using corticosteroids. Although the low-risk patients from the CareRA[147] study who received corticosteroids had a better course, the differences between groups were not statistically significant. This may be attributable to the small sample size. On the other hand, in high-risk patients, the various combinations of corticosteroids with MTX or added to LEF and/or SSZ were not associated with different outcomes, these findings supporting the use of initial treatment with MTX and moderate doses of corticosteroids[147].

The GDG believes that the results of the studies identified can be directly applied to our health system, given that both glucocorticoids and the various combinations of DMARDs assessed in these studies are commonly used in our setting. Furthermore, given that all these studies have included populations with recent-onset RA, results may be extrapolated to Spanish patients who are newly diagnosed with RA.

In accordance with the studies reviewed, the use of initial therapy with glucocorticoids at doses greater than or equal to prednisone 30 mg/day or equivalent improves the prognosis of patients with RA in terms of disease activity, functional capacity and radiological damage. Further, the addition of high doses of prednisolone to MTX has shown to be as effective as the addition of initial therapy with IFX, this being the best option from an economic point of view. The direct comparison between moderate (30 mg) and high (60 mg) doses has shown them to have similar results. Nonetheless, given that no studies were found directly comparing doses ≥ 30 mg/day with doses ≤ 10 mg/day, the GDG considers that it is not able to state that the use of moderate-to-high doses is

the most appropriate option. The use of low doses (< 10 mg/day prednisone) in the initial treatment of RA has shown to improve signs, symptoms and radiological progression of the disease, and may well be associated with fewer adverse effects than the use of moderate-to-high doses.

Clinical question 3

In patients with rheumatoid arthritis, what is the efficacy of initial treatment with triple conventional DMARD therapy?

Summary of the evidence

In methotrexate-naïve patients with early rheumatoid arthritis, the efficacy of treatment with triple therapy (methotrexate, sulfasalazine and hydroxychloroquine) plus corticosteroids at 12 months is not lower than that of methotrexate plus corticosteroids[144].	1+
In methotrexate-naïve patients with early rheumatoid arthritis, the efficacy of treatment with triple therapy (methotrexate, sulfasalazine and hydroxychloroquine) is greater than that of methotrexate without corticosteroids[156-158].	1+

Recommendations

Although triple therapy is not recommended as the initial treatment for rheumatoid arthritis, it could be considered in patients in whom glucocorticoids are contraindicated **(Grade C recommendation)**.

The treatment and prognosis of patients with RA have changed greatly in recent decades. For many years, conventional DMARDS have been the cornerstone of treatment. The current trend is to start the treatment earlier, taking advantage of the window of opportunity. In relation to this, the refinement of existing strategies and the discovery of new ones will facilitate the treatment of RA. Triple DMARD combination therapy is one such strategy that is worth assessing as an alternative to current, more established treatment regimens including DMARD monotherapy and biological therapy.

Quality of the evidence

One systematic review was found that sought to compare treatment regimens including MTX in patients who were naïve to or had a poor response to MTX. The results of the Bayesian random-effects network meta-analysis showed that triple therapy was

better than MTX alone at the beginning of the treatment in DMARD-naïve patients, without increasing the risk of adverse effects[159]. The systematic review included two RCTs assessing the efficacy of triple therapy, in MTX-naïve patients, compared to monotherapy and the combination of two DMARDs. One of these trials compared triple therapy with the combination of two DMARDS (MTX plus SSZ or MTX plus HCQ)[160]; however, the RCT that best addresses the clinical question is the tREACH study that compared triple therapy (MTX, SSZ and HCQ) with MTX (in combination with corticosteroids in both cases). The results showed no differences in disease activity (DAS28), disability or radiographic progression of the disease after 12 months of treatment. Further, no differences were found in adverse effects (Level of evidence 1+).

Other studies have indicated the superiority of triple therapy over MTX without corticosteroids. Nonetheless, such superiority has not been observed when oral or intramuscular corticosteroids were added.

An RCT included 180 patients randomly allocated to one of three treatment groups: monotherapy with MTX, SSZ or HCQ (n=60), dual therapy with MTX and SSZ (n=30) or MTX and HCQ (n=30) or triple therapy with MTX, SSZ and HCQ (n=60) with a follow-up of 24 months. Patients had similar characteristics at the beginning of the treatment and were assessed every 3 months. At the end of the follow-up period, there was a higher rate of remission as defined by the ACR criteria in the triple therapy group (60.3%) than in the dual (44.6%) or monotherapy (31.5%) groups, the differences being significant ($p < 0.007$). Regarding radiographic progression, the percentage of patients with no progression was higher in the triple (68.9%) and dual (64.2%) therapy groups than those receiving monotherapy (24.5%) ($p = 0.001$), the differences between triple and dual therapies being non-significant. Only mild adverse effects were reported and these were similar in the three groups[158] (Level of evidence 1+).

Another RCT studied 199 patients randomly allocated to one of two treatment groups: triple therapy with SSZ (50 mg/12 h), MTX (7.5-25 mg) and HCQ (300 mg/day) or a DMARD monotherapy. In both groups, disease activity was monitored closely seeking to achieve remission. At the end of the 24-month follow-up, the percentage of patients in remission was higher in the triple therapy than in the monotherapy group (37% vs 18%, p=0.003). In addition, the ACR50 response was higher in the triple therapy group. Functional capacity, measured by the HAQ, was similar in the two groups. Using the Larsen score, more radiographic progression was observed in the monotherapy group, with scores changing from 2 (0-4) at baseline to 4 (0-14) at 24 months in the triple therapy group and from 2 (0-8) to 12 (4-20) in the monotherapy group[156] (Level of evidence 1+). In subsequent analysis of data from this same study, assessing radiographic progression of these patients after 11 years, the rate of radiographic progression was found to be significantly lower with triple therapy, with mean increases in scores from baseline

of 17 (95% CI 12 to 26) in the triple therapy group versus 27 (95% CI 22 to 33) in the monotherapy group (p=0.037)[157] (Level of evidence 1+).

In drafting these recommendations, the GDG took into account that, although some studies indicate that triple therapy is a good option for the management of RA in DMARD-naïve patients, specifically the combination of MTX, SSZ and HCQ, the tREACH study concluded that this triple therapy combined with corticosteroids was not superior to MTX at 12 months. On the other hand, given that clinical practice indicates that 60% of patients with early RA respond to MTX monotherapy, the use of triple therapy in these patients would represent unnecessary drug use, this highlighting the need to identify which patients respond to MTX monotherapy and which to triple therapy. The recommendation made facilitates access to treatment for RA by a larger number of patients, reducing costs, delaying and even reducing the use of biological therapies.

7.3.2. Treatment of patients refractory to conventional DMARDs

Clinical question 4

In patients with rheumatoid arthritis who do not respond to methotrexate monotherapy, is it more effective to add a biologic DMARD or use a combined therapy with conventional DMARDs?

Summary of the evidence

En pacientes con AR de reciente comienzo que han fallado a metotrexato, la triple terapia (metotrexato, hidroxicloroquina y sulfasalazina) y la combinación metotrexato y anti-TNF son comparables en cuanto a eficacia clínica; aunque la primera tarda más tiempo en alcanzar el efecto[161,162].	1+, 2++
En AR de reciente comienzo que han fallado a metotrexato, la combinación de metotrexato y anti-TNF resultó más eficaz para frenar la progresión radiológica[161, 162].	1+, 2++
En pacientes con AR establecida y respuesta insuficiente a metotrexato, la combinación metotrexato - anti-TNF se mostró más eficaz que la triple terapia[163].	2+

Recommendations

In patients with rheumatoid arthritis in whom methotrexate monotherapy fails, either the use of a combination treatment with conventional DMARDs or a biological therapy is recommended, depending on patient characteristics **(Grade B recommendation)**.

The treatment and prognosis of patients with RA have significantly changed in recent decades[164]. For many years, DMARDs have been the cornerstone of treatment of the disease. Now, however, with the introduction of biological therapies, and a trend towards starting treatment earlier, taking advantage of the window of opportunity and using a T2T strategy, these drugs have become the treatment of choice[165]. It is currently known that biological drugs combined with MTX are effective in controlling the disease in many patients with a poor response to MTX monotherapy[166]. Nonetheless, given the healthcare costs associated with the use of these drugs, it is necessary to analyse the scientific evidence that compares the combination of two or more conventional DMARDS with the combination of one DMARD and a biologic.

Quality of the evidence

There is a paucity of evidence related to this question. We identified one good-quality RCT[161] and two RCTs classified as having a lower level of quality[162, 163]. We also found one observational study[167]. Further, manual searching yielded a study that only partially met the inclusion criteria in that it was based on patients with undifferentiated arthritis[168].

The good-quality trial was a double-blind multicentre RCT (the TEAR study) that included 755 patients with early RA in four treatment arms. The first two arms involved initial treatment with triple therapy vs MTX + ETN, and these were compared with the second two arms which involved initial MTX alone, with step-up treatment, adding SSZ + HCQ or ETN in patients who did not respond to MTX. No differences were observed in DAS28 scores between any of the groups at the end of the follow-up or in the percentage of patients who achieved clinical remission as measured by DAS28 (p=0.93). Further, while there were no differences between groups who received combined therapy from the outset and those in whom drugs were added, it was found that patients given biological therapy (MTX and ETN) showed smaller increases in Sharp score (0.64 vs 1.69; p=0.047) and a lower rate of radiographic progression (66.4% vs 76.8%; p=0.02). Regarding safety, no differences were found between groups[161] (Level of evidence 1+).

The second trial was a non-blind multicentre randomised trial (the Swefot trial) that compared triple therapy to treatment with MTX + IFX in 493 patients with early RA and in those with a poor response to MTX, with a 2-year follow-up. The percentage of patients with a good EULAR response was higher in the group treated with IFX at 12 months (39% vs 25%; p=0.016). At 24 months, differences in EULAR and ACR response did not reach significance, although the percentage of patients who continued to have active disease was low[162] (Level of evidence 2++).

The third trial was a double-blind multicentre trial (the RACAT study) including 353 patients with active RA (DAS28 ≥ 4.4), who had been receiving MTX and were randomly allocated to receive either triple therapy and ETN placebo or ETN and triple therapy placebo in addition to MTX. If by week 24 the DAS28 score had not reduced by 1.2, patients were switched to the treatment given in the other arm. The study population was mainly men and the target sample size was changed since the study did not achieve the expected level of recruitment. The outcomes with triple therapy were not worse than with ETN + MTX at week 48. After adjusting for the switch made in week 24, similar results were found (0.10 0.16; upper limit of the 95% CI: 0.27; p < 0.001 for no inferiority). Similarly, no differences were found between the groups in terms of DAS28 < 3.2, DAS28 < 2.6, CDAI, ACR20, ACR50 or ACR70 response, or HAQ or modified Sharp scores. No significant differences were found in response by sex. Switching at week 24 was equally common in both groups (27%) and patients who switched improved their DAS28 score by week 48 in both groups (p < 0.001 for both comparisons). The rate of adverse events was similar in both groups, although there were more serious infections in the ETN group (4.1% vs 1.8% in the triple therapy group)[163] (Level of evidence 2+).

The observational study was a multicentre prospective longitudinal study of 129 patients from the Norwegian NOR-DMARD register (patients with RA who had been treated with biological and/or conventional DMARDs) that compared the efficacy of starting conventional DMARDs to that of adding anti-TNF in patients with RA (with a 5-year disease duration) who had a poor response to MTX. The treatment was changed at the discretion of the clinician. Patients given triple therapy (MTX, SSZ and HCQ) had a significantly higher baseline DAS28 score than those given other DMARDs (5.32 vs 4.77; p=0.02). Compared to the DMARD group, the anti-TNF group had a significantly higher rate of remission (34.5% vs 12.9%) and a lower level of disease activity (54.5% vs 28.6%; p=0.02, for both), as well as a larger reduction in DAS28 (-1.91 vs -1.03; p=0.04). On the other hand, no such pattern was observed for SDAI or HAQ scores or good EULAR response. The adjustment for age and Charlson's comorbidity did not change the results[167] (Level of evidence 3).

There was another study that, although it did not meet the inclusion criteria, as it included patients with undifferentiated arthritis, was taken into account since the information it provides may address the PICO criteria. This was a blind multicentre RCT (the IMPROVED study) in 610 patients with undifferentiated arthritis or RA. Patients who did not have a DAS < 1.6 after 4 months of treatment with MTX and prednisone were randomly assigned to triple therapy and prednisone (arm 1, n=83) or MTX and ADA (arm 2, n=78). After 8 months of treatment, if DAS had fallen to < 1.6, the treatment was tapered in both arms to MTX monotherapy.

If DAS was > 1.6, patients in arm 1 were switched to MTX and ADA, while in arm 2, the ADA dosing frequency was increased to weekly, a regime that is not used in routine clinical practice. After 8 weeks, there was no difference between the arms in DAS remission rate (36% vs 35%, p=0.99). On the other hand, the percentage of patients who remained in DAS remission after tapering to MTX monotherapy was higher in arm 2 (65% vs 37%; p=0.02). After 1 year of treatment, the remission rate was higher in arm 2 than arm 1 (p= 0.01), though no significant differences were observed in terms of mean DAS (0.03; 95% CI -0.16 to 0.22) or HAQ (0.04; 95% CI 0.01 to 0.29) scores[168]

When formulating recommendations, the GDG has taken into account that the conclusions of the different studies differ and were not always obtained from populations representative of the target population for these guidelines (7). Although both treatment regimens seem to be clinically effective (EULAR and DAS response), they have different response times. This could be why triple therapy may seem less effective in reducing radiographic progression, and this may be relevant especially in RA patients with poor prognostic factors. Based on the limited evidence available, the GDG considers that the combination of MTX with a single sDMARD is less effective than MTX with anti-TNF therapy.

The GDG also considers that the results of the studies on the use of combined DMARD therapy in cases of RA with a poor response to MTX monotherapy are applicable to our health system, given that the therapeutic agents assessed have been used for some time in our setting. In the studies analysed, the DMARDs used are MTX, SSZ and HCQ, either as a triple therapy or MTX in combination with one of the others. Other combinations of agents have yet to be properly assessed.

Although the studies available have only used anti-TNF, ETN, ITX and ADA, taking into account their mechanisms of action, the results could be extended to all anti-TNF agents available to date, i.e., golimumab (GOL) and certolizumab pegol (CZP). Nonetheless, other biological therapies with different targets- tocilizumab (TCZ), abatacept (ABA) and RTX- cannot be included in these recommendations.

The studies here described mainly have an economic impact, since their findings imply that all individuals with early RA with a poor response to MTX monotherapy may be treated with triple therapy before assessing the combination of MTX and anti-TNFs, provided patients do not have poor prognostic factors or established structural damage.

Clinical question 5

In patients with rheumatoid arthritis with a poor response to conventional DMARDs, are biologic or targeted DMARDs more effective?

Summary of the evidence

The administration of baricitinib in patients with rheumatoid arthritis with a poor response to methotrexate was associated with a higher ACR20 response rate (70% vs 61%, p=0.014) and mean change in 28-joint Disease Activity Score using C-reactive protein (-2.24 vs -1.95; p < 0.001) than adalimumab, with a 3-month follow-up[169].	1+
The administration of baricitinib in patients with rheumatoid arthritis with a poor response to methotrexate achieves a reduction in radiographic progression similar to obtained with adalimumab, with a 6-month follow-up[169].	1+
In patients with rheumatoid arthritis with a poor response to methotrexate, the combination of tofacitinib and methotrexate was found not to be inferior to the combination of adalimumab and methotrexate, with a difference in ACR50 response rate at 6 months of 2% (98% CI: 6 to 11), setting the lower limit of non-inferiority at -13%[170].	1+
In patients with rheumatoid arthritis with a poor response to methotrexate, the combinations of methotrexate plus tofacitinib and methotrexate plus adalimumab were associated with higher rates of low disease activity at 6 months (Simple Disease Activity Index ≤ 11) (50 and 47%, respectively) than tofacitinib monotherapy (43%)[170].	1+
There is indirect evidence that in patients with rheumatoid arthritis who have a poor response to methotrexate, tofacitinib ≥ 5 mg is similar to adalimumab in terms of disease activity, based on 3- and 6-month follow-ups[171, 172].	1

Recommendations

In patients with rheumatoid arthritis in whom conventional DMARD therapy fails, the recommendation is to use a combined therapy, with a biologic or targeted therapy, depending on patient characteristics **(Grade C recommendation)**.

The current recommendations in Spain advocate the use of conventional DMARDs for the initial treatment of RA. Among the conventional DMARDs, MTX is still the drug of choice. When there is not a good response to MTX, other conventional DMARDs can be used in step-up combination therapy or a biologic can be added, depending on patient characteristics and the presence of poor prognostic factors. Given this situation in which either biologics or targeted DMARDs may be appropriate in patients with a poor response to MTX,

there is a need to identify the evidence that would guide the choice between these treatments.

Quality of the evidence

Just one publication was found reporting an RCT comparing the efficacy of biologics with that of targeted DMARDs after a poor response to conventional DMARDs[169], though it led to a second publication providing data on patient-reported outcomes [173]. We also found two RCTs[171, 172] that indirectly compared TOFA and ADA. Finally, we included a non-inferiority study[170] of TOFA in combination with MTX or as monotherapy, compared to the combination of ADA and MTX.

The 2017 RCT by Taylor *et al.*[169], which sought to assess the efficacy of BARI compared to placebo or ADA plus MTX in patients with moderate-to-severe RA and a poor response to MTX, BARI was found to be superior to ADA in week 12 in terms of ACR20 response (70% with BARI vs 61% with ADA, difference of 9% [95% CI 2 to 15]) and DAS28-CRP score change (mean change at week 12 of -2.24 with BARI vs -1.95 with ADA; $p < 0.001$). Further, ACR20 response was higher with BARI than with placebo (70% vs 40%; $p < 0.001$) or ADA (70% vs 61%; $p=0.014$) at week 12.

Regarding radiological progression at week 24, the percentages of patients with no progression (change from baseline, cumulative percentage) were 70.4% with placebo, 79.1% with BARI ($p \leq 0.05$) and 81.1% with ADA ($p \leq 0.05$) for change in modified total Sharp score (ΔmTSS) ≤ 0 and 70.4% with placebo, 85.2% with BARI ($p \leq 0.05$) and 86.5% with ADA ($p \leq 0.05$) for ΔmTSS ≤ 0.5. There was significantly less structural progression at week 24 with BARI and with ADA than with placebo. The authors concluded that BARI was significantly superior to placebo and numerically similar to ADA in terms of efficacy (Level of evidence 1+).

In the other publication based on the same clinical trial[173], BARI was associated with a significantly greater improvement in most patient-reported outcomes, including physical function, duration and severity of the morning joint stiffness, pain, fatigue and quality of life than placebo or ADA. The improvement was maintained until the end of the study (week 52).

The 2017 study by Fleischmann *et al.* (ORAL Strategy)[170] was a multicentre non-inferiority RCT (involving 194 centres in 25 countries) that compared the efficacy of TOFA monotherapy and TOFA plus MTX with ADA plus MTX for the treatment RA in patients with a poor response to MTX. At 6 months, ACR50 response was achieved in 147 (38%) out of 384 patients who finally received TOFA as monotherapy, 173 (46%) out of 376 who received TOFA plus MTX and 169 (44%) out of 386 patients who received ADA and MTX. The combination of TOFA and MTX was not

inferior to the combination of ADA and MTX. The difference in the percentage of patients with an ACR50 response to TOFA and MTX compared to ADA and MTX was 2% (98.34% CI -6 to 11) with a lower limit of the CI higher that the predefined non-inferiority limit (-13%). The study did not show superiority for in comparisons between the treatment groups (Level of evidence 1+).

The 2012 study by van Vollenhoven (ORAL Standard)[171] assessed the efficacy of TOFA or ADA with that of placebo in patients with active RA who had a poor response to MTX. Although this study was not designed to compare TOFA and ADA, the 6-month results show that the rate of ARC20 response was 51.5% in the TOFA 5 mg group, 52.6% in the TOFA 10 mg group and 47.2% in the ADA 40 mg group, compared to 28.3% in the placebo group ($p < 0.001$), for the overall comparison. The study also indicated a greater reduction in the HAQ-disability index (DI) score at 3 months and a higher percentage of patients with a DAS28-ESR < 2.6 at 6 months of follow-up in the active treatment groups (TOFA or ADA) than in controls. The study concluded that patients with RA receiving background MTX, TOFA was significantly superior to placebo and similar to ADA in terms of efficacy (Level of evidence 1+).

The objective of the 2012 study by Fleischman[172] was to assess the efficacy, safety and tolerability of 5 doses of oral TOFA and ADA as monotherapy compared to placebo in patients with active RA and an inadequate response to DMARDs. Their results indicated that treatment with TOFA at doses ≥ 3 mg twice daily was associated with a more rapid and effective response than placebo; the percentage of patients with an ACR20 response at week 12 was 39.2% for TOFA 3 mg; 59.2% for TOFA 5 mg; 70.5% for TOFA 10 mg; 71.9% for TOFA 15 mg; and 35.9% for patients in the ADA group, compared to 22% in the placebo group. The improvements were sustained at week 24 for ACR20, ACR50 and ACR70 response rates, as well as for remission as defined using DAS28-CRP and the DAS28-4-ESR (Level of evidence 1+).

The 2017 study of Tanaka *et al.*[174] evaluated the efficacy and safety of BARI in Japanese subpopulations of patients with RA and assessed whether the results in these samples were in line with those obtained in the overall population. A subgroup analysis was carried out based on four phase 3 clinical trials (RA-BEGIN, RA-BEAM, RA-BUILD and RA-BACON). In Japanese patients, the ACR20 response rate at week 12 was higher in those who had received BARI 4 mg than placebo (67% vs 34%), and BARI 4 mg and ADA prevented radiographic progression of structural damage at week 24 and 52, compared to placebo. Both with BARI 4 mg and with ADA there was an improvement in terms of ACR20, HAQ-Disability Index (DI) and DAS28 CRP from week 1, compared to placebo. The study concluded that BARI,

with or without MTX, seems to have a similar level of efficacy in Japanese patients to that observed in the overall study populations.

In general, the use of bDMARDs or tsDMARDs (preferably in combination with conventional DMARDs) is reserved for patients who have had a poor response to conventional drugs, in particular, MTX. No significant differences have been found in terms of efficacy and/or safety between different bDMARDs or between bDMARDs and tsDMARDs (TOFA and BARI).

Currently, there is a wealth of experience with biological drugs and there are biosimilars to some anti-TNFs, but JAK inhibitors and other biologics may be a reasonable alternative depending on patient characteristics. The GDG deemed it appropriate to formulate a recommendation that supports the use of a targeted DMARD as an alternative to bDMARDs, despite the fact that all the evidence related to this issue comes from comparison studies with ADA and that there are no comparisons with biologics against other therapeutic targets. Given the lack of direct comparisons between BARI and TOFA, the results of clinical trials do not allow us to identify clinically relevant differences between them, given that the design of the clinical trials was slightly different.

The convenience of the oral route of administration of tsDMARDs (BARI and TOFA) compared to the parenteral route of bDMARDs and the potentially more intense effect on patient-reported outcomes be may relevant factors that we should take into account (in relation to patient preference and treatment adherence), although they should not be determinant in the choice between these drugs and bDMARDs.

Regarding safety, from a qualitative point of view, the profile of adverse reactions for tsDMARDs is in line with that previously reported for biological agents, with slight differences. Although the safety profile is complex, meaning that patients should be monitored closely, this need for follow-up does not seem substantially different to the monitoring rheumatologists do routinely for RA.

7.3.3. Treatment with the first biologic or targeted DMARD

Clinical question 6

In patients with rheumatoid arthritis, what is the efficacy of the combination of any biologic DMARD with a conventional DMARD other than methotrexate?

Summary of the evidence

Combining anti-TNF therapy with leflunomide is as effective as combining it with methotrexate as measured by 28-joint Disease Activity Score (DAS28)[175-177], Health Assessment Questionnaire (HAQ) - Disability Index[175,176], ACR response[176], EULAR response[177, 178] and radiographic progression[175].	1+, 2+
Combining anti-TNF therapy with other conventional DMARDs (other than leflunomide) is as effective as combining it with methotrexate as measured by DAS28[175, 179], HAQ[175], EULAR response[178] and radiographic response[175].	2+
The combination of rituximab and leflunomide is as effective or more effective than the combination of rituximab and methotrexate as measured by DAS28[180], and more effective as measured by HAQ and EULAR response[180].	2-, 2+
The combination of tocilizumab and leflunomide is as effective as the combination of tocilizumab and methotrexate as measured by DAS28, HAQ, erythrocyte sedimentation rate and C-reactive protein[181].	2+

Recommendations

In patients with rheumatoid arthritis requiring biological therapy with contraindications or intolerance to methotrexate, we recommend leflunomide in combination with a biologic **(Grade B recommendation)**.

Several double-blind RCTs have demonstrated greater efficacy and longer drug survival when biological therapies are used in combination with MTX rather than as monotherapy[1-3].

Most patients with RA treated with a biologic are also given MTX, but when this drug is contraindicated, in routine practice, it is common that biologics are given with other conventional DMARDs, despite the lack of good quality clinical trials supporting this.

Hence, there is a need to identify other DMARDs that, like MTX, improve the efficacy of biological therapies and have an appropriate safety profile, in order that they can be prescribed when MTX is contraindicated, ineffective or not tolerated.

One of the options that we will review in more detail is LEF, as it is easy to administer, has shown good tolerance and efficacy in clinical trials[4] and has been widely studied in combination with biological therapies.

Quality of the evidence

Five studies (most of them cohort studies) were found that assess the efficacy of DMARDs other than MTX combined with other biological agents: anti-TNF, anti-CD20 (RTX) and anti-IL6 (TCZ) agents.

An observational longitudinal cohort study in a Swiss population of 1,218 patients, from the Swiss Clinical Quality Management-RA database, compared the effectiveness, continuation rates and safety of various DMARDs in combination with anti-TNF agents. Patients were divided into three groups, based on the co-therapy given, anti-TNF + MTX (n=842), anti-TNF + LEF (n=260) or anti-TNF agents + other DMARDs (n=116), and followed-up for 17 months. No significant differences were found between the three groups in the progression of radiographic damage (ANOVA; p=0.77), functional disability as measured by HAQ (ANOVA p=0.09) or disease activity as measured by DAS28 (ANOVA p=0.33). There were also no significant differences between the groups in adverse effects. The main limitation of this study was that the anti-TNF + other DMARD group had too small a sample size and was heterogeneous, limiting the conclusions that can be drawn for this subgroup. Therefore, the authors conclude that LEF and potentially other DMARDs are as effective and safe as MTX as co-therapy in combination with anti-TNF agents[175] (Level of evidence 2+).

A prospective RCT, with a sample of 120 patients, assessed the efficacy and tolerability of combination therapy with LEF + anti-TNF (n=60) vs MTX + anti-TNF (n=60). In this study, initial therapy with MTX or LEF was continued and randomly combined with another drug (ETN, ADA or INF), and patients were assessed at 4, 12 and 24 weeks. Each of the groups was divided into three subgroups of 20 patients, as a function of the anti-TNF agent added. The majority of patients were women (84.2%), the sample had a mean age of 52 years old and mean disease duration of 54 months (SD± 39.6) and baseline DAS28 scores were 5.5± 1.13 in the MTX + anti-TNF group and 5.8 ± 1.17 in the LEF + anti-TNF group. After 24 weeks, there were no significant differences between the two groups or the six subgroups (p=0.29) in terms of DAS28: the mean DAS28 score reaching 3.3 ± 1.4 (p= 0.0001) in the MTX + anti-TNF group and 3.5 ± 1.0 in the LEF + anti-TNF group (p= 0.0001). Remission (DAS28 < 2.6) was achieved in 13 patients (21.6%) in the MTX + anti-TNF group and 10 (16.6%) in the LEF + anti-TNF group. Regarding functional disability, there was a significant reduction in HAQ-DI scores in both groups at 4 (p<0.001), 12 (p<0.001)

and 24 (p<0.0001) weeks, differences between the groups not reaching significance. Similarly, there were no significant differences in rates of treatment discontinuation (p=0.63) or serious adverse effects between the two groups. Based on these data, the authors concluded that treatment with anti-TNF agents can be used in combination not only with MTX but also with LEF, with the same probability of achieving clinical improvement in patients with RA without a higher risk of serious adverse events[176] (Level of evidence 1+).

Another cohort study, based on the German biologics register RABBIT, assessed 1,760 patients treated with anti-TNF agents (ADA, ETN or INF) in combination with MTX (n=1,375) or LEF (n=394) and followed up for 36 months. Groups were similar in that most patients had a long history of RA and the rates of comorbidity were high, but patients on LEF were older and had a higher baseline DAS28 than those on MTX. In this study, 15 to 27% of patients on anti-TNF + MTX and 9 to 21% of those on anti-TNF + LEF had been previously treated with a biologic (p<0.006). Comparing the combinations of each of the three anti-TNFs with MTX and with LEF, outcomes did not differ significantly (p=0.15, ITT p=0.08). Similarly, there were no significant differences between the groups in good EULAR response or improvement in functional capacity. The 3-year survival rates were similar for the two DMARDS in combination treatments. The authors concluded that LEF is a valid alternative in terms of safety and efficacy when MTX is contraindicated or ineffective[177] (Level of evidence 2+).

Different conclusions from those of the aforementioned studies were reached in a Dutch cohort study, with a total sample of 1,933 patients from the Dutch Rheumatoid Arthritis Monitoring (DREAM) biologic registry, comparing efficacy and drug survival over 12 months in six treatment groups: anti-TNF monotherapy (n=320), anti-TNF + MTX (n=919), anti-TNF + LEF (n=80), anti-TNF + SSZ (n=103), anti-TNF + other DMARDs (n=99) and anti-TNF + MTX + other DMARDs (n=412). The sample only included patients starting their first anti-TNF therapy and there were baseline differences between groups, such as sample size and previous DMARD failures. The groups that had the poorest course in terms of changes in DAS28 and HAQ and shorter survival than with anti-TNF + MTX were the anti-TNF monotherapy (=0.572; 95% CI 0.411 to 0.734; p<0.001) and anti-TNF + LEF (=0.297; 95% CI 0.004 to 0.589; p=0.047) groups. Nonetheless, after adjusting for confounders, the HAQ score in the anti-TNF + LEF group was not significantly different. The authors concluded that the best option is the combination of MTX and anti-TNF, that the monotherapy is clearly less effective and that other DMARDs seem to be a good alternative to MTX, except LEF for which results are inconclusive[179] (Level of evidence 2+).

A cohort study based on the British Society for Rheumatology Biologics Register compared the efficacy of anti-TNF (INF or ETN) monotherapy with the combination of MTX and other DMARDs in patients with RA followed up for 6 months. The patients generally had a long history of severe RA refractory to various DMARDs and were starting treatment with their first biologic agent. The authors found no significant differences in the likelihood of achieving a good EULAR response in the MTX co-therapy group compared to the other DMARD co-therapy group (OR 1.04; 95% CI 0.71 to 1.53). Similarly, there were no significant differences between the groups in adverse effects. Therefore, they concluded that the combination of anti-TNF and DMARDs other than MTX can be considered in patients who are intolerant to MTX[178] (Level of evidence 2+).

Two cohort studies were found that assessed the efficacy of RTX. The first one was a multicentre study with a total of 2,265 patients from 10 European registers, comparing the efficacy and safety of RTX alone (n=506) and in combination with MTX (n=1,195) and LEF (n=177). The percentage of patients who achieved a good EULAR response at 6 months in the RTX + LEF group (29.1%) was higher than in the RTX + MTX (21.1%) and RTX monotherapy (19.3%) groups (p=0.02 and p= 0.01 respectively). Similar results were found at 12 months. Nonetheless, improvement in terms of reduction in HAQ was not significantly better in the LEF + RTX group than in the other groups. The rates of adverse effects observed were 10.2%, 13.2% and 13.9% in the RTX + LEF, RTX + MTX and RTX monotherapy groups respectively. The authors concluded that LEF is a safe and effective alternative to MTX in combination with RTX and that this combination was slightly better than RTX + MTX, implying that there may be a synergic effect between LEF and RTX[180] (Level of evidence 2-).

The second study is a study based on the German biologics register (RABBIT) including 907 patients with RTX-naïve RA. This study compared the same three treatments (RTX + MTX, RTX + LEF and RTX monotherapy) but with a longer follow-up of 3 years. The frequency and timing of RTX retreatment were similar in the three groups (p>0.62), as was the improvement in DAS28 over the study period (p > 0.15). DAS28 decreased by 1.5 points over the first 12 months of treatment and by a further 0.4 points between 12 and 36 months, equally in all groups. On the other hand, treatment discontinuation and dropout rates were significantly higher in the RTX monotherapy group (HR 1.7; 95% CI 1.2 to 2.3). The authors concluded that the three treatments seem to be equally effective and that for patients who are intolerant to MTX, the combination of RTX in combination with LEF is a good option even in the long term[182] (Level of evidence 2+).

Regarding TCZ, a Spanish cohort study compared its efficacy in combination with MTX or with LEF. The study included 91 patients in whom efficacy and safety

were assessed over a 6-month follow-up. There were no significant baseline differences between groups and patients generally had a long history of RA that was refractory to at least one DMARD and/or anti-TNF agent. Two-thirds (66%) were receiving concomitant glucocorticoids. The study found improvements in DAS28 by 2.23± 1.38 with TCZ + MTX and by 2.17 ± 1.43 with TCZ + LEF. Remission rates (measured by DAS28-ESR < 2.6, SDAI ≤ 3.3, CDAI ≤ 2.8 and 2010 ACR/EULAR criteria) were similar across the groups. No significant differences were observed in efficacy or adverse effects in the TCZ + LEF group between those receiving 10 and 20 mg of LEF. HAQ scores for functional disability improved by 0.64 with TCZ + MTX and by 0.62 with TCZ + LEF. The rate of serious adverse events per 100 patient/years was similar in the two groups (23.5 in the TCZ + MTX group vs 21.4 in the TCZ + LEF group) and there were no significant differences in minor adverse events. The findings indicate that LEF is a safe and effective alternative to MTX in combination with TCZ[181] (Level of evidence 2+).

The studies based on anti-TNF agents[175-177] generally agree in supporting the view that LEF is as effective as MTX, although the clinical trial of Stefano *et al.*[176] found better results in terms of DAS28 improvement, this being attributable to the fact that they studied a population of patients with early RA and no history of anti-TNF failure, as well as higher DAS28 scores and less structural damage (higher probability of good response) at baseline. In contrast, the study by Manders *et al.*[179] showed discordant results, failing to show that LEF is as effective as MTX in combination with anti-TNFs, though this may be due to the small sample of patients on LEF compared to MTX and to significant baseline differences in terms of history of DMARD use.

Regarding studies assessing DMARDs other than MTX and LEF[175, 178, 179], there is agreement that they are an effective alternative to MTX, although these DMARDs are not assessed separately (except SSZ in Manders *et al.*[179]) and furthermore the study by Finckh *et al.*[175] of patients from the Swiss registry is based on a very small sample to be able to draw firm conclusions. To our knowledge, there are no other studies that assess DMARDs other than MTX and LEF combined with biologics other than anti-TNF agents.

The two studies with RTX[180, 182] reached similar conclusions regarding the efficacy of RTX combined with LEF, but the former study reports even better results than when it was combined with MTX. This may be attributed to the fact that in Chatzidionysiou *et al.*[180], a higher proportion of patients had received biological therapy in the LEF group than in the MTX group. Further, the study by Ritcher *et al.*[182] was of better methodological quality and the data were more homogeneous since patients were from the same population.

The GDG believes that the results obtained may be extrapolated to the Spanish population given that they are all based on European patient registries and reflect the experience and daily clinical practice of rheumatologists across countries in this region, which are similar to those of these specialists in Spain. Further, it is common that in daily clinical practice in Spain, as in the cohort studies assessed, LEF is used after failure of or intolerance to MTX and then a biologic is added. On the other hand, we do have to be cautious about extrapolating these data to patients with early RA, since the majority of studies discussed here included patients with a long history of RA and a history of treatment failure with DMARDs and biologics.

Biological therapy is only approved on the summary of product characteristics in combination with MTX, but these recommendations endorse the safety and efficacy of other DMARDs (in particular LEF) in association with biological therapy and the superiority of this approach over monotherapy. This is very useful in clinical practice since LEF is a drug with a good efficacy, safety and tolerance (associated with less dyspepsia and nausea than MTX), although it is somewhat more expensive. Further, if there is not a good clinical response to MTX, it is common that patients are switched to LEF, and if the treatment is still not sufficiently effective, a biologic is added. The GDG has taken into account that since LEF has been used as a second option in the studies discussed, it may have been used in the most severe cases of RA, implying an indication bias; nonetheless, the results show a similar level of efficacy to MTX in combination with biologics.

Regarding DMARDs other than MTX and LEF, the GDG has decided not to make specific recommendations for each drug, because the findings are based on very small sample sizes and it has not been possible to perform individual subanalyses, and because there are no efficacy studies together with RTX or TZC. The GDG would like to note that the anti-TNF agents analysed are ETN, INF and ADA, but that it seems to be possible to extrapolate the data to others. No data are available from studies with ABA.

Finally, the GDG considers that more randomized studies are required to define the role of the combination of biologics with LEF and especially with other DMARDs and also to establish the persistence of the efficacy and assess the long-term progression of radiographic damage.

Clinical question 7

In patients with rheumatoid arthritis, which dose of methotrexate in combination with a biologic DMARD is associated with the best clinical outcomes, highest drug concentrations and lowest antibody production?

Summary of the evidence

In combination treatment with anti-TNF, methotrexate doses ≥10 mg/week are associated with a better clinical response than doses < 10 mg/week[183-185].	1+ +, 1+
The use of methotrexate doses < 10 mg/week in combination with adalimumab is associated with lower anti-TNF concentrations or higher production of anti-adalimumab antibodies, while using methotrexate doses ≥ 10 mg/week is associated with higher anti-TNF concentrations or lower anti-adalimumab production[183,186].	1++, 2+
Doses of methotrexate between 10 and 20 mg/week seem to have a similar efficacy when combined with adalimumab or certolizumab pegol during the first 6-12 months of treatment, although extrapolation to other anti-TNF agents and longer follow-up periods is questionable[183, 185].	1+ +, 1+

Recommendations

In patients with rheumatoid arthritis who receive combination treatment with methotrexate and anti-TNF agents, the recommendation is to use methotrexate at doses of at least 10 mg/week **(Grade B recommendations)**.

The EULAR and SER recommendations state that in patients with RA with indications for biological therapy, this should preferably be used in combination with MTX[54, 56]. This is due to the fact that, as has been demonstrated, biological therapies, especially those based on anti-TNF agents, are more effective when combined with MTX[187-190], or even with other conventional DMARDs[177, 191], than as monotherapy.

Another reason for using biological therapies in combination with MTX is the ability of this drug to reduce immunogenicity to these therapies[186]. This fact is also very significant from the point of view of the long-term survival of these therapies, given that the immunogenicity of biological therapy is associated with lower drug concentrations and loss in efficacy[192].

On the other hand, there is no consensus on the most appropriate doses of MTX when combined with an anti-TNF agent or another biological therapy.

Quality of the evidence

Five studies were identified that assess the efficacy of the combination of MTX and anti-TNF agents. No studies found were able to answer the question from the point of view of the use of biological therapies for therapeutic targets other than TNF.

A double-blind parallel-group randomised trial (the CONCERTO study) in patients with RA given the combination of MTX and ADA assessed the impact of different doses of MTX, 2.5, 5, 10 and 20 mg/week, for a period of 26 weeks, on efficacy, safety and ADA concentrations. The study included biologic- and MTX-naïve patients with active RA (N=395). Overall, 42.9%, 44.0%, 56.6% and 60.2% of patients achieved low disease activity (DAS28-CRP<3.2) with the different doses of MTX, respectively. In general, DAS28, ACR, SDAI and CDAI scores were similar with the MTX 10 and 20 mg/week doses, and in both cases, higher than for the 2.5 and 5 mg/week doses. Levels of structural damage were similar across the groups but there was a trend towards more adverse effects (gastrointestinal, infection and hair loss) with the higher MTX doses. Further, ADA concentrations were similar in the groups taking 10 and 20 mg/week of MTX, and in both cases, higher than in the 2.5 and 5 mg groups. The authors concluded that higher doses of MTX in combination with ADA are associated with a better clinical response; however, the 10 and 20 mg (per week) doses of MTX seem equivalent, even from the pharmacokinetic point of view[183] (Level of evidence 1++).

A double-blind parallel-armed RCT (the MUSICA study) assessed the result of reducing the dose of MTX at the start of combination treatment with ADA in patients with RA who had an inadequate response to MTX. The study assessed the non-inferiority in terms of clinical and ultrasound response of the 7.5 mg/week MTX dose compared to the 20 mg/week dose in combination with ADA. It included 309 patients who were randomized at the start of ADA treatment to one of the two doses of MTX and were followed up for 24 weeks. The results did not meet the non-inferiority criteria, indicating that in combination treatment with ADA low-dose MTX (7.5 mg/week) is inferior to high-dose MTX (20 mg/week)[184] (Level of evidence 1+).

Another study assessed the impact of the dose of MTX given in combination with CZP. It involved a pre-specified subgroup analysis of two phase III randomized double-blind parallel-armed studies, RAPID 1 and RAPID 2, in patients with RA who had a poor response to MTX. A total of 638, 635 and 325 patients received CZP 200 mg, CZP 400 mg and placebo, respectively, every other week. All patients received MTX doses ≥ 10 mg/week and, for the analysis, they were divided into

two groups as a function of MTX dose: <15 mg/week and ≥15 mg/week. No differences were observed between the two groups in clinical efficacy (ACR and DAS28 response) or structural damage at 24 weeks; however, there were more adverse effects in the group on the highest doses of MTX. We should highlight that the group taking <15 mg actually included patients taking doses of 10 to 15 mg/week (except some for violations of the protocol) due to the inclusion criterion of MTX ≥ 10 mg/week. The study concluded that MTX doses ≥10 mg/week in combination with CPZ were associated with similar efficacy[185] (Level of evidence 1+).

An open prospective study (the GO-MORE study) assessed GOL in combination with cDMARDs in 3,366 patients with RA. Of these, 2,663 patients were also on MTX. No differences were observed in EULAR response between the MTX doses <10 mg/week (n=142), 10-15 mg/week (n=526) or ≥15 mg/week (n=1,995), although there were confounding factors such as the inclusion in this analysis of patients on combinations of cDMARDs[193] (Level of evidence 2+).

A Dutch cohort assessed the effect of different doses of MTX on immunogenicity to ADA in 272 patients with RA. Patients were divided into four groups: no MTX (n=70), low-dose MTX (5-10 mg/week, n=40), moderate-dose MTX (12.5-20 mg/week, n=54) and high-dose MTX (≥22.5 mg/week, n=108). Patients on MTX had lower anti-ADA antibody levels than those not on this drug, and there was a trend to lower antibody levels with increasing doses of MTX, though differences were only significant between the high and low doses[186] (Level of evidence 2+).

The GDG considers that there is good agreement between studies. Specifically, there is agreement that when combined with an anti-TNF agent, MTX doses ≥10 mg/week are more effective[183-185] and those < 10 mg/week are less effective[183, 184]. The only finding that differs comes from the GO-MORE study, which did not find a lower efficacy with MTX doses <10 mg/week in combination with GOL, although there were more confounding factors in this study.

Regarding the effect of MTX dose on drug concentrations or immunogenicity to the biological agent, there is agreement that doses of MTX < 10 mg are associated with lower ADA concentrations and a higher anti-ADA antibody production, while doses of MTX ≥ 10 mg/week are associated with higher ADA concentrations and a lower antibody production[183, 186]. There is also consistent evidence that MTX doses > 10 mg/week do not offer added benefits in terms of efficacy or drug concentrations when combined with anti-TNF agents[183, 185, 186]; nonetheless, the relatively short follow-up of these studies means we must be cautious about these conclusions.

The development group considers that these results are directly applicable to our health system given that they concern a common situation in the treatment of patients with RA. In the process of drafting these recommendations, the GDG decided that the conclusions obtained with ADA, CZP and GOL can be generalized to other anti-TNF agents, given the similar clinical response pattern of these drugs. Nonetheless, we should bear in mind that the different structure of other anti-TNF agents such as IFX and ETN may have an impact on immunogenicity, and hence, on the results in terms of efficacy.

On the other hand, which is the appropriate dose of MTX when combined with an anti-TNF agent is a question of great clinical importance since it arises very often in clinical rheumatology practice and there has not been a clear answer. The recommendation of a minimum dose of 10 mg/week is conservative in the sense that it does not define whether this dose is sufficient or higher doses should be used; nonetheless, the available evidence supports the view that efficacy is similar with doses of over 10 mg, but the relatively short follow-up of the studies and some potential differences in immunogenicity has led the GDG to state the recommendation in this way.

Clinical question 8

In patients with rheumatoid arthritis, are there differences in terms of efficacy between the different biologic DMARDs used as a first-line treatment?

Summary of the evidence

Tocilizumab monotherapy has shown to be more effective than adalimumab monotherapy, as measured by change in 28-joint Disease Activity Score using erythrocyte sedimentation rate (DAS28-ESR), remission and DAS28-ESR low disease activity, good and moderate EULAR response, and ACR20, ACR50 and ACR70; however, it was not more effective as measured by the Health Assessment Questionnaire (HAQ), Short Form-36 or Functional Assessment of Chronic Illness Therapy-Fatigue scale[194].	1+
Sarilumab monotherapy has shown to be more effective than adalimumab monotherapy in reducing signs and symptoms in patients with rheumatoid arthritis in whom methotrexate cannot be used[195].	1+
Adalimumab in combination with methotrexate is as effective as certolizumab pegol in combination with methotrexate, as measured by ACR20 and DAS28-ESR low disease activity[196].	1+

Adalimumab and abatacept in combination with methotrexate have shown to have the same efficacy as measured by ACR20; ACR50; ACR70; 28-joint Disease Activity Score using C-reactive protein (DAS28-CRP); DAS28-CRP low disease activity; DAS28-CRP, Simple Disease Activity Index, CDA and Boolean remission; HAQ; RAPID3; fatigue; patient-reported outcomes and radiological score (modified Sharp/van der Heijde score)[197,198].	2+
Adalimumab and etanercept in combination with DMARDs have shown the same efficacy as measured by the persistence of treatment, DAS28-CRP and good and moderate EULAR response[199].	1-
Rituximab has shown the same efficacy as the anti-TNF agents adalimumab and etanercept as measured by ACR20, ACR50, ACR70, DAS28 remission and good and moderate EULAR response[200].	1-

Recommendations

In patients with rheumatoid arthritis, it is not possible to recommend a specific biological agent for first-line treatment in association with methotrexate **(Grade B recommendation)**.
As monotherapy, the recommendation is to use an anti-IL6 agent rather than an anti-TNF agent **(Grade B recommendation)**.

Currently, nine biologics indicated for RA are available in our setting, and they are aimed at various different pathogenic targets (TNF, lymphocyte B, costimulatory molecules and IL-6). Several drug clinical trials have shown that these agents are safe and effective in patients with RA who have a poor response or intolerance to conventional DMARDs. The selection of which therapeutic target to block and which agent to use in given patients who are going to be treated with a biologic for the first time involves complex clinical decisions, and hence, it is particularly important to provide recommendations in this area.

Quality of the evidence

Six RCTs were identified that assessed potential differences in efficacy between the different biologics used as first-line treatment for RA. In two of these, the biologic was used as monotherapy[194, 195] and in four the biologic was used in combination with a conventional DMARD[196-200].

A phase III double-blind RCT over 24 weeks (the ADACTA study) assessed the superiority of tocilizumab over adalimumab in 326 biologic-naïve patients with RA who were intolerant to MTX or in whom MTX was inappropriate. The authors concluded that TCZ monotherapy is superior to ADA monotherapy in reducing signs

and symptoms in patients with RA in whom MTX cannot be used, as measured by change in DAS28-ESR, DAS28-ESR remission and low disease activity, good and moderate EULAR response and ACR20, ACR50 and ACR70; however, this higher efficacy was not observed as measured by HAQ, SF-36 or the Functional Assessment of Chronic Illness Therapy-Fatigue scale[194] (Level of evidence 1+). A phase IV double-blind RCT over 24 weeks (the MONARCH study) of biologic-naïve patients with RA who were intolerant to MTX or in whom MTX was deemed inappropriate. Patients were randomized to receive sarilumab or ADA. The authors concluded that sarilumab monotherapy is superior to ADA monotherapy in reducing signs and symptoms in patients with RA in whom MTX cannot be used[195] (Level of evidence 1+). We do not know whether the findings of these two studies may be extrapolated to other anti-TNF monoclonal antibodies or ETN.

We found a pragmatic clinical trial with 52-week follow-up (the RED-SEA study) in 125 biologic-naïve patients with active RA despite the use of at least two DMARDs. This study reported baseline differences between the groups in history of use of HCQ and prednisolone. Patients were randomized to receive ENT or ADA. The authors emphasized that the study was designed to reflect routine practice and that, in this context, ADA was not inferior to ETN in terms of persistence of treatment at 2 years or DAS28-CRP response. The authors recognize that the fact that only a relatively small percentage of patients who started treatment with an anti-TNF agent in the participating centres participated in the study is a limitation, while another potential limitation is that the study was a non-inferiority study rather than an equivalence study[199] (Level of evidence 1-).

An RCT (the EXXELERATE study) assessed the superiority of one anti-TNF over another in 915 biologic-naïve patients with active RA on stable doses of MTX. Patients were randomized to receive either CZP + MTX or ADA + MTX. The authors concluded that treatment with CZP + MTX is not superior to that of ADA + MTX, as measured by ACR20 and DAS28-ESR low disease activity. The authors commented that their findings are only applicable to the anti-TNF agents included in the study[196] (Level of evidence 1+).

A phase III RCT (AMPLE study) assessed the non-inferiority of ABT over ADA with concomitant treatment with stable doses of MTX in 646 biologic-naïve patients with active RA and at least two of the following conditions: a) RF or anti-CCP positivity and/or b) elevated ESR or CRP. The trial assessed radiographic outcomes. The authors concluded that ABT has similar efficacy and safety to ADA and that the inhibition of radiographic progression after 1 year was similar in the two groups; further, in these patients with active RA despite treatment with MTX, treatment

with ADA and ABT led to similar improvements in patient-reported outcomes[197, 198] (Level of evidence 2+).

An open non-inferiority RCT (ORBIT study) was conducted in 329 biologic-naïve patients with active RA despite treatment with at least two conventional DMARDs including MTX and who were RF and/or anti-CCP positive. The study included patients with concomitant treatments with NSAIDs, analgesics and DMARDs, as well as changes in the doses of thereof. Patients were randomized to receive RTX, ADA or ETN. The study concluded that RTX is not inferior to an anti-TNF agent, as measured by ACR20, ACR50, ACR70, DAS28 remission, and good or moderate EULAR response. The only difference between the treatments was in the percentage of patients who continued the initial treatment with no need for switching (81% in the RTX group vs 68% in the anti-TNF group)[200] (Level of evidence 1-).

The GDG has taken into account that none of the direct comparison studies of different biological agents identified in the systematic review has shown any agent to be superior to any other, except for the case of TCZ and sarilumab compared to ADA, as monotherapy, in patients with intolerance to MTX or in whom the use of MTX was deemed inappropriate.

The GDG considers that the results can be extrapolated to the Spanish population given that the patients included in the clinical trials identified in the systematic review are similar in their demographic and clinical characteristics to the population with RA seen by Spanish clinicians. The lack of data demonstrating that any one biologic is more effective than any other after a poor response to a conventional DMARD highlights the appropriateness of decision making on a case-by-case basis. Regarding which pathogenic target to block and with which agent, this decision should be taken after considering all the individual characteristics of patients, including their medical history and comorbidities, as well as patient preferences.

Based on its summary of product characteristics, RTX is only indicated for adult patients with RA who have had a poor response or intolerance to other DMARDs, including one or more treatments with anti-TNF agents.

Clinical question 9

In patients with rheumatoid arthritis, what is the efficacy of targeted DMARD monotherapy compared to conventional DMARD or biologic DMARD monotherapy?

Summary of the evidence

In patients with active early rheumatoid arthritis who have received no or limited methotrexate, treatment with baricitinib monotherapy has shown greater efficacy than treatment with methotrexate monotherapy, improving response rates (ACR20, ACR50 and ACR70), percentages of patients with low disease activity or disease remission (Simple Disease Activity Index, Clinical Disease Activity Index and DAS28) and patient-reported outcomes (Health Assessment Questionnaire – Disability Index [HAQ-DI], and ratings of pain and the disease itself), though it does not significantly reduce the progression of structural damage (*modified total Sharp score*) at 12 months[201,202].	1+
In methotrexate-insufficient responders, tofacitinib monotherapy has shown to be effective, but less so than the combination of adalimumab with methotrexate or tofacitinib with methotrexate in improving response rates (ACR20, ACR50 and ACR70), percentages of patients with low disease activity or disease remission (Simple Disease Activity Index, Clinical Disease Activity Index and DAS28) and patient-reported outcomes (HAQ-DI)[170].	1+
Treatment with tofacitinib (at doses of 5 or 10 mg twice daily) has shown to be more effective than treatment with methotrexate monotherapy, with better response rates (ACR20, ACR50 and ACR70), higher percentages of patients achieving low disease activity or remission (DAS28), patient-reported outcomes (HAQ-DI, and ratings of pain and the disease itself), and reducing the progression of structural damage (modified total Sharp score) at 24 months[203,204].	1+
Treatment with tofacitinib is associated with improvements in bone marrow oedema and magnetic resonance imaging erosion score at 12 months, but with no significant improvement in synovitis[205].	1-

Recommendations

In patients with indications for biologic DMARD or targeted DMARD therapy in whom, for any reason, these drugs cannot be used in combination with conventional DMARDs, the guideline development group considers that the use of Janus kinase inhibitor monotherapy is a good alternative treatment **(Grade √ recommendation)**.

Since its approval in the 1980s, MTX has become the most studied and most widely used DMARD worldwide for the treatment of RA. At low doses, MTX monotherapy is more effective than any other non-biologic DMARDs in controlling the signs and symptoms, reducing disability and preventing structural damage[206]. On the other

hand, around a third of patients with RA are intolerant to MTX, and in clinical practice, MTX is commonly discontinued[207, 208]. Therefore, it is important to assess whether new therapies for RA may be an alternative to MTX in patients who cannot take or are intolerant to MTX, to understand the potential utility of any new treatment for this disease.

Quality of the evidence

The evidence found comes from comparison studies with MTX monotherapy. No comparison studies with biologic monotherapy were found. We selected three RCTs[201, 203, 205] and two other studies based on these trials[202, 204].

Treatment with BARI monotherapy has shown to be more effective than treatment based on MTX monotherapy, with better response rates (ACR20, ACR50 and ACR70), higher percentages of patients with low disease activity or disease remission (SDAI, CDAI and DAS28) and better patient-reported outcomes (ratings of pain and the disease itself, HAQ-DI)[201, 202] (Level of evidence 1+).

Treatment with TOFA (at doses of 5 and 10 mg twice daily) has shown to be more effective than treatment with MTX in monotherapy, with better response rates (ACR20, ACR50 and ACR70), higher percentages of patients with low disease activity or disease remission (DAS28), and better patient-reported outcomes (HAQ-DI, ratings of pain and the disease itself) at 24 months[203-205] (Level of evidence 1+, 1-).

Treatment with TOFA improves bone marrow oedema and bone erosion at 12 months, but with no significant improvement in synovitis[205] (Level of evidence 1-).

In the Oral Strategy study on patients with RA and a poor response to MTX, treated with ADA + MTX or TOFA + MTX or TOFA monotherapy, there is evidence of a response to TOFA monotherapy. Although the results for TOFA monotherapy in this study did not meet the criteria for non-inferiority compared with the two combination therapies, the unadjusted results of the ACR response and improvement in EULAR response are notable. We recognise that there is no formal comparison with another arm of monotherapy, but include these results as this is the only study found[170].

To our knowledge, there are no published trials that have compared these drugs as monotherapy with biologics as monotherapy.

The GDG considers that the results of the studies identified are consistent, all indicating JAK inhibitors have greater efficacy than MTX in controlling disease activity, but these studies are only applicable only to patients with early RA (a less than 2-year history of the disease) and who are treatment naïve. The GDG understands

that these results should not be extrapolated to patients with established RA and there are no data comparing their efficacy with that of biologic monotherapy.

Further, to make these recommendations, the GDG has taken into account that the results of the studies identified are not directly applicable to our health system given that they are based on patients with early RA who have not previously received conventional DMARDs. According to Spanish and European legislation, JAK inhibitors are not indicated for these patients. The GDG understands that we should not extrapolate the findings of these studies to other clinical scenarios including patients with established RA with a poor response or intolerance to conventional DMARDs, and such extrapolation should be based on data that are not yet available.

The GDG considers that until further pharmacokinetic studies provide evidence supporting an increase in the use of JAK inhibitor monotherapy in conventional DMARD-naïve patients with early RA, or until data are published from further comparison clinical trials on JAK inhibitors and conventional DMARDs in patients with established RA, this remains a theoretical question.

7.3.4. Treatment of patients in whom the first biologic fail

Clinical question 10

In patients with rheumatoid arthritis who have had a poor response to a first anti-TNF agent, is another anti-TNF agent or a non-anti-TNF biologic DMARD more effective?

Summary of the evidence

In patients with rheumatoid arthritis in whom a first anti-TNF fails, the use of biologics other than anti-TNFs (rituximab, abatacept or tocilizumab) is more effective than the use of a second anti-TNF agent: the probability of achieving a moderate or good EULAR response was higher in the non-anti-TNF than in the anti-TNF group (69% vs 52%; OR 2.06, 95% CI 1.27 to 3.37)[209].	2++
In patients with rheumatoid arthritis in whom a first anti-TNF monoclonal antibody fails, tocilizumab is more effective than abatacept in terms of 28-joint Disease Activity Score using C-reactive protein after 12 months (2.51±1.12 with tocilizumab vs 3.22±1.11 with abatacept; p= 0.016) and similarly effective to etanercept[210].	2-
In patients with rheumatoid arthritis in whom a first anti-TNF monoclonal antibody fails, there are no significant differences in terms of functional improvement between the use of non-anti-TNF agents (rituximab, abatacept or tocilizumab) and the use of a second anti-TNF agent[209].	2++

In patients with rheumatoid arthritis in whom a first anti-TNF monoclonal antibody fails, there are no data on radiographic progression, for comparing strategies involving a second anti-TNF with the use of non-anti-TNF biologics[209-211].	2++,2-

Recommendations

In patients with rheumatoid arthritis who have had an inadequate response to a first anti-TNF, it is justifiable to use a second anti-TNF agent or a biologic acting on a different therapeutic target, depending on the type of inefficacy and patient characteristic **(Grade D Recommendation)**.

Anti-TNF agents have shown to be effective in controlling signs and symptoms and improving the quality of life of patients with RA with an inadequate response to MTX[212]. Nonetheless, as many as a third of patients[213] treated with anti-TNF have an inadequate response according to international recommendations[54].

The use of a second anti-TNF agent after failure of the first one in these patients is a reasonable alternative as shown in the EXXELERATE study[196]. In particular, the lack of efficacy of one anti-TNF agent does not rule out the potential efficacy of another one given the following: the molecular structure of anti-TNF agents (ADA, CZP, ETN, GOL and ITX), their different strengths of affinity for membrane-bound and soluble forms of tumour necrosis factor-alpha, their ability to block lymphotoxin-alpha and the fact that the loss of the efficacy of biologics is due to the production of antibodies[192]. Two placebo-controlled randomized trials have shown that approximately half of the patients with RA who have an inadequate response to a first anti-TNF agent respond to a second anti-TNF[214, 215], and this is even true in the case of primary non-responders[196]. Nonetheless, switching to a therapy that does not target TNF may also be an acceptable strategy[216-218]. The most widely used non-anti-TNF biologics are ABA, an inhibitor of T-cell costimulation; RTX, that eliminates B cells, and TCZ, an IL-6 receptor inhibitor. Various different observational studies have compared a non-anti-TNF biologic to a second anti-TNF agent in patients with an inadequate response to the first anti-TNF agent[219-221].

Despite the findings of these studies and other evidence, to date, scientific societies have not established any recommendation about whether patients with RA who have an inadequate response to a first anti-TNF should be treated with a second anti-TNF or with another non-anti-TNF biologic.

Quality of the evidence

Three studies were identified that have assessed the efficacy of biologics after an inadequate response to a first anti-TNF agent.

An open RCT compared the efficacy of a non-anti-TNF biologic with that of a second anti-TNF agent in 292 patients with RA who had an inadequate response to a first anti-TNF. The specific drug was chosen by the physician in charge, once patients had been assigned in a 1:1 ratio to continue with an anti-TNF (ADA, IFX, CZP, ETN or GOL) or receive a non-anti-TNF (TCZ, ABA or RTX) at the usual doses according to the summary of product characteristics with a 54-week follow-up. The assessment was carried out by an unblinded researcher. Data on effectiveness indicate a higher probability of achieving a moderate-to-good EULAR response and low disease activity at 6 months in the non-anti-TNF group than in the anti-TNF group (69% vs 52%; OR 2.06; 95% CI 1.27 to 3.37; and 27.8% vs 44.6%; OR 2.09; 95% CI 1.27 to 3.43; respectively). No differences were observed between the groups in functional status as measured by HAQ score and no data on radiographic progression were reported. It is not possible to assess differences between individual drugs. The limitations of this study are: 1) the assessment being carried out by an unblinded researcher; 2) 40% of patients being on monotherapy; and 3) the assessment being based on the DAS28, which probably favours TCZ[209] (Level of evidence 2++).

Secondly, a sub-analysis was performed of data from a cohort study with a retrospective and a prospective component in 12 Japanese institutions. The objective was to compare the efficacy and retention rates of three biologics (ABA n=25, TCZ n=38 and ETN n=26) at 12 months after switching therapy due to failure of the first biologic, an anti-TNF monoclonal antibody. At 52 weeks, clinical efficacy, as measured by DAS28-CRP, was greater with TCZ than ABA (TCZ 2.51±1.12; ABA 3.22±1.11; p= 0.016) but not ETN. All three drugs showed good efficacy at 52 weeks in the evaluation based on CDAI. The remission and low activity rates at the end of the study were respectively: 20.7 and 49.8% with ABA; 28.6 and 68.2% with TCZ; and 20.6 and 70.6% with ETN. The study has a high risk of bias, as it involved crude analysis without any adjustment for confounding factors. Further, the sample sizes of the groups were rather small for carrying out comparisons[210] (Level of evidence 2-).

Thirdly, a prospective cohort study in nine Spanish hospitals compared the efficacy and safety at 6 months of a single cycle of RTX (n=54) with that of ETN (n=23), ADA (n=16) or IFN (n=10) in patients with RA. Mean DAS28 and HAQ score did not differ significantly between the groups (4.2±2.1 with RTX vs 4.76±1.9 with anti-TNF and 0.82± 0.7 with RTX vs 0.59±0.7 with anti-TNF). The rates of good, moderate and poor EULAR response at 6 months were: 35%, 43% and 22% with RTX, and 40%, 34%

and 26% with a second anti-TNF. The study only found a significantly lower ESR levels in the RTX group. The risk of bias of the study was high, given the sample size and the lack of adjustment for confounding factors. The subgroup of patients who received RTX had greater baseline disease activity (DAS28)[211] (Level of evidence 2-).

In the light of the limited evidence found concerning the clinical question, it was deemed appropriate to mention some studies identified that, although they did not meet all the inclusion criteria and were hence excluded from the body of evidence, have provided complementary information, which has been borne in mind at the time of drafting of these recommendations.

A controlled study with an active comparator included 139 patients with RA in whom the first anti-TNF failed. Patients were randomised to receive a second anti-TNF, RTX or intravenous ABA. The mean DAS28 scores (SD) at 12 months were similar in the three groups: 3.8±1.2 with ABA; 3.4±1.2 with RTX and 3.5±1.5 with anti-TNF (non-significant differences). Similarly, HAQ scores did not differ significantly between the groups[222].

There are three studies that are sub-analyses of data from cohort studies including clinical efficacy based on DAS28 at 6 months after administering RTX or a different anti-TNF. At 6 months, sub-analysis of data from the Swedish biologics registry ARTIS showed a larger change in DAS28 in patients receiving RTX than those receiving anti-TNF monoclonal antibodies (-1.70±1.8 vs -0.67±1.4; p<0.001); while differences were not significant comparing with those receiving ETN (-1.40±1.5, non-significant)[219]. At 6 months, Emery *et al.*[220] showed greater improvement in DAS28-ESR in patients on RTX than anti-TNF (-1.5±0.2 vs -1.1±0.2; p=0.007). Further, a higher percentage of patients achieved an improvement in DAS28-ESR of ≥ 1.6 (36% vs 29%; p= 0.01). Nonetheless, they did not find differences in improvements in DAS28-CRP (-1.3± 0.3 with anti-TNF vs -1.4± 0.3 with RTX, non-significant). In a sub-analysis of data from the British Society for Rheumatology Biologics Register[223], improvement, as measured by DAS28, was not greater with RTX than with a second anti-TNF (-1.3 with RTX; 95% CI -1.5 to -1.2 vs -1.2 with anti-TNF; 95% CI -1.3 to -1.1; p= 0.1), but a higher percentage of patients achieved DAS28-ESR remission (OR in favour of RTX: 1.34; 95% CI 1.05 to 1.70). In summary, two studies found higher rates of good or good-to-moderate EULAR response at 6 months in patients receiving RTX than anti-TNF monoclonal antibodies: 23% vs 14% (p=0.003)[219] and 55% vs 47% (OR 1.31; 1.02 to 1.69)[223].

Regarding physical function, three studies did not detect differences at 6 months in the mean change in HAQ score between groups receiving RTX and those receiving an anti-TNF[219, 220, 223]; although one found that a higher percentage of patients

improved their function by more than the minimum clinically relevant difference (difference in HAQ > 0.22); with an OR in favour of RTX of 1.49 (1.07 to 2.08)[223].

Further, six studies were also found that included patients with RA in whom anti-TNF therapy had failed at any line[221, 224-228]. These studies were excluded from the body of evidence because they did not allow us to extract specific data on patients who had received only one anti-TNF.

Three of these studies were based on data from the Swiss Clinical Quality Management RA Registry and compared the use of RTX with that of an anti-TNF in patients who had had a poor response to at least one anti-TNF agent[224-226]. The first one focused on the efficacy while the second explored the subgroups with a better response and the third study outcomes in terms of function and structural damage. At 12 months, the RTX group showed a greater improvement in DAS28-ESR than the anti-TNF group (difference between groups -0.34; 95% CI -0.14 to -0.53)[226]. At 36 months, the mean HAQ score was lower with RTX than with anti-TNF (mean difference between treatments 0.15; 95% CI 0.04 to 0.35). Only one of the three studies compared radiographic progression with RTX or anti-TNF after treatment failure with at least one anti-TNF measured by the Ratingen erosion score[226]. No differences were found in the percentage of patients who had new erosions or progression according to the index.

Two studies based on the American CORRONA RA registry compared the use of anti-TNF with RTX[228] and with ABA[221] in patients with RA who had been exposed to at least one anti-TNF agent. With RTX, a higher percentage of patients achieved a state of remission or low inflammatory activity at 6 months (as measured by CDAI): 37% vs 29% with anti-TNF (OR 1.54; 1.00 to 2.36). On the other hand, no differences were observed in the reduction in CDAI score or the percentage of patients who achieved a modified ACR50 or ACR70 response. Further, use of RTX was associated with a higher percentage of patients improving their function by more than the minimum clinically relevant difference (HAQ difference > 0.25): 34% vs 24% with anti-TNF (OR 1.66; 1.07 to 2.59). The study comparing the administration of ABA and anti-TNF found no significant differences at 6 and 12 months in change in CDAI score, modified ACR20 or ACR70 response or remission as measured by CDAI. In the ABA group, however, it found higher rates of modified ACR50 response (20% vs 15% with anti-TNF; OR 1.40; 1.05 to 1.85) and remission as measured by DAS28 (20% vs 17% with anti-TNF; OR 1.55; 1.01 to 2.36). There were also no significant differences between the two treatment options in the percentage of patients achieving a change in HAQ score of >0.25 at 6 months.

Finally, a cohort study of individuals with RA who had had a poor response to at least one anti-TNF not based on registry data compared 533 patients receiving an-

ti-TNF with 591 receiving RTX. The study did not find significant differences in reduction in DAS28-ESR between the RTX and anti-TNF groups at 6 or 12 months but did show a greater moderate-to-good EULAR response with RTX than anti-TNF (59% vs 45%; p=0.003)[227].

The GDG considers that the results of these additional studies are directly applicable to our health system given that the drugs assessed are commonly used in our setting and the question that motivates this review is very common in the management of patients with RA in daily clinical practice.

When formulating the recommendation for this question, we were only able to take into account the study by Gottenberg[209]; though we should point out that it also has some limitations related to the blinding process in the assessment of response and the very high percentage of patients on monotherapy, which may introduce a bias in favour of response to TCZ. Nonetheless, the GDG considers that the results of the other aforementioned studies do not conflict with the recommendation provided[216, 219-221, 223-229].

Finally, the GDG decided to make a recommendation that does not prioritize the use of an anti-TNF biologic over a non-anti-TNF in patients with RA who have had an inadequate response to one anti-TNF agent, given that the evidence available does not provide conclusive results regarding the superiority of one over the other.

Clinical question 11

In patients with rheumatoid arthritis, after failure of a first anti-TNF, is a second biologic or a targeted DMARD more effective?

Summary of the evidence

In patients with rheumatoid arthritis who have had an inadequate response to a biologic DMARD, treatment with either another biologic DMARD or a targeted DMARD may be effective[230-232].	1+
We have not found studies directly comparing biologic and targeted DMARDs in patients with rheumatoid arthritis who have had a poor response to a biologic DMARD[230-232].	1+
There is indirect evidence that tofacitinib (5 mg/12 h) in combination with methotrexate has a similar efficacy, as measured by ACR20, ACR50 and ACR70 response rates and Health Assessment Questionnaire score, to abatacept, tocilizumab, golimumab or rituximab in combination with DMARDs, in patients with rheumatoid arthritis who have had a poor response to biologic DMARD therapy[232].	1+

Tocilizumab (8 mg/kg) may be somewhat more beneficial than other biologic DMARDs (abatacept, tocilizumab 4 mg/kg or rituximab) and tofacitinib as measured by ACR20 and ACR50 response rates in patients with rheumatoid arthritis and failure of treatment with biologic DMARD[230].	1+

Recommendations

In patients with rheumatoid arthritis in whom biological therapy has failed, regardless of the number of drugs and their mechanisms of action, either a biologic or a targeted DMARD may be used **(Grade B recommendation)**.

With the successive emergence of more biological drugs with different mechanisms of action, the generalization of their use and, more recently, targeted drugs coming onto the market, the most common doubts nowadays related to their use is the choice of which drug to prescribe to a given patient. In this context, one of the most common scenarios is for physicians to need to choose which drug to use in a patient with RA who has had a poor response to a first anti-TNF.

Quality of the evidence

The scientific evidence assessing the efficacy of biologic and targeted DMARDs in patients in whom the treatment with a first anti-TNF has failed comes from studies that address this issue on the basis of indirect comparisons. Three meta-analyses[230-232] were identified, but as well as being based on indirect comparisons, most of the studies they included analysed patients refractory to one or more biological therapy, not only to anti-TNF.

The first meta-analysis by Lee *et al.*[230] included four RCTs and used network meta-analysis to analyse the efficacy and safety of ABA, RTX, TCZ and TOFA in patients with RA who had had a poor response to anti-TNF. Although both the methods and results sections refer to second-line therapy, examining the studies included it is found that patients were allowed to be refractory to one or more biologics and the drugs in question were not necessarily anti-TNFs. There is no comparison between the efficacy of biologics overall and that of TOFA in patients who had had an inadequate response to biological therapy; but by ranking treatments using the surface under the cumulative ranking curve, the authors showed that TCZ at a dose of 8 mg/kg would be the most effective, followed by RTX, ABA, TCZ 4 mg/kg*, TOFA 10 mg/12 hours*, TOFA 5 mg/12 hours and placebo. It can be concluded from the indirect drug-by-drug comparisons that there are no significant differences between the efficacy of different bDMARDs included in the study and TOFA in the rate of ACR70 response. On the other hand, there were significant

differences in the case of ACR50 response, TCZ, ABA and RTX being found to be more effective than TOFA at a dose of 10* or 5 mg/12 hours, and in the case of ACR20 response, with only TCZ at doses of 4* or 8 mg/Kg being significantly more effective than TOFA at the doses studied (Level of evidence 1+).

The meta-analysis by Vieira *et al.* published in 2016[232] included eight studies with data from five RCTs and used network meta-analysis to compare the efficacy and safety of TOFA with that of ABA, GOL, TCZ and RTZX in patients with poor response to anti-TNF; however, only one of the studies considered patients previously exposed to only one anti-TNF. None of the studies included directly compared TOFA with other drugs. After the indirect comparison analysis, and without considering the heterogeneity of the studies included, the RRs of achieving ACR20, ACR50, ACR70 and HAQ responses were very similar with TOFA and the other drugs analysed (with ranges of 0.74–1.24, 0.63–1.36, 0.53–1.50 and -0.04–0.1 respectively) and the authors concluded that in patients with RA who have had an inadequate response to anti-TNF therapy, the rate of efficacy with TOFA is similar to that obtained with ABA, TCZ, GOL or RTX (Level of evidence 1+).

The meta-analysis by Singh *et al.* published in 2017[231] used network meta-analysis to compare the efficacy of various different biologics (ABA, ADA, ANAK, CZP, ETA, GOL, INF, RTX, and TCZ) and TOFA with placebo or a biologic or non-biologic DMARD in patients with RA who had had an inadequate response to a bDMARD for any reason. It was based on 12 publications with data from 9 RCTs, including all the RCTs in the meta-analysis of Lee[230] and all but two of those in that of Vieria[232]. Overall, only four studies considered patients with an inadequate response to a single anti-TNF and only three used a bDMARD for comparison. Further, none of the studies included compared the efficacy of a bDMARD and TOFA in this subpopulation. While recognising these caveats, the authors concluded that the use of bDMARDs or TOFA is more beneficial than the use of MTX or another DMARD in patients who have had an inadequate response to a bDMARD (Level of evidence 1+).

Apart from the studies included in the meta-analyses, there is a study that investigated treatment with BARI in patients refractory to biologics, the RA-BEACON study[233], which assessed the efficacy of BARI in patients with a poor response to anti-TNFs. Although a poor response to one anti-TNF was required, the study also included patients with a poor response to more than one biologic and not only to anti-TNFs. Further, the study provides efficacy data for two doses of BARI in this subpopulation, but it did not compare the efficacy of BARI with that of other bio-

* Drug doses not approved in Spain.

logics. An ACR20 response was achieved in 55% of patients receiving BARI at doses of 4 mg/day and 27% of those treated with DMARDs, this difference being significant. The study also reported significant differences in DAS28-CRP and HAQ-DI, but not in SDAI ≤ 3.3. The authors concluded that BARI is effective in patients with active RA refractory to aggressive standard-of-care treatment with both DMARDs and bDMARDs.

The results of the studies identified are directly applicable to our health system. Notably, they concern patients with similar sociodemographic and disease characteristics to those in our setting.

The clinical impact of the choice of treatment in a patient with a poor response to one anti-TNF is important. From the clinical perspective, the correct choice avoids lengthening the time with poor control of the inflammatory activity. As has been demonstrated, this has an impact on the course of the disease in the medium and long term. On the other hand, this decision is also important from an economic perspective, since the correct choice also avoids the costs associated with the use of a second ineffective drug.

The fact that the great majority of the studies published include patients with an inadequate response to one or more anti-TNF and non-anti-TNF means that we are not able to make a specific recommendation for patients with a poor response to a first anti-TNF, the specific population considered in the original clinical question, and hence, this recommendation applies to patients with a poor response to biologics. The lack of head-to-head comparison studies between targeted DMARDS and bDMARDs means that we are also unable to prioritize one drug over others, and hence, the choice of drug should be made on a case-by-case basis.

7.4. Other treatments

The comprehensive management of patients with RA includes patient education, psychosocial interventions, and the implementation of measures tailored to each patient to ensure that they get proper rest and carry out physical activity, as well as the provision of dietary and nutritional advice. This implies that a multidisciplinary team of professionals should be involved in the comprehensive treatment of patients with RA.

Rehabilitation and physical therapy for patients with RA

The goals of rehabilitation therapy for RA are to reduce pain and improve functional capacity. This therapy includes measures to maintain or improve strength, resistance and joint range of motion and prevent or correct deformities[234]. Further, through health education, patients are given technical advice regarding how to maintain their level of independence in activities of daily living and improve their quality of life.

Physical exercise

In general, patients with RA have reduced physical endurance and muscle strength and often the associated pain leads to them to decrease their physical activity and avoid moving, increasing the risk of muscle atrophy.

From the moment of diagnosis, a programme of aerobic physical exercise and muscle strengthening can be implemented, including exercises to enhance flexibility, coordination and manual dexterity. A meta-analysis has shown that physical activity reduces fatigue in patients with RA[235] and physical exercise may prevent osteoporosis.

Physical therapy

The main goal of applying physical agents to affected areas of the body is to reduce pain and joint stiffness. It also helps to improve joint range of motion, muscle strength and joint function.

A meta-analysis assessed seven RCTs comparing groups receiving various modalities of *thermotherapy or cryotherapy* with a control group or those receiving a different therapy. It concluded that, alone, thermotherapy or cryotherapy had no significant effects on any clinical parameter, but that they could be used as palliative therapy to relieve pain[236]. Transcutaneous electrical nerve stimulation (TENS) reduces the intensity of pain and improves muscle strength compared to placebo in the treatment of patients with RA[237].

Low-level laser therapy seems to achieve a significant reduction in pain compared to placebo. A Cochrane review[238] concluded that such therapy is effective in the short term to relieve the symptoms of RA.

Occupational therapy

In rehabilitation, as part of occupational therapy (OT), therapists work with patients to improve or maintain their ability to perform activities of daily living. The intervention focuses on self-care, productivity and leisure, paying attention to pa-

tients' cultural and social context[239]. OT is particularly indicated in patients with advanced disease or significant functional impairment.

Regarding efficacy, a Cochrane systematic review[239] assessed the efficacy of different types of intervention as part of OT. More recently, a randomised study in employed patients with RA at risk of work disability found a significant improvement in work-related outcomes after 6 months by combining OT techniques with medical treatment[240].

Occupational therapists and medical rehabilitation specialists assess the need for technical aids and orthoses or supports. Tailored orthoses or supports are prescribed to help to maintain joint alignment, reduce pain and improve functioning, though no good quality clinical trials have demonstrated that they prevent the appearance of deformities. Podiatrists may also have an important role to play in the case of metatarsalgia and other foot problems in patients with RA[241]. Regarding tailored hand exercises, a clinical trial in 490 patients, the addition of such exercises to other measures (supports, technical aids and/or advice on muscle protection) produced an improvement in joint function over 1-year of follow-up[242].

Intra-articular treatment

Local therapies are indicated in the case of joints with active disease despite background treatment for RA or as an initial treatment until the disease is brought under control.

Intra-articular glucocorticoid injections

These injections started to be used in the mid-20th century[243]. Intra-or peri-articular injections of long-acting glucocorticoids are recommended, generally combined with a local anaesthetic, as the local treatment of choice in RA[244].

The most widely used are long-acting formulations of methylprednisolone, triamcinolone, paramethasone and betamethasone. On the other hand, a stronger and longer-lasting response has been seen with triamcinolone hexacetonide, which recently came on the market in Spain[245, 246].

There are no data from good quality clinical trials concerning the efficacy or toxicity of glucocorticoid injections or the best regimen. In routine clinical practice, as it is not known whether repeated joint injections over the long term may harm joint cartilage, it is not usual to give more than three or four injections per joint and an interval of at least 3 to 4 weeks should be allowed between injections. In addition, the joint should be rested for 24 to 48 hours after the injection[247].

Regarding contraindications, there is agreement that reasonable efforts should be made to rule out infection before giving these injections. Oral anticoagulation with acenocoumarol at therapeutic doses is not a contraindication[248] and the risk of bleeding episodes only increases with international normalized ratios of over 4[249]. In the days immediately after the injection, blood glucose levels may increase in patients with diabetes[250].

As for associated complications, due to a local inflammatory reaction (synovitis caused by crystallization), patients may experience a temporary increase in pain and inflammation after a glucocorticoid injection[251]. It is important to distinguish this from post-injection joint infection, in which symptoms tend to start later and gradually worsen. If injections are performed under aseptic conditions, the risk of infection is very low[252].

Skin atrophy, depigmentation and fat necrosis are relatively common complications that sometimes occur as a local reaction of the skin or subcutaneous tissue that comes in contact with the glucocorticoid[253]. If the injection is given into a tendon, it may cause tendon atrophy, and hence, it may be helpful to perform these injections under ultrasound guidance. The dilution of the glucocorticoid with local anaesthetic may reduce soft tissue atrophy and injection-related pain due to the deposition of steroid microcrystals[253].

Chemical synovectomy

In patients with a poor response to glucocorticoid injection, we may consider *chemical or radiation synovectomy* as an alternative to *surgical synovectomy*. Chemical synovectomy consists of the intra-articular injection of a chemical agent capable of causing necrosis of synovial tissue. The agent most commonly used is osmium tetroxide. A non-controlled study that combined the use of osmium tretroxide with triamcinolone hexacetonide reported good results in terms of efficacy and safety, although at 3 years synovitis had recurred in 80% of patients[254].

Radiation synovectomy

Radiation synovectomy (also known as isotope or radiosynoviorthesis) consists of the intra-articular administration of a radionuclide (Ytrio-90, Renio-186 or Erbio-169, among others). Clinical trials reported to date have not demonstrated that this technique is associated with better outcomes in terms of efficacy than glucocorticoid injections[255, 256], and for this reason, its use should be assessed on a case-by-case basis.

Surgical treatment in RA

In patients with RA, experts consider referral to an orthopaedic surgeon when the drug treatments and other therapies (rehabilitation, local treatments, etc.) fail[257]. Given advances in the medical treatment of RA in recent decades, the rates of RA-related surgery have decreased[258].

According to the literature, referral to a surgeon is indicated when joint function has not improved or has worsened despite systemic treatment or when persistent pain becomes disabling. It may also be indicated in other situations such as nerve compression, tendinopathy, tendon rupture, or varus or valgus deformities of the knee (realignment osteotomy). Regarding timing, the prognosis following surgery is better if patient referral is not delayed until they have developed major joint deformities or severe soft tissue contractures[259].

Before intubation and other manoeuvres involving neck hyperextension, the stability of the cervical column should be considered, given that patients with RA have an elevated risk of atlantoaxial subluxation[260]. In addition, in the preoperative assessment, we should rule out the presence of latent foci of infection (dental, urinary, skin, etc.) as they could lead to complications in the postoperative period[261] and pay close attention to the state of immunosuppression of patients and the perioperative management of their medical treatments.

Patients with RA were found to have a higher risk of infection after total joint arthroplasty than those with osteoarthritis[262]. Similarly, a prospective study based on the Norwegian register[263] found that infection rates were higher among patients with RA than those with osteoarthritis after total knee replacement and the risk of late infection (assessed at 5 years) was higher in patients with RA after total hip replacement. Further, it does seem that the risk of hip dislocation is higher in patients with RA than those with primary osteoarthritis[262]. On the other hand, the rate of venous thromboembolism was not found to be higher in patients with RA than those with osteoarthritis[262].

Among the procedures used, surgical synovectomy is indicated in patients with persistent joint inflammation that does not respond to other treatments[264] and it is also used to obtain samples for histological and microbiological analysis of synovial tissue. This procedure reduces inflammation and pain temporarily, but has not been shown to prevent radiological progression or the subsequent need for joint replacement in studies with a long follow-up[265, 266].

Joint replacement is the most effective surgical approach to halt the progressive loss of functional capacity. The main indication for this surgery is pain and the loss of joint function. The joints most commonly replaced are the knee and the hip. In

selected cases, prostheses may also be used for shoulder, elbow, wrist and/or metacarpophalangeal joints. A systematic review on hip replacement in patients with RA[267], results were not worse with uncemented than cemented components, and given the relatively low rate of complications, the authors concluded that the use of cementless prostheses was justified in patients with RA.

Patients who undergo knee arthroplasty have greater difficulties recovering from surgery than those who undergo hip arthroplasty, and hence, if both joints need to be replaced, the hip should be done first.

Arthrodesis continues to be indicated as a treatment for joints with very advanced destruction, where improvement is unlikely to be possible with joint replacement, and particularly in the cases of the ankle and wrist.

Orthopaedic surgery of the foot also plays an important role in the treatment of RA, as patients often develop structural deformities such as *hallux valgus* and subluxation of metatarsophalangeal joints which may require metatarsal osteotomy.

The results following surgery depend to a great extent on the postoperative care provided, above all rehabilitation and OT. This care is important for regaining joint range of motion as early as possible, especially after knee and shoulder arthroplasty and hand surgery.

8. Treatment of RA in special situations

8.1. RA as a complex disease

RA is a systemic disease and it is considered complex due to the numerous symptoms and entities related to it. It is also difficult to differentiate the extra-articular manifestations of RA from the comorbidities associated with the disease, since the pathogenic mechanism of many of these conditions is precisely sustained inflammation[268].

In many cases, the level of control of the inflammatory disease will determine the level of control of the comorbidity. It is important to adjust treatment as a function of extra-articular manifestations and associated comorbidities since these can also increase morbidity and mortality in patients with RA. The full range of conditions associated with RA should be monitored by the rheumatologist with the support of the primary care physician and other specialists[268, 269].

Extra-articular manifestations of RA

The rates of severe extra-articular manifestations in patients with RA have fallen in recent years due to the development of more effective treatments[269]. Although severe extra-articular manifestations (e.g., interstitial lung disease, pericarditis, and pleurisy) may precede articular signs and symptoms in some cases, it is more common that they appear in patients with a long history of RA[270].

Rheumatoid nodules

The most common extra-articular manifestations are subcutaneous rheumatoid nodules, which are found in 7% of patients at diagnosis and 30% over the course of the disease.

Secondary Sjögren's syndrome

This syndrome affects some 17 to 25% of patients with a 10- to 30-year history of the disease, and it is more common in elderly patients. It tends to be benign, with mild or imperceptible symptoms (dryness of the eyes and mouth) which are related to disease activity. Patients with secondary Sjögren's syndrome have generally more severe disease, a greater probability of developing non-Hodgkin's lymphoma and higher mortality. It is managed by treating symptoms and the underlying disease[271,272].

Blood dyscrasias

- *Anaemia:* the majority of patients with RA have mild normocytic hypochromic anaemia associated with disease activity. It may also be multifactorial (associated with iron, vitamin B12 or folic acid deficiency)[273].
- *Thrombocytosis:* this is often found, related to the inflammatory activity[274].
- *Felty's syndrome (<1%):* this is the triad of RA, neutropaenia and splenomegaly. There are no controlled clinical trials of a specific treatment[275].

Lung diseases

These are one of the most common causes of morbidity and the second cause of death in patients with RA after cardiovascular diseases. In 10 to 20% of patients, this type of disease precedes articular symptoms. At the beginning, patients may not have any symptoms or these may be masked by a low level of physical activity due to the underlying disease[276].

- *Pleural disorders:* these include pleural effusion and thickening, empyema, nodules, and pneumothorax, the most common being pleural effusion.
- *Interstitial lung disease:* see Section 8.4 of the guidelines.
- *Bronchiectasis (2-3.1%):* patients with bronchiectasis associated with RA have more infectious complications, poorer course and prognosis, and a higher mortality than those with other types of bronchiectasis. According to experts, antibiotic prophylaxis should be considered in patients with repeat infections.
- *Rheumatoid nodules:* these are related to smoking, RF positivity and the presence of subcutaneous nodules, although they may also occur as an adverse effect of treatment.
- *Pulmonary hypertension:* very rare.

Cardiac manifestations

These are relatively uncommon and tend to occur in patients with a long history of the disease or highly active disease[277].

- *Pericarditis:* is the most common manifestation (being found in as many as 40% of autopsies, though only 2% of cases are symptomatic).
- *Myocarditis:* rare.
- *Valvular heart disease:* he most common type being mitral insufficiency, followed by aortic insufficiency, and most patients are usually asymptomatic.

- *Coronary heart disease:* patients with RA have a greater risk of ischaemic events, and hence, it is considered an independent cardiovascular risk factor (see Section 8.3 of the guidelines).
- *Congestive heart failure:* usually with diastolic impairment but preserved systolic function.

Ocular manifestations

As well as dry eye syndrome (xerophthalmia), some patients have scleritis, episcleritis or both, although they are uncommon. These manifestations are associated with a long history of the disease and are related to the level of inflammatory activity[278]. Close collaboration between rheumatologists and ophthalmologists is essential[279].

Kidney dysfunction

It is directly associated with age, female sex, disease duration and RF and/or ACPA positivity. There is also an association with the presence of cardiovascular risk factors (in particular arterial hypertension)[280, 281].

Vasculitis

Though very uncommon (3.6% at 30 years after diagnosis), this condition is observed and is associated with disease severity and activity and a poor prognosis. It is more common in men and tends to be associated with a long history of the disease. Active smoking and RF and/or ACPA positivity together with genetic predisposition and the presence of rheumatoid nodules are predictive of rheumatoid vasculitis. It is more common in small and medium-sized blood vessels. The main clinical manifestations are[282]:

- *Skin manifestations:* telangiectasia, digital ischaemia, livedo reticularis, palpable purpura, painful nodules and gangrene.
- *Neurological manifestations:* distal sensory or motor neuropathy, mononeuritis multiplex.
- *Ocular manifestations:* scleritis, corneal ulcers.

Amyloidosis

Secondary amyloidosis is a complication that tends to occur in patients with a long history of RA (at least 10 years after diagnosis). It is becoming rarer (<1%) due to increasingly more effective treatments. It most commonly affects the kidney and pa-

tients present with proteinuria and/or renal impairment, although other organs, such as the thyroids, heart and digestive system, may also be involved[283].

Comorbidities in RA

Patients with RA have an elevated risk of developing comorbidities[63]. The development of comorbidities in patients with RA is a key factor in the selection of their treatment, since the presence of particular conditions may be a contraindication to starting certain treatments while newly-appearing comorbidities may be a reason for changing current treatments[284]. They may also affect the course of the disease by modifying disease activity, physical functioning and quality of life[63, 269]. For this reason, rheumatologists must also identify potential comorbidities and current risk factors in patients with RA, especially those that are potentially preventable or may affect the development of the disease or treatment[268].

Elderly patients with a long history of RA and/or active disease have more comorbidities. This may be related to them being given less intensive treatment due to their age or to contraindications to concurrent conditions or concomitant treatments. For all these reasons, special care should be taken with this type of patient and they should generally be given intensive treatment, always taking into account their comorbidities[63, 268, 285, 286]. Experts underline that it is important to properly document any long-term treatments given for comorbidities[268, 287]. Women have a different profile of comorbidities, with a greater prevalence of depression and osteoporosis[286]. The comorbidities associated with a higher mortality rate are: cardiovascular and pulmonary diseases, cancer and depression[288].

The role of rheumatologists in the monitoring and prevention of comorbidities is not clear, although EULAR has recently published a series of recommendations concerning screening and prevention of comorbidities in patients with chronic inflammatory rheumatic diseases[289].

Table 9 summarises the consensus reached by experts on actions to take if we suspect comorbidities associated with RA.

Table 9. Actions to take if we suspect or diagnose comorbidities associated with rheumatoid arthritis[4, 268, 290]

Comorbidity	Recommendation
Lung disease	If suspected, refer to a pulmonologist
Cardiovascular diseases	If they develop, refer to an appropriate specialist (cardiologist, neurologist, internist, etc.) Yearly monitoring of cardiovascular risk factors
Gastrointestinal diseases	If suspected, refer to a gastroenterologist

Table 9. Actions to take if we suspect or diagnose comorbidities associated with rheumatoid arthritis[4, 268, 290]

Comorbidity	Recommendation
Infections (HBV, HCV, TB, severe infections)	Vaccination Dental hygiene
Cancer	Screening (for breast, cervical, colon, skin and/or prostate cancer), in accordance with the current published guidelines and depending on risk factors. Annual monitoring of lymph node involvement
Psychiatric disorders (depression)	No specific screening
Osteoporosis	Densitometry using dual-energy x-ray absorptiometry (at least once) and monitoring of risk factors. Treatment if fractures
Fibromyalgia	Management in accordance with current guidelines
Arthrosis	Management in accordance with current guidelines
Carpal tunnel syndrome	Depending on the degree of involvement, consider conservative treatment or surgery

8.2. Patients in remission/dose reduction

Clinical question 12

In patients with rheumatoid arthritis receiving biologics who have achieved remission of disease activity, what is the rate of recurrence when the dose of biologics is reduced?

Summary of the evidence

The rate of recurrence in patients with rheumatoid arthritis, after optimising biological therapy, varies between the studies selected:

- 23.5% with adalimumab[291] 2-
- 39% with adalimumab, etanercept and infliximab, measured overall[292] 2+
- 13-55% with adalimumab and etanercept, measured overall[293,294] 1+
- 42.5-45% with tocilizumab[295] 3
- 50% with abatacept[296] 1+

Recommendations

In patients with rheumatoid arthritis who have achieved remission or low disease activity with biological therapy for at least 6 months, the recommendation is to progressively taper the dose of the biologic, despite the risk of relapse **(Grade B recommendation)**.

The use of biologics has undoubtedly been a major advance in the treatment of RA, allowing us to achieve an adequate control of the disease in a high proportion of patients. The chronic nature of the disease, implying a need for long-term treatment, safety concerns and the economic implications of biological therapy have long raised questions concerning the need to adjust treatments, reducing the dose, once the treatment target for each individual patient has been reached. The practice of dose reduction has been a reality in our setting for years and the SER and the Spanish Society for Hospital Pharmacy published recommendations on the optimisation of biologics in 2015[297].

Quality of the evidence

There is a growing body of published evidence concerning the possibility of dose reduction in biological therapy, although the quality of the studies is very varied from the point of view of evidence-based medicine. The highest quality studies have been those analysing ADA and ETN, alone or in combination, as the treatments to be optimised.

The PRIZE study analysed the results of reducing and withdrawing ETN after 1 year of induction therapy in patients who had not previously received the treatment and had achieved remission. In two publications, one research group have reported the results of this strategy in terms of various measures of disease activity, and although it was not the primary objective of the study, comparison analysis of the two doses of ETN used allowed the authors to conclude that dose reduction is feasible in some patients, although they underlined the need for comprehensive monitoring of disease activity after dose reduction[298, 299] (Level of evidence 1+).

After an open treatment phase during which patients received ETN, the PRESERVE study analysed, in a randomised double-blind phase, whether treatment response was maintained after a 50% reduction of the dose in patients with low disease activity. The authors concluded that, despite the study having insufficient statistical power to demonstrate differences between the two doses, the results suggest similar outcomes with both doses[300, 301] (Level of evidence 1+).

Similarly, after a first open phase of treatment with ETN, the DOSERA study analysed, in a second randomised phase, the effect of a 50% reduction in ETN dose in patients with low disease activity. Although this study did not directly compare the doses, the authors concluded that the efficacy of ETN was maintained with the lower doses[302] (Level of evidence 1+). In a prospective randomised clinical trial (for which the published methods do not clarify whether it was blinded), the ETN dose was reduced by 50% in patients in remission for at least 12 months. This study did not provide data on efficacy comparing the ETN doses, but does give data on radiological progression and this was similar in both groups[303]. A prospective observational study assessed the impact on treatment response of reducing the ADA dose by 50%. The authors applied this strategy to patients with RA on ADA and MTX at stable doses and in remission, and assessed disease activity measured by DAS28 after the reduction. They concluded that dose reduction is feasible in patients who achieve remission[291] (Level of evidence 2-). Further, a randomised clinical trial (the STRASS study) that analysed the results of tapering doses of ETN and ADA in patients in remission after treatment with the full dose. The authors failed to show the non-inferiority of the lower dose, the primary endpoint, due to the small sample size and observed a higher rate of flares in the lower-dose group[293] (Level of evidence 1+). An open-label trial (the DRESS study) compared the results of reducing the doses of ADA and ETN together with those of usual clinical practice. In this study, doses were reduced in three steps, every 3 months, until drug withdrawal in the context of a T2T protocol in patients with previously sustained low disease activity while on stable drug doses. The authors analysed the cumulative incidence of major flares as the primary outcome and concluded that a dose reduction strategy with ADA or ETN was not inferior to usual care[294] (Level of evidence 1+).

A retrospective observational study compared long-term disease activity in patients in remission or with low disease activity on stable doses in whom ADA, ETN or IFX doses were reduced by about 25% to that in patients who remained on the full dose in two different cohorts, one in Spain and the other in the Netherlands. The authors concluded that dose reduction of biologics is feasible in patients with low disease activity[292] (Level of evidence 2+).

Regarding other anti-TNF agents (CZP and GOL), no specific data have been published, although some results have been reported in abstract form. The only data available come from a study that analysed all anti-TNFs together and provides overall data, the quality of this study being poor from the point of view of evidence-based medicine[304].

In the case of ABA, a double-blind randomised clinical trial, that included patients from the AGREE study in remission after 2 years of treatment with ABA, found

that a 50% lower ABA dose managed to maintain low disease activity[296] (Level of evidence 1+).

Regarding TCZ, two studies, one pilot study[305] with a small sample size and a retrospective observational study[295] assessing dose reduction of this drug in patients in remission and with low disease activity, respectively, after treatment with full doses, support view that dose reduction is feasible in these patients (Level of evidence 2- and 3, respectively).

Further, various different studies have analysed the results of optimisation of all biologics and obtained positive results, supporting the view that dose reduction is feasible: the open-label prospective RETRO[306] study, which reported overall data without specific data for each treatment; a cross-sectional observational descriptive study on various diseases[307]; a small retrospective observational study[308]; a study seeking to assess the value of ultrasound for predicting the result of dose reduction[309]; and finally, another retrospective study[310].

Regarding RTX, it is difficult to define the best approach to dose optimisation. There has been research on how to use this drug in terms of length and number of treatment cycles. Concerning the dose, three systematic reviews have been published comparing various different doses of the drug, though one these was an update of another by the same group. These three studies consistently demonstrated that the efficacy was similar with 2,000-mg and 1,000-mg cycles. Nonetheless, the variability in study design means that we are not able to assess whether the efficacy is the same with the lower dose from the start of treatment or after achieving control of disease activity with one or more higher-dose cycles[311-313] (Level of evidence 1+). The evidence in terms of treatment regimen used is less consistent. One study found, after 1 year of follow-up, similar efficacy when RTX was used as a fixed dose, every 6 months, or on demand, after disease reactivation[314], while a second study found higher efficacy after treatment with a fixed dose of RTX than when the drug was administered on demand[315]. A third publication reported the indirect comparison of results of different clinical trials. It found better results in terms of efficacy using a T2T strategy to decide whether to give a further dose of RTX than when the decision was based on the opinion of the physician treating the patient[316].

The GDG deems that the results of the various different studies, with different designs and populations with different characteristics and levels of evidence, are generally consistent. They all indicate a higher rate of flares in disease activity after dose reduction of various different biologics, but the studies that explored this issue concluded that re-intensification of treatment after such episodes was successful in regaining control of the inflammatory activity. For this reason, despite the higher

rate of flares after doses are reduced, all the authors concluded that dose reduction is feasible.

Some characteristics such as disease duration, level of disease activity and the length of time with this level of activity at the time of starting to taper doses may help to define the profile of patients in whom dose reduction is most likely to be successful.

The GDG believes that the results of the studies identified can be directly applied to our health system. They were based on patients with similar sociodemographic and disease characteristics to those in our setting.

The impact of dose reduction in biological therapy is significant. Its impact is both eminently clinical in that it means a reduction in toxicity, due to the use of less of the drugs, and also economic, since a lower dose also means lower treatment costs and hence a better distribution of resources.

The risk of a higher rate of flares after reducing the dose is perfectly acceptable, since it has been demonstrated that patients are able to achieve their pre-dose reduction status after treatment re-intensification.

8.3. Cardiovascular risk

It has been demonstrated that cardiovascular mortality is higher in patients with RA than others of the same age and sex[317, 318]. This is due to the rapid development of accelerated atherogenesis[319]. Specifically, the relative risk of a cardiovascular event in patients with RA is twice that in individuals of the same age and sex without this condition[320]. Further, ischaemic heart disease secondary to coronary atherosclerosis is the leading cause of cardiovascular mortality in patients with RA. The higher rate of cardiovascular events in patients with RA is independent of the presence of traditional cardiovascular risk factors[320]. Genetic factors, such as having the HLA-DRB1*0401 or HLA-DRB1*0404 alleles, and persistent chronic inflammation favour the development of cardiovascular events in these patients[321].

Subclinical cardiovascular disease in patients with RA

Patients with RA have a higher risk of heart failure[322] and subclinical atherosclerosis[323], which can be diagnosed using non-invasive techniques.

A transthoracic echocardiography study in individuals with a long history of RA with no traditional cardiovascular risk factors confirmed that patients with RA have a higher rate of left ventricular diastolic dysfunction and subclinical

pulmonary hypertension[324]. These findings may explain the higher rate of congestive heart failure observed in these patients.

Various different tests used for detecting subclinical atherosclerosis have also shown to be useful for confirming accelerated atherogenesis in patients with RA[323]. These include the use of brachial artery ultrasound imaging, to assess endothelial function, a marker of early atherosclerosis[325], which revealed endothelial dysfunction in patients with a long history of RA without traditional cardiovascular risk factors[326] and in young patients with recent-onset RA[327].

Another non-invasive marker of atherosclerosis that is useful for RA is the measurement of carotid intima-media thickness (cIMT) with common artery ultrasound imaging[323]. One research group observed abnormally high cIMT in a series of patients with a long history of RA with no traditional risk factors for atherosclerosis and no history of cardiovascular events compared to that in a control population[328]. It was also found that these patients with no traditional cardiovascular risk factors had a higher incidence of carotid atheromatous plaques, associated with disease duration and with extra-articular manifestations of RA[328]. In addition, it has been reported that persistently high CRP values are associated with higher cIMT in patients with a long history of RA[329]. Finally, a prognostic association was observed between the presence of subclinical carotid atherosclerosis, cardiovascular events and long-term mortality in patients with RA. In relation to this, a 5-year follow-up study confirmed that cIMT has a high predictive value, a thickness greater than 0.90 mm being associated with a higher risk of cardiovascular events during the follow-up of these patients[330].

In a recent study, it was found that carotid atheromatous plaques independently predicted the development of acute coronary syndrome in patients with RA[331]. Further, the incidence of this syndrome was 2.5- and 4.3-fold higher depending on whether the presence of plaques was observed in one or both carotid arteries[331].

An interesting use of computed tomography is to assess the *coronary artery calcium score*, which is a proxy for coronary atherosclerosis for the stratification of cardiovascular risk. Coronary artery calcium is characteristic in advanced atherosclerosis and has shown to be an independent predictor of coronary events in the general population. A recent study found a higher coronary artery calcium score in patients with RA than paired controls, especially in those with a long disease duration (>10 years)[332].

Impact of the treatment of RA on cardiovascular risk

Tests having provided evidence of a higher cardiovascular risk in RA, the next step is to establish a treatment strategy focused on reducing cardiovascular risk in patients with this disease.

In relation to this, it was found that active treatment of the disease reduced the risk of cardiovascular death[319]. Recent research has confirmed a reduction in mortality in RA, associated with a decrease in the incidence of myocardial infarction, attributable to more intense treatment of the rheumatic disease[333].

Krause *et al.* observed that patients with RA who had a good clinical response to background MTX also had lower cardiovascular mortality than those who did not respond well to this treatment[334]. Choi *et al.* showed that, despite having poorer prognostic factors for mortality, patients treated with MTX did not have a higher rate of cardiovascular events in follow-up[335]. Although MTX increases homocysteine levels, its beneficial effect on disease activity and especially its anti-inflammatory properties would explain the lower rate of accelerated atherogenesis and, in turn, cardiovascular mortality during the follow-up of patients with RA.

Recent population studies have shown that the use of biological therapies in patients with RA who have a poor response to conventional therapy reduces all-cause mortality, and in particular, cardiovascular mortality in this population[336]. Biological therapy with anti-TNF agents improves endothelial function in patients with RA who have a poor response to MTX[337-339]. Similarly, it has been shown that, in patients with a poor response to anti-TNF therapy, the use of MTX is able to rapidly improve endothelial function and improvements persist[340]. In the future, given that endothelial function is a key mechanism in the development of atherosclerosis, this type of improvement potentially achieved with these drugs could be adopted as a treatment target in patients with severe RA. On the other hand, although one study did not show regression of subclinical carotid atherosclerosis with the use of anti-TNF in a series of patients with a long history of severe RA in a 3-year follow-up[341], a later study described a beneficial effect of these drugs in patients with RA, namely, a significantly reduction in cIMT[342].

The use of biological therapies in patients with RA, in particular, anti-TNF therapy, has a protective effect against cardiovascular events. A meta-analysis of 16 studies showed a 31% reduction in cardiovascular events and a 19% reduction in acute myocardial infarction[343]. Further, the risk of cardiovascular events (acute myocardial infarction, stroke and cardiovascular-related death) in patients enrolled in the CORRONA registry was lower in the group that received anti-TNF than those who

received MTX or another DMARD (HR 0.39)[344]. This effect was probably due to a reduction in the inflammatory load associated with RA.

A more recent study found that treatment with TCZ could reduce pro-atherothrombotic risk in patients with RA through the recovery of endothelial function, reduction in oxidative stress and inhibition of the pro-thrombotic and inflammatory properties of monocytes[345].

Regarding JAK inhibitors, extension studies of clinical trials found that TOFA was associated with a lower incidence of cardiovascular events[346].

NSAIDs increase cardiovascular morbidity and mortality rates in the general population. This risk is probably partially counterbalanced in patients with RA by the beneficial effects of these drugs in controlling inflammation, and in turn, improving physical activity. Nonetheless, we should be very careful when prescribing them, especially in patients with a history of cardiovascular disease or traditional cardiovascular risk factors[347].

Glucocorticoids also have a dual effect. On the one hand, they promote atherogenesis by inducing negative effects on the lipid profile, glucose metabolism and blood pressure, especially when they are used for a long time. On the other, when they are used acutely (for short periods), these drugs can be beneficial in reducing inflammation and improving mobility, especially in early stages of the disease. Given that cardiovascular risk increases with the cumulative dose of glucocorticoids[348], they must be prescribed at the lowest possible dose and for the shortest possible time[347].

Impact of non-rheumatologic treatments in reducing cardiovascular risk in patients with RA

The strict control of traditional cardiovascular risk factors is of key importance in patients with RA for reducing associated overall cardiovascular risk. In relation to this, patients tend to have abnormal lipid profiles, as a result of the chronic inflammation associated with RA[319], and the monitoring of lipid levels is a key component of the therapeutic management of the disease. A long-term clinical trial reported that treatment with statins was associated with an improvement in endothelial function in patients with RA[350, 351]. Similarly, the RORA-AS study found atherosclerotic regression (as assessed by carotid plaque height) in patients with RA treated with rosuvastatin for 18 months[351].

Stratification of cardiovascular risk in patients with RA

Given that RA is currently itself considered an independent cardiovascular risk factor, we must evaluate overall cardiovascular risk in individual patients over the course of the disease.

The use of Systematic COronary Risk Evaluation (SCORE) risk charts adapted for each population group and clinical assessment of disease severity are two key components in the management of cardiovascular risk in patients with RA. Nonetheless, there is currently no clear agreement, in clinical practice guidelines, on what to recommend concerning this key clinical aspect of the treatment of these patients. In Spain, statin therapy should be started in accordance with the Spanish guidelines on cardiovascular risk, which are adapted for southern Europe according to the SCORE guidelines and allow us to estimate the 10-year risk of cardiovascular death as a function of sex, age, systolic blood pressure, smoking habits and total cholesterol[352].

We should note that a recent study has shown that the cardiovascular risk associated with RA is similar to that observed in patients with type 2 diabetes[353]. For this reason, in order to properly establish the cardiovascular risk in patients with RA, it is important to identify the factors inherent to this chronic inflammatory disease that have been found to be associated with the development of accelerated atherogenesis and cardiovascular events.

In relation to this, it was found that individuals who were RF or anti-CCP positive had more severe disease and a poorer cardiovascular prognosis[354]. On the other hand, anti-CCP positivity was commonly associated with HLA-DRB1*04 alleles which are related to an elevated cardiovascular risk[355]. In line with this, evidence of an association of HLA-DRB1*0401 and HLA-DRB1*0404 with the development of endothelial dysfuction[326] and with an elevated risk of cardiovascular events[321] underlines the prognostic value of anti-CCP positivity.

Finally, RA duration and having disease with more severe clinical signs and symptoms (specifically, extra-articular manifestations) are other cardiovascular risk factors in RA[328, 329]. For this reason, the *EULAR Standing Committee for International Clinical Studies Including Therapeutics* recommends multiplying the estimated SCORE cardiovascular risk value by a factor of 1.5[347].

Unfortunately, the use of this multiplying factor in RA is insufficient in many cases[356, 357] and the EULAR consensus advocates the use of non-invasive diagnostic tools, in particular carotid ultrasound, to better identify patients at risk of cardiovascular events. Given that carotid plaques are associated with a very high car-

diovascular risk, use of this technique may be particularly appropriate in patients with RA in the moderate risk category according to the SCORE charts[347].

Clinicians assessing patients with RA must, as a first step, establish a strategy for the primary prevention of cardiovascular events, initially based on the provision of general lifestyle advice, namely, to take regular moderate physical activity and eat a heart-healthy diet with low intake of saturated and hydrogenated fats, cholesterol and refined sugars, as well as control their body weight and blood pressure, and stop smoking. Regarding the management of hypertension in patients with RA, the recommendations are the same as for the general population[347]. Further, according to the SCORE guidelines for the southern European region, in individuals with RA, treatment with statins should be started in very high-risk patients (SCORE > 10%) to reach the target for LDL cholesterol (< 70 mg/dl) or at least achieve a greater than 50% reduction in LDL cholesterol[358].

8.4. Interstitial lung disease

Interstitial lung disease (ILD), also known as diffuse parenchymal lung disease, is the most common pulmonary manifestation of RA. It has an estimated incidence between 4 and 4.5 cases per 1,000 patient-years[359-361]. The reported prevalence is highly variable, ranging from 10 to 30% in early RA (with history of ≤ 2 years), and 3.6 to 42% in established RA, and this largely attributable to differences in diagnostic methods[359, 362-367].

Regarding the histological type of lung disease, the two most common are usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). The prevalence rates seem to be similar, though according to some series, UIP is somewhat more common[359, 366, 367]. In a minority of cases, other patterns have been described including organising pneumonia, lymphoid interstitial pneumonia, desquamative interstitial pneumonia, acute interstitial pneumonia, respiratory bronchiolitis-associated ILD, and combined pulmonary fibrosis and emphysema[366, 367].

The main risk factors for the development of ILD are smoking (OR: 3.76) and ACPA positivity (OR: 6.67)[366-368]. In addition, ACPA has prognostic value, levels being correlated with ILD severity[365, 369]. Other risk factors are being male, advanced age, late onset of RA, and severe erosive joint disease. Rheumatoid nodules and RF positivity have also been reported in some studies (though findings are mixed)[366-368].

Regarding clinical manifestations, we should bear in mind that ILD is often not detected clinically (being asymptomatic or paucisymptomatic) until advanced stages[366, 367]. For this reason, we should ask patients about their functional capacity, perform auscultation to detect Velcro-like crackles (75%) and check for acropachy.

When ILD is symptomatic, it is associated with persistent, dry cough and exertional dyspnoea, and may progress more or less rapidly towards respiratory failure, with signs of *cor pulmonale* in advanced stages.

In early stages, the sensitivity of chest X-ray for diagnosis is very low[365-367], and hence, if ILD is suspected, the initial examination must include pulmonary function tests (PFTs) that include spirometry and diffusing capacity of the lungs for carbon monoxide (DLCO). In typical cases, as well as low DLCO, spirometry showing restrictive ventilatory defects. Nonetheless, in early stages, it is not uncommon that low DLCO is the only abnormal finding.

To confirm the diagnosis of ILD, high-resolution computed tomography (HRCT) should be performed, as the findings are well correlated with the histological diagnosis at least in most "typical" cases[370]. Further, this technique is useful to assess the potential reversibility of lesions (alveolitis/fibrosis) and make a prognosis, as well as assessing treatment response. Bronchoalveolar lavage should not be performed systematically; it should only be used if it contributes to the differential diagnosis, particularly with infections. Lung biopsy is reserved for establishing a histospecific diagnosis in "atypical" cases.

Monitoring of inflammatory activity and treatment response is carried out with PFTs, which should include the measurement of total lung capacity, the 6-min walk test, and an assessment of dyspnoea with one of the various clinical scales available. In advanced stages, Doppler echocardiography is also useful to detect the development of secondary pulmonary hypertension. The differential diagnosis for this complication mainly includes infections, drug-induced pulmonary toxicity and heart failure.

Although there has been significant improvement in the prognosis over the last 15 years, ILD remains the second cause of death associated with RA[359, 360, 366, 367, 371-373]. In a variable proportion of patients, ILD hardly progresses, remaining subclinical, with very few or no symptoms. In others (the majority according to some studies), pulmonary function worsens rapidly, especially in those with UIP[374] (mean survival after the diagnosis of ILD varying across studies from 2.6 to 3 years, to a maximum of 8.1 years)[359, 360, 366, 367, 371-374]. Poor prognostic factors for all types of interstitial pneumonia include: 1) PFT results: a forced vital capacity (FVC) <60% and/or DLCO < 40% at baseline (indicating severe disease according to the Spanish Society of Pulmonology and Thoracic Surgery), or a ≥ 10% decrease in FVC and/or ≥ 15% decrease in DLCO during follow-up; 2) HRCT: extension of the fibrosis ≥ 20% or extent of the lung involved ≥ 50% at baseline or evidence of worsening of the fibrosis during follow-up; 3) 6-min walk test: oxygen saturation < 88% at baseline or a > 50-m decrease in the distance covered during follow-up; and 4) development of pulmonary

hypertension[359, 360, 367, 371-375]. Specific predictors of poor prognosis in RA-associated ILD (RA-ILD) include being male, advanced age and a UIP pattern[359, 360, 367, 371-374].

It also seems to be useful to apply the GAP (gender, age, physiology) model, which includes sex, age, FVC and DLCO, to predict the risk of death at 1, 2 and 3 years[376]. Finally, some biomarkers associated with greater progression and poorer prognosis have been identified, including higher anti-CCP titre, and serum levels of Krebs von den Lungen-6 and IL-6 (these also being associated with higher mortality)[369].

In the treatment of ILD, we should keep in mind the following three considerations:

General measures

Smoking cessation; pulmonary rehabilitation and treatment of gastroesophageal reflux, which may worsen over the course of the disease; systematic influenza and pneumococcal vaccination; appropriate and early treatment of concurrent respiratory infections; psychosocial support, and home oxygen therapy, in cases that progress towards chronic respiratory failure.

If medical treatment fails, we must always consider the possibility of lung transplantation in patients who meet the criteria, and provide palliative care in the final stages of the disease.

Drugs that should be avoided

Given the prevalence and potential severity, the treatment of patients with RA-ILD is clinically difficult, among other reasons because there is a growing body of evidence in the literature suggesting that some drugs commonly used in the management of patients with RA may trigger or worsen ILD.

Regarding the question of whether there is a risk of induced or exacerbated ILD in patients treated with MTX, according the conclusions of a meta-analysis of controlled trials (22 studies with 8,584 patients with RA), the use of MTX in patients with RA is associated with an increased risk of respiratory infections (RR: 1.11) and acute pneumonitis (RR: 7.81)[377]. This meta-analysis did not, however, observe that the treatment with MTX increased the risk of death due to lung disease (RR: 1.53; 0.46-5.01).

Therefore, there is currently no evidence supporting the view that there is chronic MTX toxicity[378, 379]. Acute or subacute pneumonitis tends to occur during the first year of treatment and is due to a hypersensitivity mechanism, being independent of the cumulative dose[378, 379]. It occurs rapidly with fever (low-grade or higher),

non-productive cough and dyspnoea that tends to progress towards respiratory failure[378, 379]. Eosinophilia is commonplace in peripheral blood, but not in bronchoalveolar lavage fluid, and the radiological pattern is that of NSIP or diffuse alveolar damage[378, 379]. Some diagnostic criteria have been proposed to rule out other causes, especially infections (Table 10)[380].

The main risk factor for the development of MTX-induced pneumonitis is a history of ILD secondary to RA (OR: 7.1; 95% CI 1.1 to 45.4)[381]. This represents a significant confounding factor for establishing a causal relationship with the drug. In relation to this, a meta-analysis has recently been published that analyses the same issue in other conditions treated with MTX, but in which there are no pulmonary manifestations (psoriasis, psoriatic arthritis and inflammatory bowel disease)[382]. The results do not demonstrate any increase in the risk of respiratory complications (infectious or noninfectious). This analysis seems to indicate that, even applying strict criteria for a causal relationship, MTX-induced pneumonitis is overdiagnosed and a good many of these cases are actually attributable to RA activity.

LEF has also been implicated as a possible cause of induced or exacerbated ILD in patients with RA, particularly in Japanese populations[383], but a recent meta-analysis did not confirm this association in Western populations[384].

The safety of biologics approved for this condition is discussed in response to the next clinical question.

Table 10. Proposed criteria for the diagnosis of methotrexate-induced pneumonitis[380]

Major criteria	Minor criteria
1. Histopathological: hypersensitivity pneumonitis 2. Radiological: diffuse interstitial pattern and/or nodular or patchy alveolar infiltrates 3. Microbiological: negative blood and sputum cultures, bronchoalveolar lavage and serological analysis	Dyspnoea for < 8 weeks Non-productive cough Oxygen saturation < 90% Diffusing capacity of the lungs for carbon monoxide < 70% White blood cell count < 15,000/mm^3

Definitive: meets major criterion 1 or major criteria 2 and 3 plus three of the five minor criteria
Probable: meets major criteria 2 and 3 plus two of the five minor criteria

Drugs that are effective for lung involvement

Clinical question 13

In patients with rheumatoid arthritis and interstitial lung disease, which is the safest biologic DMARD?

Summary of the evidence

The use of infliximab, etanercept, adalimumab and certolizumab pegol has been associated with the development and worsening of interstitial lung disease in patients with rheumatoid arthritis[385,386].	3
Worsening of interstitial lung disease related to anti-TNF agents may have fatal consequences in elderly patients[387].	3
In patients with rheumatoid arthritis, the use of abatacept has not been associated with interstitial lung disease or with a worsening of the interstitial lung disease related to anti-TNF agents[386,388].	3
The use of tocilizumab has been associated with the development and worsening of interstitial lung disease in patients with rheumatoid arthritis. In some cases, the worsening of the lung disease related to tocilizumab may have been due to poor control of inflammatory activity[385,389].	3
In small series, rituximab has not been associated with worsening of interstitial lung disease[390].	3

Recommendations

In patients with rheumatoid arthritis and interstitial lung disease who require treatment with a biologic, abatacept is recommended as the safest option **(Grade C recommendation)**.
As an alternative, rituximab could be used **(Grade D recommendation)**.

ILD is the most common pulmonary manifestation of RA. The risk of developing this complication is much higher in patients with RA than in the general population (HR: 8.96; 95% CI 4.02 to 19.94), with an incidence of 4 to 4.5 cases per 1,000 patient-years. As well as being common, ILD is the second leading cause of death among patients with RA, after cardiovascular events, accounting for 10-20% of deaths.

Due to its prevalence and potential severity, the treatment of patients with RA and ILD is clinically complex, because there are no well-designed trials assessing the efficacy of the treatments available for this complication and there is a growing body of evidence in the literature that suggests that some of the drugs that are

usually used in the management of patients with RA may trigger or worsen this complication.

Given this, there is a need to assess whether there is a risk of induced or exacerbated ILD in patients with RA treated with biologics.

Quality of the evidence

Anti-TNF agents and, to a lesser extent, TCZ have been implicated both in the development of ILD and worsening of pre-existing ILD in patients with RA.

The idea of anti-TNF involvement is mainly based on systematic reviews of case series and case reports[385, 391-393], a retrospective case-control study[386] and some observational studies[387, 394]. According to these studies, the prevalence of induced or exacerbated ILD attributable to anti-TNF therapy is between 0.5 and 3%[385, 391, 394]. This complication has been described with all anti-TNF agents[385,386, 391-394]. It occurs within the first 6 months of starting the biological therapy (in most cases within the first 20-26 weeks)[385, 386, 391, 392] and tends to be severe and potentially fatal (the mortality rate in published cases being as high as 29 to 35%)[385-387, 391-394].

As well as the classical patterns of ILD[385, 391, 392], sarcoid-like lesions have also been described, with the development of non-caseating granulomas in the lung, especially in patients treated with ETN[395, 396].

The main risk factors involved in the development of this complication in patients treated with anti-TNFs are advanced age (which is a risk factor for the development of ILD in patients with RA[367]), a personal history of ILD and concomitant treatment with MTX or LEF, which have also been related both to the development of ILD and the worsening of a pre-existing ILD in patients with RA[377, 383, 384]. Given the large number of confounders, it is very difficult to establish whether there is a causal relationship or not.

The potential causal relationship has been further questioned after the recent publication of two retrospective observational studies (both based on data concerning clients from American medical insurance companies) that did not find statistically significant differences in the rates of ILD, either comparing the use of anti-TNF with that of DMARDs (HR anti-TNF versus DMARDs: 1.03; 95% CI 0.51 to 0.27)[397], or comparing the use of different anti-TNFs with that of other biologics (RTX, ABA or TCZ)[398].

In this context, not even the national registries of biological therapies provide concordant results. According to data from the British Society for Rheumatology Biologics Register, the incidence of ILD is higher in patients treated with anti-TNF

(2.9% with anti-TNF vs 1.8% with DMARDs; p=0.02) and their cause of death was more likely to be attributed to this complication (21% with anti-TNF vs 7% with DMARDs)[394]. On the other hand, in a study based on the Spanish registry of adverse events related to biological therapies (BIOBADASER), neither the incidence of ILD nor the mortality due to this complication was higher in patients treated with anti-TNFs compared to those in another cohort of patients with RA who had not received biological therapy (EMECAR)[399].

In summary, the evidence of causality to support the view that anti-TNF is involved in the development of ILD and/or worsening of a pre-existing ILD in patients with RA is in most cases of poor quality and difficult to interpret due to confounding factors (Level of evidence 3), except for a retrospective case-control study (Level of evidence 2). Further, two studies with the same quality (Level of evidence 3) produced opposite results.

In any case, we should underline that the currently available evidence is insufficient to be able to make definitive recommendations one way or another. The fact that this complication has been described in patients on monotherapy and that cases of ILD have been reported in patients treated for ulcerative colitis, spondyloarthritis or psoriatic arthritis oblige us to be cautious, as we are unable to rule out that there is a risk, even though it is not yet well defined and probably over-estimated.

Treatment with TCZ has also been related to both the development of ILD and worsening of pre-existing ILD in patients with RA. The idea of TCZ involvement is based on case reports[385, 391, 393] (Level of evidence 3), some patients having died, and a post-marketing surveillance study[400] analysing cumulative safety data from 7,901 Japanese patients treated with TCZ (Level of evidence 2+). In this latter study, the incidence of ILD in the group treated was 10 cases per 1,000 patient-years, significantly higher than that generally described in RA (i.e., between 4 and 4.5 cases per 1,000 patient-years). For this reason, the summary of product characteristics includes a specific warning about this risk in the adverse effects section.

Nonetheless, as with anti-TNFs, we are unable to rule out that the risk has been overestimated. A recent case-control study (Level of evidence 2-) retrospectively reviewed data on 395 patients with RA treated with TCZ, the sample being divided into two groups: patients with and without ILD[389]. The study compared the characteristics potentially relevant to the development of *de novo* ILD and studied potential risk factors for the worsening of pre-existing ILD. The comparative analysis of TCZ with ILD (n=78) vs TCZ without ILD (n=317) indicated that age > 60 years, smoking and high RF levels are associated with a higher risk of developing this complication. In the subgroup of patients who had ILD worsening (n=6), the

only factor found to be significantly involved was poor control of inflammatory activity (CDAI >10 at 24 weeks). Based on these results, the authors indicated that worsening of ILD in these patients seems to be more closely related to RA activity than drug-induced pulmonary toxicity[389]. In line with this, as mentioned earlier, a recently published retrospective observational study did not find significant differences in the rate of ILD between biologics (anti-TNF, RTX, ABA and TCZ)[398].

RTX has also been associated with the development of various types of respiratory complications including ILD. Nonetheless, this adverse effect seems to only occur in patients treated for blood cancer in whom RTX is combined with other chemotherapy agents. A systematic review of the literature to June 2010 identified 121 cases of ILD, of whom only 3 were in patients with RA. Of these patients, one had lymphoma and another had Castleman disease. Further, two of them had also received MTX (Level of evidence 3). Subsequently, between July 2010 and January 2017 [the date of drafting these guidelines], no other cases were reported in patients with RA.

Other data supporting their safety, beyond that of the aforementioned study398, come from two open-label studies[390, 401] (Levels of evidence 2- and 3) and three other observational studies the results of which have been reported at various conferences[402-404]. The results of these studies taken together suggest that, without being infallible, RTX seems to be a potentially useful drug for the treatment of this complication, being able to stabilise and sometimes even improve pulmonary function parameters in 70-80% of patients. No cases of exacerbation have been reported, although a higher risk of respiratory infection has been described.

Regarding ABA, only two cases of induced or exacerbated ILD have been reported to date[405, 406]. Further, a post-marketing surveillance study gathering integrated safety data analysis on 3,173 patients included in pivotal trials, followed up over 8 years, indicated that the incidence of ILD in the group treated with ABA was 1.1 cases per 1,000 patient-years (95% CI 0.06 to 0.20), even lower than that generally reported in RA[407] (Level of evidence 2+). Other studies, including published case series[388, 408] and a retrospective registry presented at the most recent ACR meeting, have confirmed its safety in this scenario and indicated a potential beneficial effect, namely, the improvement or stabilisation of PFT results[409].

It is also not possible to establish a causal relationship between biological therapy and organising pneumonia[410, 411].

The GDG considers that in the case of anti-TNFs and TCZ, the various studies identified (most of which are of poor quality) show contradictory results. The currently available evidence is insufficient to be able to make a definitive recommendation

one way or another. In the case of ABA and RTX, if we only consider the population with RA and ILD, most of the studies analysed (which are also of poor quality) have provided consistent results showing that the use of these two drugs in this group of patients is safe.

The GDG believes that the results of the studies identified are directly applicable to our health system, given that all the therapeutic agents assessed in this review are commonly used in rheumatology clinics and departments; however, the GDG considers that the available evidence is insufficient and/or inadequate to be able to provide a definitive recommendation.

Given these limitations, the best strategy to minimize the risk in patients with RA and ILD who require treatment with biologics is always to use the options that seem the safest (namely, ABA and RTX). Despite a lack of conclusive evidence to justify advising against the use of anti-TNF and TCZ, their use in these patients must be carried out on a case-by-case basis, until there is further evidence on this issue (in the meantime, extreme care must be taken).

Clinical Question 14

In patients with rheumatoid arthritis and interstitial lung disease, which drugs have shown to be effective for the treatment of the lung disease?

Summary of the evidence

Patients with rheumatoid arthritis and interstitial lung disease treated with rituximab improve or maintain their condition in terms of forced vital capacity and diffusing capacity of the lungs for carbon monoxide[412,413].	2-, 3
The factors significantly associated with the progression of interstitial lung disease include a radiographic pattern of usual interstitial pneumonia (p = 0.020), a personal history of interstitial lung disease progression (p=0.001) and diffusing capacity of the lungs <46%[412].	2-
Smoking and concomitant treatment with conventional DMARDs are not associated with interstitial lung disease progression[412].	2-
We have not found enough studies that assess the use of mycophenolate mofetil, cyclophosphamide or ciclosporin A in patients with rheumatoid arthritis and interstitial lung disease. The studies that have been identified provide aggregated data on the efficacy of the treatment for lung disease secondary to these rheumatic diseases and include few patients with rheumatoid arthritis. Treatment with these drugs is associated with a tendency towards improvement or stabilization of lung function[414-416].	2-, 3

Recommendations

Although some retrospective studies have suggested that rituximab and abatacept may be effective for the treatment of interstitial pneumonia, especially in patients with non-UIP, the GDG considers that the available evidence is insufficient and/or inadequate to be able to make a definitive recommendation in patients with rheumatoid arthritis and interstitial lung diseas **(Grade D recommendation)**.

Despite its prevalence and potential severity, we still do not know which treatment for patients with RA and ILD is the best, as no RCTs have yet focused on this complication and there are no specific consensus recommendations from scientific societies.

Quality of the evidence

In daily clinical practice, glucocorticoids and immunosuppressants, such as cyclophosphamide (CP), azathioprine (AZA), mycophenolate mofetil (MMF) and ciclosporin A, are commonly used for the treatment of RA-ILD.

No RCTs have assessed the efficacy of these drugs for the treatment of RA-ILD. The evidence supporting the use of these immunosuppressants is mainly limited to case reports and case series. In the specific case of CP and MMF, their use is also based on the extrapolation of its efficacy in the treatment of scleroderma-associated ILD demonstrated in two RCTs (*Scleroderma Lung Study I and II*)[412, 413]. Additionally, two retrospective cohort studies in connective tissue disease-associated ILD included patients treated with MMF[414] (Level of evidence 2-) or with CP[415] (Level of evidence 2+) and a cases series of patients treated with ciclosporin A[416] (Level of evidence 3). All these papers provide aggregated results, without reporting data for patients with RA separately, but in general terms, treatment with these drugs was associated with stabilisation or improvement in lung function in most cases.

Recently, a Cochrane review has also been published concerning the efficacy of CP in the treatment of connective tissue disease-associated ILD[417]. The main conclusions of this review are: 1) the beneficial effect of CP is modest, achieving an improvement in FVC, but not in DLCO; 2) the efficacy of MMF is similar to that of CP, though with fewer adverse effects; and 3) no differences are observed in the efficacy of CP as a function the underlying type of connective tissue disease.

Further, there is some experience in the use of biological therapies in patients with RA-ILD, though most of it has only been reported at conferences. So far, two relevant studies on this topic have been published: one on RTX and the other on ABA.

The study on RTX[418] was a retrospective cohort study that provides data on efficacy based on 44 patients with moderate-to-severe ILD assessed using PFTs. At the end of follow-up, there was improvement or stabilization in lung function in 68% of patients (improvement in 16% and stabilization in 52%), with significant increases in mean FVC and DLCO. The other patients (32%) did not improve, more than half of them dying due to ILD progression. The rate of serious infections was 7.7/100 patient-years. In this study, a UIP pattern was identified as a predictor of poor prognosis, as were baseline impairment and a history of ILD progression as assessed using PFTs (Level of evidence 2-).

The study on ABA is based on a retrospective multicentre registry of 63 patients with RA-ILD. Data were only provided on follow-up, including PFTs and HRCT scans of the chest after starting treatment, for some of these patients (less than half), and from this, we infer that only these patients had active ILD[419]. In this group, treatment with ABA achieved improvement or stabilization of pulmonary function parameters (FVC and DLCO) and changes in HRCT pattern in 85-90% of patients. No differences in response were observed by type of pneumonia (there being a similar response in UIP and non-UIP). Patients who did not have dyspnoea at the start of treatment with ABA remained asymptomatic during follow-up. In 17% (11/63) of the patients, ABA treatment was withdrawn due to inefficacy (6%) or adverse effects (11%). The rate of infections was low (8%). Three patients (5%) died, two due to progression of the ILD (Level evidence 2-).

We should highlight that various studies have found that UIP-pattern patients with RA respond less well to treatment and have a poorer prognosis than non-UIP-pattern patients (a pattern not yet described in scleroderma-associated ILD)[371, 372, 418]. Nonetheless, in all these studies, the radiological pattern was not predictive of mortality in the multivariate analysis, after adjusting for confounders, the best predictors of poor prognosis being the degree of impairment found in baseline PFTs and the progression of the disease during follow-up. Therefore, although there is a lower rate of response, there is evidence of the efficacy of immunosuppressive treatments/biological therapies in patients with UIP, both real-world data from patients with connective tissue diseases including RA[418, 419] and data from RCTs on scleroderma-associated ILD[412, 413].

To conclude, there is a paucity of studies assessing the efficacy of drugs in the treatment of RA-ILD, and those available are of poor quality. Hence, the evidence available is considered insufficient to be able to make a definitive recommendation.

Pending further research, there are preliminary data that indicate that both RTX and ABA are effective in the treatment of RA-ILD, especially in patients with non-UIP histological diagnoses.

The results of the one study published on RTX are consistent with those in other series presented at conferences[402, 403, 420, 421] and a prospective open-label pilot study based on 10 patients[401]. In general terms, this drug achieves patient stabilization or improvement of pulmonary function parameters in 70% of cases, without no significant differences in response by histological pattern, and the treatment can be considered relatively safe (although it tends to be associated with higher rates of respiratory and urinary infections, most these not being severe). The experience with ABA reported, apart from the aforementioned study, is limited to two case series in which the drug was also found to be effective[388, 408].

The results of the studies identified are directly applicable to our health system, as the therapeutic agents assessed are commonly used in our setting. Given the potential severity of this complication, it is important to identify treatment options for these patients. The data set out in this review, although preliminary, may help clinicians in decision making.

8.5. Serious infections

Clinical question 15

In patients with rheumatoid arthritis on biological therapy who have had a serious infection, is it safe to restart biological therapy?

Summary of the evidence

After a serious infection, the rate of subsequent serious infection is lower with anti-TNF agents (both alone: 18.1 per 100 patient-years, and combined with non-biologic DMARDs: 17.3 per 100 patient-years) than with a non-biologic DMARD alone (21.4 per 100 patient-years)[422].	3
After hospital-acquired infections in patients with rheumatoid arthritis who were on treatment with anti-TNFs, most patients continue with the same anti-TNF, only a small percentage switching drug. The lowest rates of hospital-acquired infections are obtained with abatacept and etanercept[423].	3
Patients who have not received any biological therapy after a first serious infection have been found to have a high rate of subsequent infection (36.7%-40.5%)[422,423].	3

Recommendations

Patients with rheumatoid arthritis who have developed a serious infection while on biological therapy should subsequently be treated with abatacept. If an anti-TNF is preferred, the recommended agent is etanercept **(Grade D recommendation)**.

Patients with RA (like those with other autoimmune diseases) have a higher risk of developing serious infections than the general population due to underlying immune system dysfunction. In parallel, numerous studies have also demonstrated an elevated risk of infection associated with immunosuppressive treatments given for controlling disease activity. Some studies indicate a higher risk in patients on anti-TNF than those on conventional DMARDs[424]. The 2015 ACR recommendations suggest switching to a non-anti-TNF biological therapy (ABA) under these circumstances, although the level of evidence is very low[4].

Quality of the evidence

There is a paucity of scientific evidence related to this question. We have only identified two studies that assess the safety of biological drugs administered after a serious infection[422, 423]. These have been classified as case series because, from the methodological point of view, they cannot be considered cohort studies since there was no nonexposed comparison cohort. They studied the incidence of serious infection, but treatment was used as an explanatory variable to adjust the incidence and not to explore which drug is associated with a greater level of risk.

In the first study, the objective was to compare the risk of hospital-acquired disease after a serious infection associated with biological therapy in patients with RA, previously hospitalised for a serious infection, while on anti-TNF therapy. After the index hospitalisation, the majority of patients restarted the same anti-TNF agent (79%), 2% switched to another anti-TNF, and 3% started a non-anti-TNF biologic, while 16% of patients did not receive any biological therapy for 18 months. Among the patients who restarted therapy with the same anti-TNF, 10% switched to different biologics during the follow-up. During the follow-up, there were a total of 2,666 hospitalisations for infection. The crude incidence ranged from 27.1 to 34.6 per 100 patient-years. Compared to those who used the same anti-TNF agent after the index hospitalisation, the HR for the subsequent hospitalisation for infection was 0.86 (95% CI 0.72 to 1.03) for non-anti-TNF biologics and 1.10 (95% CI 0.89 to 1.35) to switch to another anti-TNF. The crude incidence in patients who did not receive any biological therapy during the follow-up was 40.5 per 100 patient-years. Pneumonia was the leading cause of infection, and the type of infection did not vary significantly by drug. In the analysis by drug, the crude incidence of subsequent

hospital-acquired infections was the lowest with ABA and somewhat higher with ETN. In adjusted multivariate analysis, ABA (HR: 0.80; 95%CI 0.64 to 0.99) and ETN (HR: 0.83; 95% CI 0.72 to 0.97) were associated with a significantly lower risk of infection than IFX. The authors concluded that among patients with RA who have a hospital-acquired infection while on anti-TNF therapy, most patients continue with the same anti-TNF after the initial infection has resolved and only a small percentage of patients switch to another biologic. Comparing different biologics, the lowest rates of subsequent hospital-acquired infections were seen with ABA and ETN[423] (Level of evidence 3).

In the second study, the objective was to describe the incidence of subsequent serious infection after a serious infection, in patients given anti-TNF or other biologic agents after the first infection. For this, the study included adult patients diagnosed with RA, psoriasis, psoriatic arthritis or ankylosing spondylitis who had a serious infection between 1 January 2006 and 31 December 2011 and had at least once received treatment with an anti-TNF, a non-biologic DMARD or another DMARD after a first serious infection. The study did not include patients given no systemic therapy after the first serious infection. A total of 4,658 subsequent infections occurred after a first infection over 24,264 patient-years of follow-up, yielding an infection rate of 19.2 per 100 patient-years. Nearly two-thirds (64.9%) of infections occurred in inpatients. Patients given anti-TNF therapy after a first serious infection event had a lower rate of subsequent serious infection (18.1 per 100 patients-year in those given anti-TNF alone and 17.3 per 100 patient-years in those given an anti-TNF in combination with a non-biologic DMARD) than those given a non-biologic DMARD alone (21.4 per 100 patient-years). ETN alone (adjusted HR 0.87, 95% CI 0.77 to 0.99) or in combination with a non-biologic DMARD (adjusted HR 0.76, 95% CI 0.66 to 0.88) and IFX (alone or in combination with a non-biologic DMARD) (adjusted HR: 0.80; 95% CI 0.67 to 0.95) were associated with significantly lower rates of subsequent serious infection than a non-biologic DMARD alone. Patients who did not receive any biological therapy after the first serious infection had a high crude rate of infection (36.7 per 100 patient-years). The authors concluded that their study did not demonstrate an elevated risk of subsequent infection in patients treated with anti-TNF after a serious infection. Additionally, patients given an anti-TNF in combination with a non-biologic DMARD seemed to have a lower risk of subsequent infection than those given a non-biologic DMARD alone[422] (Level of evidence 3).

The main limitations of the first study are that the patients were not randomly allocated to the treatments and that patients covered by Medicare are usually

older, and hence, the results cannot be generalised to healthier younger patients with RA.

In the second study, data on serious infections were only collected when patients sought medical care and their condition was coded as such by the attending physician, and this may have led to under- or over-diagnosis. Further, the study did not include patients who after a first serious infection did not receive any systemic therapy, precisely the group at the highest risk of developing a second infection; and, although the majority of the patients included had RA as the underlying disease, some patients in the sample had psoriatic arthritis or spondyloarthritis. This is a clear source of bias in favour of anti-TNF, given that non-anti-TNF biologic drugs are not used in the treatment of these diseases. The same is the case for the anti-TNF monotherapy, which is much more widely used in spondylopathies than in RA. For all these reasons, the GDG considers that the latter study, given its low quality associated with the sources of bias, does not provide relevant data on which to base recommendations.

To conclude, despite the low level of evidence, we are able to deduce from the first study that what really increases the risk of a serious infection after a first serious infection is the increase in disease activity, and resulting use of systemic corticoids to control symptoms related to switching or withdrawal of biological therapy in patients previously in remission; and therefore, given the low rate of subsequent serious infections associated with drugs such as ETN or ABA, we should restart biological therapy as soon as possible, in order to get the patient back into remission.

Nonetheless, given the paucity of evidence available and the limited applicability of the results, we need further, large scale studies, with more specific objectives to be able to strengthen this recommendation.

8.6. Cancer

Clinical question 16
In patients with rheumatoid arthritis and a history of cancer, what is the safest biological therapy?

Summary of the evidence

There were no significant differences in the relative risk of relapse between patients with a history of breast cancer who did and did not receive anti-TNF therapy[425].	2+
The use of anti-TNF in patients with rheumatoid arthritis and head and neck cancer was not associated with an elevated risk of recurrence or death[426].	2+
In patients with rheumatoid arthritis and a history of cancer, no significant differences were observed in the incidence of cancer over a mean follow-up of 5 years comparing anti-TNF, rituximab and DMARD therapy[427].	2+
There are no data allowing us to assess the impact of individual drugs on the rate of cancer relapse[425,426,428,429].	2+

Recommendations

The recommendation is to assess patients with rheumatoid arthritis and a history of cancer who are due to start biological therapy on a case-by-case basis and reach a consensus between the patient, the oncologist and other specialists involved **(Grade C recommendation)**.
There is no evidence for recommending any specific biological therapy.

RA is characterised by chronic inflammation. There is evidence to support the idea that this proinflammatory state may predispose individuals to develop cancer, because it leads to cell proliferation, mutagenesis, activation of oncogenes and angiogenesis. The longer the duration of the inflammation, the higher the risk of associated carcinogenesis[430] and factors such as disease activity and smoking increase the incidence of cancer in patients with RA[431]. Rheumatologists often face difficult clinical situations with respect to potential risks and the impact of immune suppression on patient comorbidities, such as a history of cancer.

Notably, TNF is known to play a key role in the physiopathology of RA, its inhibition leading to a significant improvement in signs and symptoms in the majority of patients. In addition, however, it has other physiological functions such as in host defence and tumour survival[432]. For this reason, there has always been some

concern about the safety of administering anti-TNF agents, since the inhibition of TNF, in theory, would increase the risk of developing a tumour, the rate of tumour growth and the malignant potential of existing tumours. More recent publications on the risk associated with anti-TNF have not identified a higher risk of cancer in general[433-435], although there have been some reports of increases in certain types of skin tumour such as melanoma[436, 437]. In the case of RTX, before being approved for RA, it had already been approved as a treatment for B-cell lymphoma, and hence, in general, there is less concern about its use in patients with a history of cancer, although the approved indication was for a blood cancer, not a solid tumour.

That said, data on the risk of non-lymphoma cancer among patients receiving RTX remain scarce and are often difficult to interpret due to previous exposure to anti-TNF[438, 439]. It is essential to ascertain what is the current evidence regarding the management of the biological therapy in general, and of anti-TNF in particular, in patients with a history of cancer.

Quality of the evidence

Five cohort studies were identified assessing the safety of biological therapies in patients with RA and a history of cancer[425-428].

A study that analysed data from the British Society for Rheumatology Biologics Register (14,000 patients) assessed 293 patients with a history of cancer (excluding carcinoma in situ and non-melanoma skin cancer), 177 patients treated with anti-TNF and 117 treated with DMARDs. Out of the 177 patients in the anti-TNF cohort, 46 received more than 1 anti-TNF. Eighty percent of cancers in both cohorts were solid tumours. The diagnosis of cancer was made >10 years before the treatment in 58% of the anti-TNF cohort and 39% of the DMARD cohort. Thirteen cases of incident malignancy were detected in 11 patients in the anti-TNF compared to 9 cases in 9 patients in the DMARD cohort. The rate of incident malignancy was 25.3 events/1,000 person-years in the anti-TNF cohort compared to 38.3 events/1,000 person-years in the DMARD cohort. The incidence rate ratio (IRR) was 0.58 (95% CI 0.23 to 1.43) for patients given anti-TNFs compared to those given DMARDs. Stratifying by time since the previous malignancy, the age- and sex-adjusted IRR was 0.71 (95% CI 0.18 to 2.79) for malignancies that had occurred less than 10 years before the start of the study and 0.63 (95% CI 0.10 to 4.11) for those that had occurred earlier. Based on these data, the authors concluded that differences between cohorts were not significant, implying anti-TNF does not seem to increase the risk of relapse or development of new disease in patients with a history of cancer[428] (Level of evidence 2+).

Based on a population of 5,120 patients, a German study assessed the risk of new cancers or recurrence thereof with follow-up periods of 3 to 60 months. Overall, 122 patients had a history of cancer, and of these, 67 had received anti-TNF and 55 conventional DMARDs. Among these 122 patients, there were 124 prior malignancies: 6 cases of lymphoma (DMARD: 2, anti-TNF: 4) and 118 solid tumours (DMARD: 54; anakinra [ANAK]:9; anti-TNF: 55). Analysing these patients with a history of cancer, it was observed that at inclusion all nine patients with a history of prostate cancer had received biological therapy (anti-TNF: 7 and ANAK: 2), and among those with a history of bladder cancer, three had received DMARDs and one ANAK; while, at the time of inclusion, patients with a history of breast cancer had less often been treated with biologics (n=11) than DMARDs (n=14). The time between the onset of the previous malignancy and study entry did not differ between the treatment groups, the median being 5 years (interquartile range 2 to 9) with biological therapy (anti-TNF: 4 years [2 to 10]; ANAK 6 years [5 to 9]) and 5 years (3 to 11) with DMARDs (p=0.77). During the follow-up, 15 recurrences were detected in 14 patients, 14 cases of disease of the same type and at the same site and 1 case of metastasis with an unknown origin (9 recurrences in 8 patients given anti-TNF, 1 in a patient given ANAK and 5 in patients given DMARDs), yielding crude incidence rates of 45.5 (95% CI 20.8 to 86.3)/1,000 patient-years in the anti-TNF group; 32.3 (95% CI 0.8 to 179.7)/1,000 patient-years in the ANAK group and 31.4 (95% CI 10.2 to 73.4)/1,000 patient-years in the DMARD group (IRR anti-TNF vs DMARDs: 1.4 [95% CI 0.5 to 5.5], p= 0.63). The mean times between diagnosis of the first tumour and diagnosis of the recurrence were 9.5 (SD: 7.8), 9.1 and 9.2 (SD: 8.8) years in the anti-TNF, ANAK and DMARD groups, respectively. In three patients (anti-TNF: 2; DMARD: 1), recurrence was detected less than 5 years after the first cancer and among all patients with recurrence, four out of the five who received DMARDs only, one of the eight patients who received anti-TNF and the one who received ANAK died. In patients with a history of cancer, this study did not observe a significantly higher risk of recurrence in patients treated with anti-TNF than those treated with DMARDs. As limitations, we should highlight that the study assessed the general risk of cancer (non-organ-specific), the sample size was small and the observation period was short (no more than 4 years)[429] (Level of evidence 2+).

A study conducted in Sweden, based on the ARTIS register, assessed the risk of recurrence of breast cancer in women with RA. The study compared 120 patients who received anti-TNF with 120 biologic-naive patients, with a minimum follow-up of 4.9 years and maximum of 12 years. The mean time between breast cancer diagnosis and starting anti-TNF therapy was 9.4 years. During 592 person-years of follow-up of the anti-TNF group, 9 patients developed breast cancer recurrence (crude incidence rate of 15/1,000 person-years) compared to 9 people in the bio-

logic-naive group during a follow-up of 550 person-years (crude incidence rate of 16/1,000 person-years). Comparing the anti-TNF group with the biologic-naïve group, the HR for recurrence was 0.8 (95% CI 0.3 to 2.1), and after adjusting for lymph node involvement, type of surgery and chemotherapy, the HR was 1.1 (95% CI 0.4 to 2.8). Stratifying by the time between cancer diagnosis and starting anti-TNF therapy, the HRs for recurrence were 1.4 (95% CI 0.2 to 8.6) among patients who started anti-TNF therapy within 5 years after cancer diagnosis and 0.8 (95% CI 0.3 to 2.4) among those for whom the interval was longer (p=0.6). The relative risk of recurrence did not differ significantly between the groups. The cumulative incidence of deaths during the follow-up was similar in the two groups (17 in each group) and all were due to causes not related to their cancer. Only 15% of patients started anti-TNF therapy within the 5 years after the diagnosis of cancer. The authors concluded that there were no significant differences between patients with a history of breast cancer a median of 9.4 years before starting anti-TNF and others with a similar history of breast cancer who did not take this drug. Conclusions cannot be drawn regarding women with active cancer or a poor prognosis[425] (Level of evidence 2+).

A retrospective study, conducted in the USA, analysed 180 patients with RA who had a history of head and/or neck cancer, 31 of whom subsequently (after their cancer diagnosis) received anti-TNFs and 149 DMARDs, with a follow-up period of 4 months. The study assessed the rate of recurrence of cancer and related mortality. The cancers were diagnosed a mean of 12.3 and 12.6 years after the diagnosis of RA in the anti-TNF and DMARD groups, respectively (p=0.05), and there were no significant differences between the groups in terms of tumour stage and/or type of treatment received. Recurrence or death due to head and/or neck cancer was seen in 5/31 cases (16.1%) in the anti-TNF group and 44/149 (29.5%) in the DMARD group (p=0.17), the time to these events being a mean of 17 months after the diagnosis in the anti-TNF group and 16.7 months in the DMARD group. Multivariate analysis performed to explore risk factors associated with recurrence or head and/or neck cancer-related death concluded that stage at diagnosis and stage 4 disease were significant risk factors (HR 2.49; 95% CI 1.06 to 5.89; p = 0.04); also that treatment with surgery or radiotherapy was associated with a lower risk of recurrence or cancer-attributable death (HR 0.35; 95% CI 0.17 to 0.74; p = 0.01 and HR 0.39; 95% CI 0.20 to 0.76; p = 0.01, respectively), and that exposure to anti-TNFs was not a risk factor (HR 0.75; 95% CI 0.31 to 1.85; p = 0.54). For this reason, they concluded that anti-TNF therapy seems to be safe and not associated with an increase in the risk of recurrence or head and/or neck cancer-related death in patients with RA. The population included was largely composed of men[426] (Level of evidence 2+).

The aim of the most recent cohort study, conducted in 2016, was to update a previous document published in 2010 on the incidence of cancer in patients with RA and a history of cancer who had been treated with anti-TNFs, as well as explore the influence of another biologic, namely RTX. The study analysed three cohorts: 14,168 patients given anti-TNF; 4,179 patients given RTX, and 3,878 patients given DMARDs as a comparison group, with a follow-up period of 3.9 to 6.8 years. A total of 425 patients had a history of cancer (243 in the anti-TNF cohort, 23 in the RTX cohort and 159 in the DMARD comparison cohort). The previous type of cancer was similar across the three cohorts, with more than 80% of patients having had solid tumours, the other types being lymphoproliferative cancer or melanoma. Proportionally, more of the diagnoses of cancer had been more than 10 years earlier in the anti-TNF cohort (56.8%) than in RTX (17.4%) or DMARD (37.1%) cohorts. Further, the anti-TNF cohort was younger and contained proportionally more women, while the DMARD cohort had a less aggressive RA. The cumulative follow-up was 855, 1,591 and 81 patient-years for the DMARD, anti-TNF and RTX cohorts respectively. Patients on RTX had a mean follow-up of 3.9 years (interquartile range 3.3-4.6), compared to 6.8 years (interquartile range 3.5-8.8) for the anti-TNF and 6.6 years (interquartile range 4.4-7.8) for the DMARD cohorts. The number of incident malignancies in the DMARD, anti-TNF and RTX cohorts were 46, 53 and 2, respectively. The unadjusted HR was 0.51 (95% CI 0.33 to 0.79) for the anti-TNF cohort and 0.45 (95% CI 0.11 to 1.87) for the RTX cohort, compared to the DMARD cohort. A sensitivity analysis censored at a follow-up of 5 years (total time DMARDs: 609 patient-years, anti-TNF: 971 patient-years and RTX: 81 patient-years) identified 64 incident malignancies: 36 in the DMARD cohort, 26 in the anti-TNF cohort and 2 in the RTX cohort. The unadjusted HR was 0.45 (95% CI 0.27 to 0.75) for the anti-TNF and 0.42 (95% CI 0.10 to 1.75) for the RTX compared to the DMARD cohort. The analysis was adjusted for smoking, as it is a risk factor for many types of cancer, but this did not reveal significant differences. The most common type of cancer in the three cohorts was breast cancer, followed by melanoma in the DMARD and anti-TNF cohorts and lymphoma in the RTX cohort. Recurrence of the previous cancer (local or metastasis) was detected in 5% (13/243) of the anti-TNF cohort and 4% (1/23) of the RTX cohort compared to 12% of the DMARD cohort. These results indicated that, with a mean follow-up of 5 years in patients with RA and a history of cancer, there were no differences in the rate of incident malignancies between the three comparison groups (anti-TNF, RTX and DMARD cohorts). Compared to previous research, this study was based on a larger number of patients with a longer follow-up, but we should take into account a major limitation to the validity of the results, namely, given its nature as an observational study, treatment was not randomly allocated[427] (Level of evidence 2+).

Besides these studies, one systematic review[440] and a cohort study[441] were identified but have not been included, the former because it did not meet the criteria of the review and the latter because it was a letter to the editor.

The GDG considers that the results of the studies reviewed are consistent with the conclusion that there are no differences in recurrence of cancer between patients treated with conventional DMARDs and those given anti-TNF therapies. Regarding other biological therapies such as TCZ and ABA, there is insufficient evidence to answer the question of interest.

The GDG also believes that the results of the studies identified are directly applicable to our healthcare system given that they concern diseases, inflammatory arthritis and cancer, that have a high prevalence and because the use of biological therapies is increasingly common in our patients. The studies have not found significant differences in the recurrence of cancer between patients treated with anti-TNF vs DMARDs, but given that it has become standard practice to use anti-TNFs and, moreover, for long periods of time, these agents should be used with caution because we still lack data on the real risks they pose to the population.

There is not a robust body of evidence identifying the risk of treating or not treating patients with RA and a history of cancer with anti-TNF agents. It is not yet possible to determine the influence of each drug on the recurrence of cancer or define a safe time for using them after a diagnosis of cancer. For this reason, the final decision of whether or not to treat these patients must be made on a case-by-case basis (considering risk factors, limitations, etc.) and together with the oncologist. Long-term prospective studies are needed to specifically assess each drug and each type of cancer.

9. Management of risk in the treatment of RA

9.1. Screening

The treatment of RA has changed dramatically over the last 20 years. The availability of new biologics, used as monotherapy or in combination, has allowed us to reduce the harmful effect of the disease on joints. Nonetheless, their use has been associated with an increase in the risk of infection due to opportunistic and pathogenic germs, as well as the reactivation of latent infections[442, 443]. Furthermore, this risk is related to other coexisting factors such as comorbidities, steroid treatment, history of infections, and age, and hence, we must analyse all these factors and their associated risk before treating the disease.

Various scientific societies (ACR, EULAR and SER) have made efforts to assess how to reduce the incidence of adverse effects in patients with RA. After analysing data from registries and post-marketing surveillance studies, experts have established that before starting treatment, with either conventional DMARDs or biological therapies, the following tests should be performed[444]:

- Blood tests including a complete blood count, assessment of kidney function, and measurements of transaminase, ESR and CRP levels. The results will allow us to rule out active infections that would contraindicate treatment, cytopaenia that might restrict the use of combined therapies or certain drugs, and kidney or liver dysfunction that would restrict the use of DMARDs, as well as assess patient baseline status, before treatment.
- Screening for hepatitis B and C viruses (HBV and HCV). All patients with no known history of hepatitis must be screened for HBV core and surface antibodies before starting treatment with prednisone doses above 20 mg/day, conventional DMARDs, bDMARDS, or JAK inhibitors. It is also a good idea to screen for HCV, although some experts only consider this necessary in patients with a history of parenteral drug use or sexual promiscuity in the 6 months before starting treatment and in healthcare professionals. If patients test positive, the need for treatment of the infection should be assessed, bearing in mind the risk of infection reactivation. The presence of latent infection should be taken into account in the selection of the drug. In relation to this, anti-TNF agents are the most studied drugs. In the case of chronic HBV infection, the results are contradictory, varying from reactivation of the virus, this even being associated with liver failure[445], through unchanged liver function[446, 447], to a reduction in viral load[448]. In the case of HCV infection, the cases reported suggest that the

use of anti-TNF may be safe[449, 450]. In both cases, the opinion of the hepatologist should be sought.

- Ophthalmological assessment: if the treatment includes HCQ, a retinal examination and a visual field test should be performed before starting treatment or during the first year.
- Active and latent tuberculosis must be ruled out in patients who are going to start biological therapy or JAK inhibitors. Proper screening and treatment before starting treatment have been found to achieve as much as a 7-fold reduction in the risk[451] of reactivation of latent tuberculosis[442, 452]. For this, we should take a medical history focusing on high-risk contacts and perform a tuberculin skin test (Mantoux test), repeating the test 1 week later if the results are negative, or alternatively, an interferon-gamma release assay (e.g., the QuantiFERON TB Gold In-Tube test). Further, given the high incidence of false negatives in these tests in patients with RA and treated with glucocorticoids, a chest X-ray should be performed to check for lesions suggesting active infection. In the case of recent contact with a person diagnosed with tuberculosis, a history of incomplete treatment of tuberculosis, positive test result or X-ray findings suggestive of latent disease, treatment is recommended with isoniazid (5 mg/kg/day up to a maximum of 300 mg/day) and vitamin B6 for a period of 9 months[453].
- As for hepatitis, high-risk patients should be screened for human immunodeficiency virus (HIV). In infected patients, there is a risk of reactivation if the viral load is not controlled. Some series have also suggested an increase in the risk of bacterial infection[454, 455] in this population.

9.2. Treatment monitoring

According to experts, regular monitoring of patients treated with traditional DMARDs, biologics or JAK inhibitors allows us to assess treatment response and the development of potential adverse effects. The goal of the current treatment strategy is to achieve clinical remission of the disease, or if not, the lowest possible level of disease activity. Assessments should be fairly regular (every 1-2 months) if the patient has moderate-to-severe disease activity, to evaluate potential changes in treatment that might improve control of the inflammation. On the other hand, they can be spaced out to every 3-6 months in patients in remission or with low disease activity[63].

International consensus statements conclude that patient assessment should include:

- *Physical examination:* at each visit, carry out a complete patient examination, assessing joint status, by counting painful and swollen joints, and ruling out extra-articular manifestations of the disease (e.g., nodulosis, lung or skin involvement, splenomegaly) and drug-related adverse effects (e.g., drug-induced skin reaction, aphthous ulcers, or hepatomegaly).
- *Blood tests:* during routine assessments, request tests including:
  a. Measurement of ESR and CRP levels, to assess inflammatory status and calculate composite indices
  b. A complete blood count to rule out drug-related bone-marrow toxicity or changes indicating disease activity (anaemia) or secondary complications (neutropenia, thrombocytopenia)
  c. Assessment of liver function, through transaminase levels, to rule out liver toxicity
  d. Measurement of electrolyte and creatinine levels, to assess any effects on glomerular filtration
  e. Measurement of the lipid profile, to assess cardiovascular risk and the potential effects of some biologic drugs
- *Imaging tests:* in patients with early RA, perform anteroposterior X-rays of the hands and feet every year for the first 3 years to monitor for progression. Radiological abnormalities have a clear relationship with the persistence of inflammatory activity, especially early in the disease, and a moderate correlation with physical disability, which strengthens over time[456, 457]. As has been described, it is currently possible to detect radiological progression in patients with RA after periods of as short as 6 months[458].

9.3. Vaccinations

Infectious morbidity and mortality are higher in patients with RA than in the general population. Though there are numerous reasons, among the most important are the autoimmune nature of the disease itself, the abnormal blood cell counts and the immunosuppressive drugs administered, including glucocorticoids, conventional DMARDs and biological therapies. In this context, preventive measures should be taken to avoid infections and early diagnosis and treatment of infection is advised. In this type of patient in general, and those

on biologics in particular, adequate vaccination may be very valuable in the prevention of various infectious diseases[459].

Experts agree that, as well as being aware of the list of vaccines available both for the general population and immunosuppressed patients, rheumatologists should implement the current recommendations concerning the vaccines most widely used in this type of patient, especially those for influenza, pneumococcus and hepatitis B. The ACR has issued some recommendations on the appropriate use of vaccines in patients with RA[4]. Tables 11 and 12 summarise the vaccines currently used and their applicability in rheumatology, respectively following the recommendations of the ACR[4] and the SER consensus on risk management in the use of biologics in rheumatic patients[453], in particular the vaccines for pneumococcus, influenza, hepatitis B, papilloma and herpes zoster. As can be seen from these tables, if a patient is taking an immunosuppressive drug, the use of live-attenuated vaccines is not recommended, given the risk of disease reactivation, these being administered, when possible, before starting biologics. Specific mention should perhaps be made concerning use of the herpes zoster vaccine before prescribing JAK inhibitors since these have been associated with a higher rate of infection by this virus; however, experts indicate that we should only consider this in patients at high risk of herpes infection due to factors such as age, combination with glucocorticoids, and other comorbidities and concomitant treatments, as well as a history of herpes infection. Further, we should note that this is a live-attenuated vaccine and therefore it is not recommended during treatment with conventional DMARDs or biologics. The efficacy of certain inactivated vaccines may decrease in patients on RTX and possibly also those on MTX, and therefore the vaccination programme should be started before prescribing these drugs. Table 12 indicates the main characteristics of the vaccines available in Spain[453].

Table 11. ACR recommendations on the use of vaccines in patients with rheumatoid arthritis[4]

Drug	Inactive vaccines			Recombinant vaccines	Live-attenuated vaccines
	Influenza	Pneumococcus	Hepatitis B	Papilloma	Herpes zoster
	Before starting treatment				
DMARD monotherapy	Yes	Yes	Yes	Yes	Yes
Combined DMARDs	Yes	Yes	Yes	Yes	Yes

Table 11. ACR recommendations on the use of vaccines in patients with rheumatoid arthritis[4]

Drug	Inactive vaccines			Recombinant vaccines	Live-attenuated vaccines
	Influenza	Pneumococcus	Hepatitis B	Papilloma	Herpes zoster
	Before starting treatment				
Biologics					
Anti-TNF	Yes	Yes	Yes	Yes	Yes
Others	Yes	Yes	Yes	Yes	Yes
	During treatment				
FAME monoterapia	Yes	Yes	Yes	Yes	Yes
FAME combinados	Yes	Yes	Yes	Yes	Yes
Biologics					
Anti-TNF	Yes	Yes	Yes	Yes	No
Others	Yes	Yes	Yes	Yes	No

Tabla 12. Vaccines available in Spain[453]

Vaccine	Type of vaccine	Active ingredient	Recommendation
Varicella	Live-attenuated	Live-attenuated varicella virus, OKA strain	Contraindicated
Mumps, measles, rubella	Live-attenuated	Attenuated mumps virus, attenuated measles virus, attenuated rubella virus	Contraindicated
Yellow fever	Live-attenuated	Yellow fever virus, 17D-204 strain	Contraindicated
Typhoid fever	Live-attenuated	Attenuated Salmonella Typhi virus, Ty21a strain	Contraindicated
	Simple polysaccharide	Salmonella typhi, PSC Vi	Possible
Poliomyelitis	Inactivated	Inactivated Poliovirus serotypes 1, 2, and 3	Possible
Influenza	Fractional	Fractional influenza virus	Recommended
	Subunit	Influenza surface antigens H and N	

Tabla 12. Vaccines available in Spain[453]

Vaccine	Type of vaccine	Active ingredient	Recommendation
H1N1 influenza A	Subunit	Influenza surface antigens	Possible
Haemophilus influenza B	Conjugate	Polyribosylribitol phosphate-tetanus toxoid conjugate	Possible
Hepatitis A	Inactivated	Inactivated hepatitis A virus	Possible
	Virosome-based	Inactivated hepatitis A virus	
Hepatitis B	Recombinant	Recombinant hepatitis B surface antigen	Recommended
Human papillomavirus	Recombinant	L1 proteins of the virus	Possible
Meningococcus C	Conjugate	De-O-acetylated meningococcal C polysaccharide-tetanus toxoid conjugate	Possible
Pneumococcus	Simple polysaccharide	23-valent pneumococcal polysaccharide	Recommended
	Conjugate	Pneumococcal saccharide-CRM197 conjugate	
	Conjugate	Pneumococcal polysaccharide Protein D conjugate	
Diphtheria	Toxoid	Adult diphtheria toxoid	Possible
Tetanus	Toxoid	Tetanus toxoid	Possible
Whooping cough	Toxoid	Pertussis toxoid	Possible

9.4. Pregnancy and breastfeeding

It has been described that as many as 75% of women with RA experience an improvement in clinical activity during pregnancy and as many as 69% experience worsening during the immediate postpartum[460-462]. The presence of disease activity at the beginning of pregnancy indicates that the disease is likely to remain active during the entire period and seems to increase the risk of flares during the puerperium[463]. Active RA is associated with a higher risk of preeclampsia, caesarean sections and low birth weight[464-467]; nonetheless, the majority of pregnancies proceed without complications and with no increase in the rate of miscarriage[468]. Key

recommendations, on which there is agreement between experts, are to achieve patient remission (or if not, the lowest disease activity possible) with non-teratogenic drugs, at the time of planning pregnancy (at least 6- to 12-months before conception), and to carry out multidisciplinary monitoring of the pregnancy in high-risk patients[469, 470]. In the case of mothers who are anti-Ro or anti-La positive, there is a greater risk of neonatal lupus[471].

Treatment during pregnancy

The main conclusions of experts regarding the clinical management of pregnant women with RA are as follows:

- If NSAIDs are required, do not administer them during the first weeks or last trimester of pregnancy, and NSAIDs with short half-lives such as ibuprofen or ketoprofen are preferred, as these are associated with early closure of the ductus arteriosus. Data on COX-2 inhibitors are more limited, and hence, they are not recommended. Regarding glucocorticoids, it is possible to use non-fluorinated corticosteroids such as prednisone and prednisolone at low or moderate doses[472].
- Synthetic DMARDs such as MTX, LEF, MMF and JAK inhibitors are completely contraindicated during pregnancy; however, we can safely use SSZ or HCQ[469, 472]. Regarding biological therapy, among anti-TNFs, CZP does not cross the placenta, and hence, has a better safety profile[473-475]. RTX is able to cross the placenta in the second and third trimester of pregnancy and causes a transient decrease in B lymphocytes in newborn infants with the corresponding increased risk of infection, and therefore, this drug must be discontinued from conception or as soon as pregnancy is confirmed.
- There are insufficient data on ANAK, ABA and TCZ[476]. For this reason, the opinion of experts is to discontinue these drugs as soon as pregnancy is confirmed, if they were not withdrawn before conception[470].
- Immunoglobulin G (IgG) monoclonal antibodies do not cross the placental barrier in the first trimester. Rather, they start crossing the placenta when neonatal Fc receptor (FcRn) is expressed from the end of the second trimester, this increasing through the third trimester. CZP is a pegylated anti-TNF fragment, which differs from other anti-TNFs in that it does not have an Fc region. This region plays a key role in placental transfer, by binding to FcRn, and since CZP does not have this region, it does not cross the placenta[477]. No anti-TNFs have shown to lead to obstetric complications or teratogenicity in animal models using doses 100-fold higher than those recommended in humans; however, no controlled studies have been carried out in humans and, therefore, these drugs

are in US Food and Drug Administration (FDA) category B. Several studies in patients with inflammatory bowel disease treated with anti-TNFs have shown that these drugs are safe, and usually, gastroenterologists do not withdraw them; rather they are continued until the end of the second trimester (approximately week 30 of pregnancy)[478, 479]. Hence, anti-TNFs can be considered safe during pregnancy, but there is a lack of data regarding the longer-term outcomes in infants. Experts conclude that in the case of patients with RA who are pregnant or breastfeeding, who require biological therapy, CZP may be used[56]. Recently, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has approved the use of ADA under these circumstances; however, given that the safety for the foetus of the placental transfer of anti-TNF agents, in terms of infections or response to vaccinations, is not well established, the panel recommends the use of CZP instead (see Table 15 in the appendix).

Treatment during breastfeeding

Experts conclude that maternal breastfeeding is not contraindicated in patients with RA, and that, if treatment is required during this period (this not being unusual as patients often relapse during the puerperium), drugs compatible with breastfeeding must be used. There is a paucity of evidence on pharmacological safety during breastfeeding. According to the opinion of experts, the drugs that are not compatible with breastfeeding include: ciclosporin, tacrolimus, MTX, LEF, MMF, chlorambucil, and biologics. On the other hand, NSAIDs, glucocorticoids, AZA, SSZ and antimalarial drugs may be administered in this period. In the case of corticosteroids, if the dose is above 40 mg/day, mothers should try to wait at least 4 hours after taking the drug before breastfeeding their infant. In the case of anti-TNFs, it is concluded that they are probably safe, and there are some data on CZP, such as those from the CRADLE study, that show that little or no CZP is transferred to breast milk. None of the 17 women included in that study had a CZP concentration in breast milk above 0.076 micrograms/ml (<1% of the plasma concentration expected for a therapeutic dose)[480].

Appendix 5 provides two tables listing the main active ingredients used in rheumatology that may serve as a guide for clinicians in their use in patients with RA during pregnancy and breastfeeding (Tables 15 and 16). These tables summarise the classification of each drug as a function of their safety (FDA classification), the risk for the mother/foetus/breastfed infant, and some explanatory comments, among other information[482]. The GDG has taken into account that although, in this guide, we have used the FDA letter-based classification of the risk of drugs during pregnancy and breastfeeding, the FDA itself is proposing replacement of this system by a more detail

description, close to that advocated by the EMA, including a summary of the risks during pregnancy and breastfeeding, together with a discussion of the data available to help the prescribing physician in decision making and providing advice to women regarding the use of drugs during pregnancy and breastfeeding[483].

10. Treatment adherence

Clinical question 17

In patients with rheumatoid arthritis, which individual-, disease- and treatment-related factors are associated with poor treatment adherence/persistence?

Recommendations

The recommendation is to supervise treatment adherence, especially in women, elderly and comorbid patients **(Grade D recommendation)**.

Patient education programmes should be run and a relationship of trust fostered between patients and clinicians, to improve treatment adherence **(Grade D recommendation)**.

Poor adherence to treatment in a chronic disease such as RA is a challenge for the adequate management of the disease. It is important for the clinician managing the patient to know which treatments are appropriate at each stage of the disease, but it is equally important to identify poor adherence to treatment.

Despite the progress made in research on treatment adherence, the rates of non-adherence have not changed for decades[484]. Some of the risks associated with non-adherence include: 1) more intense flares, which could worsen the general course of the disease, and over time, reduce the likelihood of a good treatment response; 2) disability and potential joint damage; and 3) an increased risk of becoming resistant to the medications prescribed.

Table 13 summarises the factors with a considerable long-term effect on adherence to treatment according to the World Health Organization.

Table 13. Factors that influence adherence to treatment[485]

Socioeconomic factors
• A low socioeconomic status and poverty • Illiteracy and low level of education • Unemployment • Lack of social support networks and family dysfunction. • Unstable living conditions • Living far away from the treatment centre • High costs of public transport and medication • Changing environmental conditions • Culture and lay beliefs about the disease and treatment

Table 13. Factors that influence adherence to treatment[485]

Healthcare system-related factors
• The negative effects of deficient health care services provided • Too few health professionals being available to see patients and hence medical consultations being short • Weak capacity of health systems to educate patients concerning their disease and self-management • A lack of knowledge among health professionals on treatment adherence
Disease-related factors
• Disease progression (acute or chronic) • Symptom severity • Level of disability (physical, psychological and social) • The availability of effective treatments
Therapy-related factors
• Complexity of modern therapeutic regimens • Poor health culture • Lack of understanding of the benefits of treatment • Occurrence of non-discussed adverse effects • Problems with the regimen prescribed (adverse effects) • The cost of medications • Insufficient instructions • Poor patient-clinician relationships • Lack of patient agreement with the treatment • Memory difficulties
Patient-related factors
• Resources available to the patient • Individual attitudes • Beliefs and knowledge about the disease and the therapy • Motivation for treatment adherence

There are also studies on patients with chronic diseases that have underlined the importance of psychological factors, indicating that risk of non-adherence to treatment is higher in patients with depression[486]. To assess the consequences of non-adherence/lack of persistence with treatment in patients with RA, we have reviewed several different studies.

Fautrel *et al.* assessed the influence of the route of administration and other factors on adherence in patients with RA and dyslipidaemia. Their results indicate that there are no differences attributable to different drug formulations/routes of administration. Poor adherence and lack of persistence were associated with higher levels of disease activity, pain, and disability, as well as poorer mental health.

Poor adherence to biological therapy leads to increased resource use and medical costs. The following were found to be useful as indicators of good treatment adherence: a history of DMARD use, satisfactory contact with health services (in terms of the number of visits to the rheumatology unit), reception of a large amount of healthcare information, male sex and younger age. Poor treatment adherence is associated with expensive medication, use of oral MTX, low incomes and Hispanic ethnicity in the USA[487].

López-González *et al.* reviewed the level of adherence to biological therapy in patients with RA, psoriatic arthritis and spondylarthritis. There was great variability between the studies included. The influence of age on adherence remains unclear, although the rate of treatment discontinuation was found to be higher in over-60-year-olds. They also found rates of treatment adherence and persistence to be lower among women and drug survival to be shorter in patients with more comorbidities, according to Charlson's index. Further, costs and co-payments do influence adherence to biological therapy. Use of MTX and other DMARDs may increase adherence to biologics[488].

Salt *et al.* reviewed adherence to DMARDs in patients with RA. The studies included in this review indicate very different adherence rates assessed using different measures including self-report, pill counts, and measurement of the drug in urine and blood. The studies reviewed agreed in that a good patient-healthcare provider relationship and greater knowledge of the disease were associated with better treatment adherence. Other factors also associated with better adherence were use of corticosteroids, belief in the necessity of medications, trust in clinicians and patients not being caregivers of children at home. The results concerning anti-TNF agents were mixed and those concerning educational programmes relate to drugs little used in RA such as HCQ[573].

Joplin *et al.* analysed the effectiveness of various measures used to improve treatment adherence or compliance. Various studies indicated that adherence is better in patients who attend educational programmes and when patients are aware of the risks and benefits of treatment. On the other hand, adherence is poorer among patients who are older, with cognitive impairment, and with high treatment costs as well as in those in employment. The results were unclear and inconclusive regarding disease activity, the use of various different drugs and the efficacy of educational interventions[574].

A systematic review by Pasma *et al.* assessed the factors associated with treatment adherence in patients with RA and undifferentiated inflammatory arthritis. They identified and grouped 64 factors in accordance with the Health Belief Model into demographic and psychosocial characteristics, cues to action and perceived bene-

fits versus perceived barriers. Belief that the medication is necessary and DMARD use prior to anti-TNF use were found to be strongly associated with adherence. The authors found some limited evidence of positive associations of adherence with ethnic status and general cognition, as well as satisfactory contact with and adequate information from the healthcare provider. They also observed negative associations of adherence with weekly anti-TNF costs, having a busy lifestyle, receiving contradictory information and information being delivered in an insensitive manner by the rheumatologist. They concluded that one of the strongest positive relationships with adherence was the belief that the medication was necessary and that this indicated potential for improving adherence as it is a modifiable factor[575].

There is general agreement across all the studies reviewed regarding the consequences of lack of adherence and which factors increase adherence, as well as the profile of patients who may have better adherence; however, they do not provide data on the relationship between adherence and disease progression, disease activity or symptom control. These depend on adherence but are influenced by multiple factors. Among other factors, Patients' attitude and empowerment are important as are access to the health system, among other factors.

The majority of the results seem to be applicable to most patients with RA, except regarding the factors related to social variables and national health systems, as both factors may differ greatly between countries. For example, in Spain, the health system provides universal coverage with small co-payments compared to those in other countries. Cultural factors also differ markedly between countries.

Adherence is important for treatment efficacy and disease control. Poor adherence is associated with higher rates of hospitalisation, more hospital visits and poorer health outcomes, and this has an impact on both patients and health systems.

11. The role of nursing

Clinical question 18
In patients with rheumatoid arthritis, what is the efficacy of educational intervention programmes run by nurses?

Summary of the evidence

In general, structured educational interventions for patients with rheumatoid arthritis are associated with small short-term (3-9 weeks) benefits in variables assessing functional disability, joint counts, patient global assessment, psychological status and depression; however, the effects of these interventions are short lived (3-14 months)[489].	2++
Other interventions based on specialised educational programmes on arthritis have been associated with statistically significant but not clinically relevant improvements in scores on global well-being, self-efficacy on the Other Symptoms Scale, and patient activation, and reductions in 28 joint-Disease Activity Score and pain scores[490].	1+
In other international contexts, authors have indicated the importance of the role of nurses in the management of patients with chronic inflammatory conditions as a facilitator of knowledge acquisition, communication and management of the disease[491,492].	4

Recommendations

The recommendation is that specific individual or group educational programmes led by nurses are included in the routine follow-up of patients with rheumatoid arthritis **(Grade D recommendation)**.
Specific educational programmes led by nurses should be ongoing **(Grade √ recommendation)**.

Nurses have been working in the field of rheumatology for many years[493] and therefore have experience and knowledge to contribute when involved the management of patients with RA[494].

Quality of the evidence

Two studies were identified that assess programmes involving nurses in the management of patients with RA. In addition, two EULAR recommendation documents have been identified that include various recommendations concerning the role of nurses.

A systematic review evaluated the efficacy of educational interventions, some of which were led by nurses, in patients with RA. It only included RCTs and evaluated the results using validated measures of pain, functional disability, painful/swollen joint counts, and acute phase reactants, as well as patient and physician global assessments. The authors also decided to include scales assessing psychological status. The educational programmes reviewed included interventions for "formal structured instruction on arthritis" and "modern psychobehavioral methods to promote changes in health behaviours". The systematic review also included interventions with complementary activities such as "exercise", "biofeedback" and "psychosocial support".

The study showed a small beneficial effect of educational interventions in the short term (between 3 and 9 weeks) for functional disability (SMD -0.17; 95% CI -0.25 to -0.09; Z=3.9; p=0.00007; N=2275); joint counts (SMD -0.13; 95% CI -0.24 to -0.01; Z=2.14 p= 0.03; N=1158); patient global assessment (SMD= 0.28; 95% CI -0.49 to 0.07; Z=2.65; p=0.008; N=358); psychological status (SMD = -0.16; 95% CI -0.28 to -0.04; Z=2.66; p=0.008M N=1138); and depression (SMD= -0.14; 95% CI -0.23 to -0.05; Z=2.94; p=0.004; N=1770). The effect of the interventions was not however sustained in the long term (3-14 months)[489] (Level of evidence 2++).

An RCT assessed the efficacy of an educational programme led by a nurse lasting nearly 10 hours spread over 3 group sessions and 1 individual session in patients with polyarthritis (RA, psoriatic arthritis and non-specific polyarthritis) compared to usual care without an educational programme. The study included a total of 141 patients (71 patients in the intervention group and 70 in the usual care group). The educational programme covered topics such as the arthritis process, problem solving, self-management, how to live with arthritis, goal setting and motivation, medical treatments, how to assess side effects, healthy lifestyles, and community resources. A before-and-after analysis was conducted assessing the differences between the two groups after 4 months. Data were collected on joint counts, clinical history, and blood test results including CRP levels as well as sociodemographic and economic characteristics. The primary outcomes of the intervention were assessed with the following scales: the Arizona Integrative Outcomes Score (well-being); and Self-Efficacy Other Symptoms Scale, a subscale of the Arthritis Self-Efficacy Scale, that gathers information on fatigue, physical activity, pain, and psychological status.

The results showed that intervention group outcomes were statistically significantly better in global well-being (mean difference 8.21; 95% CI 2.3 to 14.1; p=0.01); self-efficacy on the Other Symptoms Scale (mean difference 4.17; 95% CI 0.2 to 8.1; p=0.04) and patient activation (mean difference 5.98; 95% CI 1.8 to 10.2; p=0.01), and

these patients reported less pain (difference in VAS -9.41; 95% CI -16.6 to -2.2; p=0.01), but the effect sizes were not considered clinically relevant. In the before-and-after analysis, there was an improvement in the global well-being score and a more notable improvement in pain and DAS28 (from 3.1 to 2.78; p<0.001). It was concluded that the intervention did not have clinically relevant efficacy except with regards to the slight improvement in DAS28, which could potentially be due to better treatment adherence, but this was not evaluated in the study[490] (Level of evidence 1+).

The GDG considers it appropriate to also mention the content of two other publications, EULAR recommendation documents, which may provide complementary information (Level of evidence 4). One of them presents a list of recommendations concerning the role of nurses in the management of patients with chronic inflammatory diseases[491]. The recommendations are as follows:

- Patients should have access to a nurse for education to improve knowledge of chronic inflammatory arthritis and its management throughout the course of their disease
- Patients should have access to nurse consultations in order to experience improved communication, continuity and satisfaction with care
- Patients should have access to nurse-led telephone services to enhance continuity of care and to provide ongoing support
- Nurses should participate in comprehensive disease management to control disease activity, to reduce symptoms and to improve patient-preferred outcomes
- Nurses should identify, assess and address psychosocial issues to minimise the chance of patients' anxiety and depression
- Nurses should promote self-management skills in order that patients might achieve a greater sense of control, self-efficacy and empowerment
- Nurses should provide care that is based on protocols and guidelines according to national and local contexts
- Nurses should have access to and undertake continuing education in order to improve and maintain knowledge and skills
- Nurses should be encouraged to undertake extended roles after specialised training and according to national regulations
- Nurses should carry out interventions and monitoring as part of comprehensive disease management in order to achieve cost savings

The second document presents recommendations on the role of nursing staff and their educational requirements in the management of patients with inflammatory arthritis[492]. Specifically, the recommendations are that:

- Patient education should be provided for people with inflammatory arthritis as an integral part of standard care in order to increase patient involvement in disease management and health promotion
- All people with inflammatory arthritis should have access to and be offered patient education throughout the course of their disease including as a minimum; at diagnosis, at pharmacological treatment change and when required by the patient's physical or psychological condition
- The content and delivery of patient education should be individually tailored and needs-based for people with inflammatory arthritis
- Patient education in inflammatory arthritis should include individual and/or group sessions, which can be provided through face-to-face or online interactions, and supplemented by phone calls, written or multimedia material
- Patient education programmes in inflammatory arthritis should have a theoretical framework and be evidence-based, such as self-management, cognitive behavioural therapy or stress management
- The effectiveness of patient education in inflammatory arthritis should be evaluated and outcomes used must reflect the objectives of the patient education programme
- Patient education in inflammatory arthritis should be delivered by competent health professionals and/or by trained patients, if appropriate, in a multidisciplinary team
- Providers of patient education in inflammatory arthritis should have access to and undertake specific training in order to obtain and maintain knowledge and skills.

12. General recommendations on patient management

The management of patients with rheumatoid arthritis should take into account the individual characteristics of each patient **(Grade D recommendation)**.
Treatment should be started as early as possible, and for this, prompt diagnosis is essential. It is also essential not to delay changes in treatment when the patient does not respond well to a treatment or when they experience a flare **(Grade D recommendation)**.
Before starting treatments, patients should be adequately informed about the pharmacological properties of the medication, the treatment duration and the expected benefits as well as potential adverse effects, and patients' preferences should be taken into account **(Grade D recommendations)**.
Before prescribing biologics, the following should be considered: age, previous treatments received, tolerance, adverse effects, the possibility of pregnancy and lower cost alternatives with equivalent efficacy **(Grade D recommendation)**.
In the treatment of rheumatoid arthritis, it is essential to include investigation and treatment of comorbidities **(Grade D recommendation)**.
Patients and/or their families should receive education concerning joint self-care and self-management of biological therapy **(Grade D recommendation)**.

13. The patient perspective

"The lived body can, in natural conditions, be forgotten and be left in the background but in particular conditions such as a chronic illness the body is definitely in the forefront"

van Manen 1990. Researching Lived Experience.
State University of New York Press, New York, NY.

Gathering data on how patients with RA experience or perceive their health status may help the professionals involved in their care to understand other factors that have an impact on the disease process. In the development of these guidelines, the view of patients with RA has been incorporated in three ways: direct involvement of two patients with RA in the GDG; the inclusion of the main results of a systematic review of existing studies on the experience of patients with RA and their families and/or caregivers; and finally a qualitative study, conducted as part of the guideline development process, with patients who volunteered to share their experience and concerns.

Review of the evidence

A review was conducted of the scientific evidence available, prioritising studies with a qualitative methodology that gathered data on the concerns, worries and needs of patients with RA regarding the diagnosis and treatment of the disease or on areas on which they themselves, or their families and caregivers, need more information.

Below, we summarise the information obtained from reviewing the studies selected.

The diagnosis	
Perception of the disease[495-502]**:** The life of patients changes after their diagnosis. This is true to the extent that any delay hinders the process of accepting the disease: the earlier the definitive diagnosis, the sooner the patient is able to start to deal with the disease. Feelings of irritation, frustration and uncertainty emerge as the psychological consequences of a long diagnostic process; while the response to receiving the diagnosis include a sense of relief of knowing what they have and the adoption of positive strategies to live with the disease. Various factors influence the diagnostic process. Sometimes delays are attributable to patients' attitudes, in that they consider their symptoms to be routine pain, and hence, delay seeking medical attention. They may not believe that the symptoms are serious or severe compared to those of other diseases that are considered more severe or in more urgent need of diagnosis. When the symptoms are really evident, patients wait less time before contacting their general practitioner. In cases in which the symptoms gradually increase or are difficult to interpret, there seems to be a longer delay. This process is also influenced by how in tune patients are with their own bodies: the more in tune they are, the fewer the barriers and the shorter the delay before contacting their health centre. But once they seek medical attention, it may be that clinicians have to deal with vague symptoms or the presence of other conditions, which may cause confusion, and hence, contribute to delays in referral to a rheumatologist. Finally, the diagnosis of RA is initially associated with a sense of relief, as it often occurs after a long history of symptoms, but later there is phase of unease and concern over how to manage their future life with the disease.	Q+, Q++
Hereditary disease?[503-505]**:** In connection with the diagnosis, there is a factor to take into account among first-degree relatives, namely, fears about whether the disease is hereditary, and if so, they then become concerned about the potential impact of the disease on their own lives. Relatives request further information; and to address this, strategies should be developed to communicate information about risks in an effective manner, as well as provide tools seeking to reduce the psychological burden associated with this information.	Q+, Q++

The symptoms of the disease	
Pain[506-512]**:** This is the main symptom in RA, especially in the early stages of the disease, and according to patients, it is the one that is most difficult to handle. Pain leaves no room for pleasure. Patients refer to a life dominated by the painful symptoms of the disease. Daily pain has been described as follows: "the pain was felt as although it wandered about in different parts of the body and was either severe or dull"506. And as the pain is in already-swollen joints (hands and feet), patients are left with a sense of limited mobility, for both small and large movements (from moving fingers to walking or climbing stairs), and this makes it difficult to plan activities of daily living. Various factors may be associated with an increase in pain and associated functional disability. In particular, stressful or strenuous situations and an inability to cope with them increase the likelihood of experiencing pain. Further, living with chronic pain seems to be a challenge that may have a negative impact on mental wellbeing and lead to a feeling of exhaustion, this impairing quality of life.	Q+, Q++, Descriptive studies
Tiredness ≈ Fatige[506, 508, 513-518]**:** Patients are very familiar with fatigue. They sometimes describe it referring to overwhelming physical exhaustion which makes it difficult to move. In most cases, they always have fatigue; although it is a type of fatigue that is "variable" and "unpredictable" in duration and intensity. Further, it does not always appear at the same times of day or on the same days of the week. Fatigue impairs patients' ability to perform physical activity, and hence, has an impact on their physical and cognitive skills and, in turn, on their mood. If their body gets tired and weakened by pain, patients have less energy and it becomes increasingly difficult for them to perform activities of daily living. Adding to this, the difficulty of finding a comfortable position in bed and, hence, fall asleep, daily problems seem insurmountable. The experience of fatigue seems to be influenced not only by the specific characteristics of the disease but also by psychological and social factors. In relation to this, positive interpersonal relationships and social activities have a positive effect on perceived fatigue, especially in the case of women.	Q+, Q++, Descriptive studies
Morning stiffness[519-521]**:** The majority of patients with RA regard the symptoms of pain and stiffness as concepts that may be related but are, nonetheless, different. They emphasize the highly variable nature of the stiffness, in duration and intensity. As it is difficult for patients to get out bed and they need several hours until their body responds and works and they are able to start their morning routine, patients learn strategies to tackle stiffness: stretching, gentle movements while in bed, and support or manipulation of joints. In this way, over years living with the disease, people with RA, and above all their families, get used to it and manage the stiffness.	Q+, Q++

Treatment	
Choice of treatment[506,508,522-527]**:** From the perspective of patients, the main goal of pharmacological treatment is to help regain their health and be able to live a normal life. By this, they mean regain physical function: stop feeling limited in their ability carry out household chores and self-care, and also normal social functioning. All this implies recovering their self-confidence. Treatment is strongly associated with an expectation of improvement. Sometimes this does not happen and patients develop feelings of insecurity, disappointment and frustration. This is particularly the case when they feel that they received insufficient information regarding the potential inefficacy of drugs. Some clinicians note that they are not able to find, for each individual patient, a single effective treatment without having to try all the potential options. This is a particular problem when some patients with active RA are not open to the possibility of changing to a biological therapy. When clinicians are asked about factors that influence them when prescribing a given drug, the most important factor for them is generally patient´s attitudes and preferences; though, in some studies, these factors have not been at the very top of their list. For many patients with RA, starting on biological therapy is a milestone. After a long time on daily medications and various changes of drugs due to a poor response or adverse effects, the use of biologics is a notable change. The period before treatment with biologics is seen as a dark time, marked by major physical, social and emotional impacts; a time "not to visit again"526. After starting on biological therapy, everything becomes possible again. It is a time for recommitting to physical activities that they had thought would never again be possible, taking advantage of every opportunity. This leads to a sea change in mood and increases the psychological feeling of wellbeing.	Q+, Q++
Adverse effects of medication[507,510,528-534]**:** Patients' understanding of the disease process in general, and the cause of their disease in particular, influence their perception of the value of medication. Some patients feel that the longer they are on a treatment, the more likely that it will be harmful and they will become dependent; while for others, more major concerns are that the treatment will not work in the long term or will be associated with adverse effects. The experience would be better if they were to receive more information about what adverse effects may develop and about how they can dispel unnecessary concerns in advance. Patients depend on medication to be able to function properly; but seeking to reduce the adverse effects some go as far as self-adjusting the dose of a drug or stop taking it without consulting their doctor. There is also the possibility of resorting to alternative therapies (e.g., acupuncture or herbal medicines), despite their usefulness usually being questionable and any form of relief or improvement associated with their use being short-lived.	Q+, Q++

Optimisation[535]/Remission of RA[536]: The possibility of dose reduction is viewed very positively by most patients. Nonetheless, some of them feel that there is a need to be more realistic because they fear a flare of the disease, and if the treatment has to be restarted, they know how long they might have to wait until it took effect again. In the case of patients in remission, the decrease in symptoms makes them feel normal, as if the disease was not present in their lives anymore.	Q+, Q++
Treatment adherence: Patients´ beliefs regarding medications they are on, their perception of RA and their level of satisfaction with the information they have received about the drugs influence treatment adherence. The medication may have a negative effect on the general wellbeing of patients that may not be "well understood" by the rheumatologist. These are cases in which the clinician assesses the clinical activity of the disease to be low, but the patients still report struggling to cope with their RA and hence they are not happy with the treatment[512, 537]. In the case of biologics, good communication by clinicians may play a key role in patients' starting to use the drugs and treatment adherence. If rheumatologists are aware that recently diagnosed patients may have a negative perception of the medication in general, or biologics in particular, and offer them culturally suitable information, this may increase treatment adherence[534, 538-540]. In relation to this, some studies have shown that patients value a good relationship with their doctor. In fact, trust in their doctor is seen as one of the facilitators of medication adherence. Further, the more drugs taken, the greater the adherence. Another facilitator is the establishment of routines for taking medication[499,541,542].	Q+, Q++, Descriptive studies Q+, Q++
Living with the disease day by day	
Changes in physical self-image: The disease involves radical changes and limitations in patients' lives. It is difficult to accept that one's body is becoming weaker and does not function as before. It changes patients' perception of time because they need more time than before to carry out activities of daily living and there is never enough. They, therefore, have to adjust and learn new routines to save time. The sense that they find it hard to have control over their own lives is added to their fear of the omnipresent threat of complications of the disease. This is in addition to the worries and concerns about the possibility of the disease progressing to other non-affected joints[503,506,510,511,543].	Q+, Q++, Descriptive studies Q+, Q++

Bodily sensations change with the disease. It is difficult to recognise oneself when one's physical skills and mobility are reduced due to joint pain, stiffness and fatigue. This has negative consequences in daily life in terms of not being able to remain active for work and household chores; do exercise; or keep up with the pace of family life. There is constant battle to deal with life and manage the disease[506, 507, 509, 526, 544-546]. Once again, in this context, morning stiffness is a great burden for many patients. They see themselves as severely disabled, this leading them to feel insecure about their own bodies, as they lack confidence in their functional ability, and in turn, they develop a tendency to pay too much attention to their own bodies[503, 506, 507, 509, 510, 519]. Sometimes, patients try to hide the visible bodily changes, but this is difficult to achieve because, for example, changes in their hands are easily seen by people around them. Foot problems are a constant feature of the life of patients with RA, even when they are on biological therapy. The effect of footwear on patients' self-image, together with psychological suffering, emerge as major themes. Unmet footcare needs become evident due to the effect of pain on mobility, as well as the perception that insufficient importance is given to foot problems during consultations[526, 545, 547-550]. People with RA know that after the diagnosis they have to learn to live with the disease. For this reason, it is essential for them to be aware of their own body, the signals it gives and its limitations. This will help them to normalise their lives. To this end, various different strategies are used, depending on the phase of the disease they are in: acceptance, avoidance of self-pity, planning the pace to do things, and/or making continual efforts to keep. In short, it is about moving from dependence to independence. Some patients are continuously engaged in searching for solutions and strategies to gain some relief, manage the disease and normalise their situation and some meticulously plan their tasks, while others place emphasis on seeking to enjoy small things in life[545]. Changes in mental self-image: In people with RA, the disease brings to the surface negative emotions that tend to dominate their mental image of their state of health. Reports of physical pain are often accompanied by an emotional burden. These emotions of suffering derive from the problems that arise from coping with daily life: loss of identity or confidence, sadness, anxiety, concerns, frustration, anger, fear of being left by their partner or feeling old and being continuously moody[506, 509, 544, 551]. Patients admit that it is very easy to become irritated when they have to cope with pain and physical limitations of RA. They feel annoyance, when they compare their current lives with their lives before the disease; frustration, due to a body that does not work properly, this being exacerbated when people around them fail to empathise with their situation; and sadness and helplessness, due to the constant physical pain and loss of bodily function, this resulting in a decline in independence and ability to live their life to the full[509-511, 545]. The limitations perceived regarding their free time, ability to travel and social life have an impact, leaving them with feelings of loss, loneliness and despair[506].	Q+, Q++

Depression: On the one hand, people who are predisposed to depression have been shown be more vulnerable in how they manage chronic pain. On the other, patients with more symptoms of pain get more depressed. In individuals with a history of depression, if the daily pain increases so does the effort needed to deal with their pain when expressing their feelings, and this leads to a significant worsening in their mood, compared to that in individuals who have never been depressed[507, 552, 553].	Q+, Q++, Descriptive studies
Sexuality: In many patients with RA, sexual satisfaction decreases compared to the situation before the onset of the disease, and in some patients, sexual relationships lessen in importance and stop being part of their sexuality[544, 554]. Nonetheless, studies show different points of view and report both positive and negative attitudes: • Some people indicate an inability to have the sexual life they would like due to being tired or the effect of medication on their interest in sexual relations[507, 510]. • For others, the sense of being severely disabled makes them feel blocked and they have to fight with possible feelings of shame and with their own sexual dissatisfaction[519, 544]. • But there is also a group of patients among whom, if both they and their partners accept potential changes in their sexual relations, the tension in their relationship decreases and they regain sexual satisfaction[544].	Q+, Q++, Descriptive studies
Strategies for managing the disease: There are various different strategies for managing RA: • Adopting a positive attitude to experiencing chronic pain and identifying strategies for coping with pain are particularly important[555]. • Finding a balance between activity and rest to cope with the condition is also key[512]. • Making efforts to maintain an attractive appearance and taking pleasure in personal grooming activities to improve one's external appearance are other strategies employed[519]. • Enjoying the small things in life is what it is all about[509]. • Doing physical exercise for joints and maintaining accessible flexible physical activity tailored to patients' needs are known to be beneficial and important respectively, though another matter is ascertaining whether patients have information on what is the most suitable type of exercise. These strategies help patients to remain able to perform activities of daily living; as well as have positive feelings in relation to social interaction, because they enable them to be close to physically active people, and thereby sense that they can participate socially, on equal terms with people who do not have RA[546,556-560].	Q+, Q++, Descriptive studies

Family and social environment	
Need for support: At the beginning the disease is invisible. Patients feel that nobody understands the nature of RA and its effects on them. Sometimes, they also feel accused of exaggerating their symptoms. They describe a lack of public awareness of the causes of the disease and its negative impact on quality of life. As well as becoming more aware of their own disease, they have to convince others that it is something real, not fictitious or invented, and they feel they have to be repeatedly explaining the same things. It is especially hard that workmates do not believe they are ill or that their fatigue is real. These doubts are difficult to manage emotionally[503, 504, 506, 507, 512, 513, 543]. The disease hinders the maintenance of social roles and relationships, and adds to the perception that patients are a burden on others. This leads to feelings of inadequacy or uselessness that represent a barrier to living as a couple. If the relationship and communication with their partner are good, patients cope better with the burden of the disease and there is less pain catastrophizing[497, 506, 507, 510, 561]. Family and social support are very important for people with RA. Despite everything, these factors have a great influence on how people with this disease address the task of maintaining or regaining their participation in activities of daily living and most patients rely on family and friends for support during each stage of the disease[496, 562].	Q+, Q++, Descriptive studies
Loss of independence: Often living with RA is experienced as a decline in independence, in terms of care. Family support is seen as something very positive, but given concerns about it becoming a burden, patients feel the need for healthcare and home care[506, 510, 512].	Q+, Q++, Descriptive studies
Work: Patients with RA often face numerous challenges and have to make adjustments to keep their jobs. Various issues related to the disease, such as not being able to use their hands, not being able to choose their rest breaks and mobility problems, represent obstacles to keeping their job[507, 563]. Nonetheless, other factors are seen as more important[564,565]: • Fatigue is the factor that most restricts the employment possibilities of people with RA. Due to misconceptions about the tiredness associated with arthritis and the fact that it is not visible, some colleagues and bosses do not understand or accept it.	Q+, Q++

• The invisible, variable and unpredictable nature of arthritis is also an important issue, especially in terms of interpersonal relations at work. Relationships with colleagues become strained, especially in the case of those who work in teams. Patients' fear of resentment from colleagues and desire to not be seen to get special treatment are major barriers to requesting work-related adjustments that would help improve the employment situation of people with RA. • Workplace adjustments and improvements are important: adequate facilities, ergonomic changes that are well designed and supervised by a professional therapist (e.g., a more comfortable chair or an adapted computer keyboard) and more flexible working hours.	
The perspective of the caregiver	
It is sometimes difficult for caregivers to live with people with RA. On the one hand, the caregiver plays a key role, providing physical and emotional support to patients; but at the same time, to enable that, it implies caregivers themselves having to make changes in their activities of daily living and leisure. In turn, this has other implications such as[498]: • Psychological consequences: emotional overload, feelings of guilt and discouragement • Work absenteeism due to having to care for their family member • Impacts on social relationships and networks: reductions in free time and leisure activities • The burden grows as the patient becomes less independent • There are few organisations that provide support	Q+, Q++
Relationships with health professionals	
Positive clinician-patient relationships are highly valued because they help to increase the trust in the treatment received. Satisfaction levels are higher if communication by the doctor is open and patient centred, rather than more didactic and paternalistic approaches, since the former features help patients to gain a sense of shared responsibility for the management of the disease. The experience and support of doctors are valued, but patients feel more able to cope with their arthritis when they are actively involved in their own care, rather than feeling like passive receivers of advice and treatment[566]. Through the diagnostic process, patients may leave their doctor to decide what it is the best treatment. Nonetheless, with time, patients may start to play a more collaborative role. Clinicians should understand that patients differ in the level of autonomy they show and that they should talk to patients to find out to what extent they want to be involved in decisionsn[532].	Q+, Q++

This underlines the importance of patients being heard, listened to and understood. Patients need to "be seen" and "be believed". For patients, to "be seen" means being treated as an individual and not a mere diagnosis, while to "be believed" means credence being given to pain and suffering they report. Patients differentiate between different roles. Rheumatologists are considered the experts in their field, while patients considered themselves to be the experts in their own bodies and in what it means to live with RA. For this reason, they expect to be respected and viewed as a valuable voice in decision-making[510, 512, 537, 566, 567]. Information needs: Patients underline their need to receive more information, both of a clinical nature and concerning how to manage their RA; sometimes they comment that the information offered is unclear or ambiguous[496, 497, 504, 507, 510, 568, 569]. They also recognise the role of nurses, and that they have knowledge and skills that are useful for providing psychological support when patients are seeking to cope with symptoms such as pain and mood disturbances. Additionally, they rate nurse-led educational programmes positively, because they tend to be simple and easy to follow, helping them obtain the information they need to knowr[570-572].	Q+, Q++,

Qualitative study

In order to explore experiences with disease of patients with RA in our cultural setting, a primary qualitative study was conducted, based on a group discussion technique. The information retrieved was transcribed and categorised to facilitate interpretation of the results. In this way, it was possible to identify and analyse the most important issues for these patients. This information was used to complement that obtained from the systematic review of the literature.

The main conclusions of the qualitative research are summarised below:

Categories	Analysis
Diagnosis	**Before** For the majority of patients, the diagnostic stage is dramatic and pivotal, and they ask themselves "Why has this happened precisely to me". Patients try to find a cause of their disease and have developed their theory, based partially on what they have heard, partially on what the doctor has told them, and partially on how they have taken on board the disease. Many patients associate their condition with a previous injury resulting from a sports accident (skiing, playing tennis, etc.), which made them go to the emergency department or a trauma specialist. From then, they start a process of moving between different health professionals and treatments that may provide initial relief, but that later are found ineffective. *"The disease comes to light after trauma".* **The process and the subsequent relief** For older patients, the process of identifying and diagnosing their condition is described as a stage of great suffering. Perhaps because, at the time, referral to a rheumatologist was not the first or the most common care option, they were unlucky to first be sent to specialists totally unrelated to rheumatology. *"I used to play tennis and my feet hurt a lot, … then my wrists, and I was told that this was normal, that it was tiredness and they said that it was gout, and I started to be treated for that, until I finally managed to get to a rheumatologist".* *"…A lot of pain, but in the emergency department they told me it was acute tendinitis, until they did some tests and found that I had rapidly-progressing rheumatoid arthritis".* *"I was seen by trauma specialists and they gave me injections, and 2 years went by like this with injections, until I was not even able to use my elbow".* *"In the past, some specialists (in trauma) were not aware of this disease; I was sent back and forth for nearly 2 years; and by that time, I was unable to move; my hands, my knees, … everything hurt, even my jaw became stiff, … a year of sick leave at the age of 26".* Then, when the diagnosis of the disease is made, being able to give their condition a name is a great relief. From this point, patients have to develop the ability to start to accept that they have a chronic disease and what this implies for their life.

Categories	Analysis
Signs and Symptoms	Daily life There is agreement between patient reports in their description of daily life with the disease. The chronic nature of the disease means always being in pain and tired; these two symptoms are a recurrent theme in their comments and in all cases have a negative impact. *"Daily life is, well, really bad, I suffer in bed; to turn over, I have to do complicated manoeuvres, because I can't just turn over".* *"And when the night comes, we all know what that means…"* *"I couldn't bear the pain".* *"For me, the worst has been my hands and feet".* *"I have been recognised as having complete incapacity for work".* *"It's a level of tiredness that means you can't get up from a chair, that you can't cope with life".* It is very important to highlight a feature of the discourse of women, namely, their experience of maternity. It is a process that raises the perceived pain to an even higher level. *"You have to plan your pregnancies…. stop your treatment for some time, put up with the pain for some months, until you become pregnant".* *"During pregnancy, the disease gets a lot better, but then, after the delivery, it flares with vengeance; a fortnight after giving birth, really terrible pain; I couldn't cope with life".*
Treatment	Choice of drugs One of the main themes in the discourse of patients concerns treatment and two opposing views emerge regarding pharmacological treatments. This reveals the influence of a lack of awareness about the types of medication available. Some patients are very frightened of biologics, while others are staunch defenders of their benefits, supporting their use and preferring them above all for the change that they have meant in their lives. *"I had heard that biologics are a rigmarole, … because they send you back and forth for some months, for tests, exams, … I don't know what else".* *"They really frighten me… because you never know what is going to happen later …"* *"They send me to try to convince people (to talk in meetings) to stop being afraid of biologics".*

Categories	Analysis
Treatment (cont.)	For most patients, starting on biological therapy is a milestone, before which, there is frustration and hopelessness, and after which, recuperation and an ability to rebuild their lives, and to feel normal again. There are, however, some people for whom biological therapy does not go so well. *"They gave me all sorts of things, gold salts, methotrexate, and it was no good; it looked like I was headed for a wheelchair, … until they gave me the biologic".* *"… I was put on the biologics programme and this has given me a new life, … I´m a different person, I´m not in pain, …, I live a normal life, I sleep at night, and what I say to the doctor is: you have given me back my life".* *"Initially, my wife had to dress me, wash me; I couldn't even put my socks on, … and now I lead a normal life, I play tennis. The biologic has worked wonders".* *"I got involved in the trial and there were people who had to drop out, as it wasn't working for them".* *"We mustn't despair, because if plan A doesn't work there is plan B or plan C. Before, there was only plan A and nothing else".* Lifestyle adjustments Some of the changes are really striking, such as those seen in patients whose life is changed by the disease in that they manage to give up unhealthy or harmful habits such as smoking. *"I was allowed to start on biological therapy because I gave up smoking, … and I gave up smoking, something I´d never managed to do before, but then did because of the pain".*
Mood	The emotional sphere In the emotional sphere, the disease ends up affecting people's character and it is common that patients develop symptoms of depression or anxiety, as well as social isolation, which tend to further worsen their psychological well-being. *"Because I was about to fall into depression, above all in the mornings, as I had a level of disability that was like not having a life … emotionally, this disability takes its toll".* The patients share the view that the characteristics of RA are not well known by the rest of the general population. Further, it is difficult for something that people know little about to become accepted. And this generates feelings of powerlessness and sadness. *"I think that the worst thing is peoples' lack of knowledge about this condition; it gets confused with arthrosis and with rheumatism".*

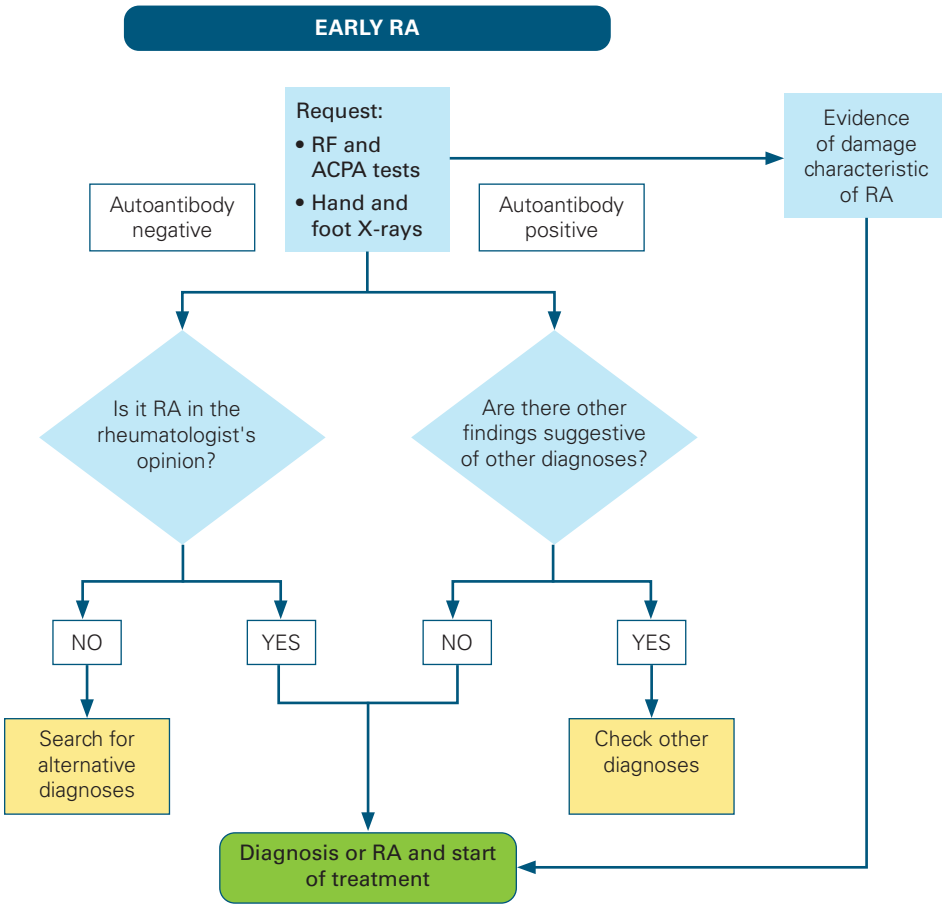
Categories	Analysis
Adjustment	**Coping** Little by little, patients seek and discover resources to cope with the difficult phases of their disease and fight to ensure that it does not take over their lives. At these times, family members, and the support they offer, are key to overcoming emotional crises. *"You slip into a dark place and say to yourself, I´m dying; …. until you say, this is not going to sink me and you come out of it".* *"In the bad period, from the point where you´re told you are going to need to be dressed or helped, you would be lost if you didn´t have support from your family".* *"Despite the disease, you can be a normal person".* **Seeking a positive attitude** Patients feel that the disease should not be the end of their lives. They have had to go through a period of adaptation; but this has made them develop a fighting spirit and positive coping strategies. On the other hand, they recognise that the disease will always be there, not letting them forget the bad times. *"Not let oneself … This is not going to get the better of me".* *"What I have always had is a lot of willpower; one shouldn't be intimidated".* *"I get a flare every 3 months or so and it serves to remind me what a bad time I had at the beginning".* **Fighting for as normal a life as possible** Patients underline the importance of physical activity for feeling better and for not allowing the condition to defeat them. Doing physical activity is something they become almost religious about. It helps improve their symptoms, and thereby, their functioning and quality of life. *"For me, what has helped me carry on is that I have never stopped doing things: going to the pool, using an exercise bike, … and that has enabled me to avoid a wheelchair".* *"I´ve seen that you can get the pain to go away if you do exercise".* **Positive attitude to the future** Patients respond to the disease by generating positive mechanisms to allow them to cope with it. In this way, they manage to look at the future with optimism. From the moment the disease is under control, their fear of it disappears and they are up for anything, even planning travel that they had thought would be impossible. *"I´m walking the Camino de Santiago … albeit making sure to never overdo it".*

Categories	Analysis
Work	Transformation of work The disease also affects the work sphere. The physical limitations influence patients' capacity to work. Decisions about whether to make changes in their current employment or not are influenced by the characteristics of patients and their personal situation and state of mind; though in most cases, patients opt to keep going with their job. *"… In the workplace, if you are not ashamed to say that you are ill, people help you".* *"I have been off work a lot, … but I´m not going to give up work"* *"I was in work; I had a company and I had to retire because I couldn't work. … It's not the disease; it's where it takes you".*
Care process	Relationship with clinicians Describing their relationship with clinicians, all patients are full of praise for the specialists in rheumatology units. They report that these clinicians offer care and support with treatment, and also underline that the information provided tends to meet their needs. *"The way you are treated couldn't be better".* *"They recognise you; they remember your name. It's been many years".* *"I've moved to be able to continue being under the care of Dr. _".* If there are any complaints, they are to bring to light that specialised and primary care are "not in tune with one another". *"I have to go to the hospital as my general practitioner doesn't want to request blood tests for me so often, questioning why they are needed when I´m in such good form, even though it's what I was advised to do by the rheumatologist".*

14. Diagnostic and therapeutic strategies

Algorithm 1

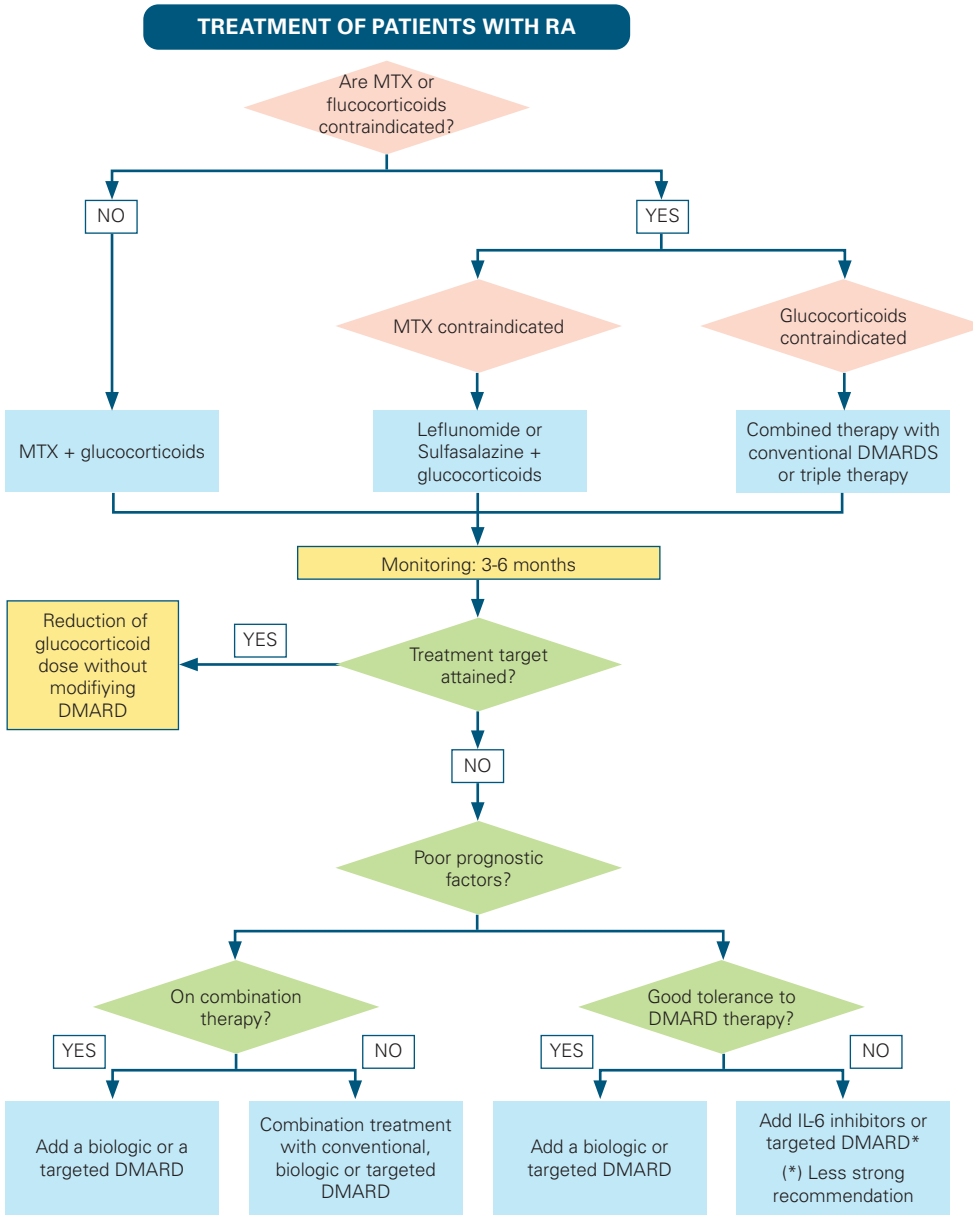
Algorithm for the diagnosis of rheumatoid arthritis



RA: rheumatoid arthritis; RF: Rheumatoid factor; ACPA: anti-citrullinated protein antibody

Algorithm 2

Algorithm for the treatment of rheumatoid arthritis



RA: rheumatoid arthritis; MTX: methotrexate; DMARD: disease-modifying anti-rheumatic drug

15. Dissemination and implementation

Dissemination strategy

The process of achieving adherence of health professionals to recommendations in clinical practice guidelines starts with a strategy for their dissemination. The programme to promote the adoption of these guidelines for the management of patients with RA includes the following interventions:

- Announcement of the completion and availability of the guidelines through the members' newsletter through the SER website
- Publication of the guidelines in electronic format on this website
- Dissemination of the guidelines through social media: Twitter, LinkedIn and Facebook
- Presentation of the guidelines to the various scientific societies involved
- At all presentations of the guidelines, emphasis will be placed on the informative material developed for patients to encourage its distribution to all clinicians and in turn to patients with this health problem
- Publication of the guidelines in scientific journals
- Targeted and effective distribution of the guidelines to all the groups of health professionals involved (rheumatologists, cardiologists, pulmonologists, general practitioners, rheumatology nurse specialists, trauma specialists and rehabilitation specialists) to facilitate dissemination
- Evaluation of whether they are effectively adopted, with the establishment of decision support systems, integrating the guidelines and indicators selected into the computer software used in primary care
- Presentation of the guidelines at scientific events (conferences, seminars and meetings)

Proposal of indicators

The manual of the AGREE II tool highlights the importance of the development of criteria that make it possible to monitor and evaluate adherence to the main recommendations in guidelines. The guideline authors have sought to provide a useful tool for health professionals interested in evaluating the care provided to patients with RA. This consists of quantitative indicators which, if measured on a regular basis, allow us to monitor the progression of patients over time. The team

responsible for assessing the impact of the CPGs and the care provided to patients should select appropriate sources of data and an appropriate time period for each indicator (Table 14).

Table 14. Proposed indicators

Area	Type of indicator	Name of the indicator	Cut-off for quality	Care level (1: primary, 2: specialised)
Referral	Process	Percentage of patients with joint pain referred from primary care	50%	1
Referral	Process	Percentage of patients with rheumatoid arthritis referred from primary care within the first 3 months after the onset of symptoms	50%	1
Treatment	Process	Percentage of patients who initiate background methotrexate in combination with glucocorticoids	90%	2
Treatment	Process	Percentage of patients treated using a treat-to-target strategy	70%	2
Treatment	Process	Percentage of patients who receive appropriate risk management before starting biologics or targeted DMARDs	100%	1,2
Treatment	Process	Percentage of patients who start biologics or targeted DMARDs after optimisation of methotrexate or other conventional synthetic DMARDs	90%	2
Treatment	Process	Percentage of patients who start biologics with anti-TNFs in combination with a conventional synthetic DMARD	90%	2
Treatment	Process	Percentage of patients who quit smoking	100%	1,2
Treatment	Process	Percentage of patients who undergo regular cardiovascular risk assessment	100%	1,2

Table 14. Proposed indicators

Area	Type of indicator	Name of the indicator	Cut-off for quality	Care level (1: primary, 2: specialised)
Treatment	Process	Percentage of patients on long-term glucocorticoid therapy who undergo osteoporosis risk assessment	100%	2
Treatment	Process	Percentage of patients in whom biological or targeted DMARD therapy is optimised once the treatment target has been attained in a sustained way	90%	2
Treatment	Process	Percentage of patients who receive nurse-led training on the disease, recommendations, self-care and treatment adherence	100%	2

16. Future lines of research

During the guideline development process, certain priority areas for future research were identified. In particular, these include the need for:

- More research on the pathogenesis of RA, searching for pathogenically-different subtypes of the disease, to be able to tailor treatment for patients depending on the characteristics of their disease
- Studies focused on preventing the development of RA in individuals who are asymptomatic but autoantibody positive and have risk factors and in those who already have inflammatory arthralgia
- Further research in the field of biomarkers, for diagnosis but especially for prognosis, to be able to provide the most appropriate treatment as a function of the disease characteristics and potential severity
- High-quality studies that demonstrate the efficacy and cost-effectiveness of starting biological therapy with the goal of providing intensive treatments and then being able to discontinue them for long periods of time
- Further research to identify measures for assessing the disease that combine the most important outcomes for patients and physicians in an effective way and which are more accurate than currently used, reflecting the reality of the disease and less influenced by confounding factors such as subjective states or concurrent conditions
- More high-quality RCTs comparing biologics with targeted DMARDs in different clinical scenarios, such as patients with early RA, who have a poor response to conventional DMARD therapy or who are resistant to biologics
- Studies to assess the efficacy of biological therapy or targeted DMARD monotherapy in all clinical scenarios
- Further research to identify the indications and protocols for dose reduction once patients have attained desired therapeutic targets
- Well-designed long-term studies on the indication and treatment of choice for certain comorbidities associated with RA, such as depression, cardiovascular conditions and lung disease
- High-quality studies to identify nurse-led programmes providing health education that would be applicable in our setting and help to achieve good outcomes in patients with RA

Appendices

Appendix 1. SIGN Levels of evidence and grades of recommendation

Levels of scientific evidence[10]	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of bias and with a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of bias and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g., a case reports, case series
4	Expert opinion

Qualitative research[1]

[1] This category includes studies based on qualitative methods and is not covered by the SIGN recommendations. The methodological quality of this type of research was assessed and only the most rigorous studies included.

Grades of recommendation[2]	
A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population of the guidelines; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence of level 3 or 4; or extrapolated evidence from studies rated as 2+

√[3]	Recommended best practice based on clinical experience and consensus among the guideline development group
Q+, Q++	Evidence taken from relevant high-quality qualitative studies. This category is not part of the SIGN guidelines

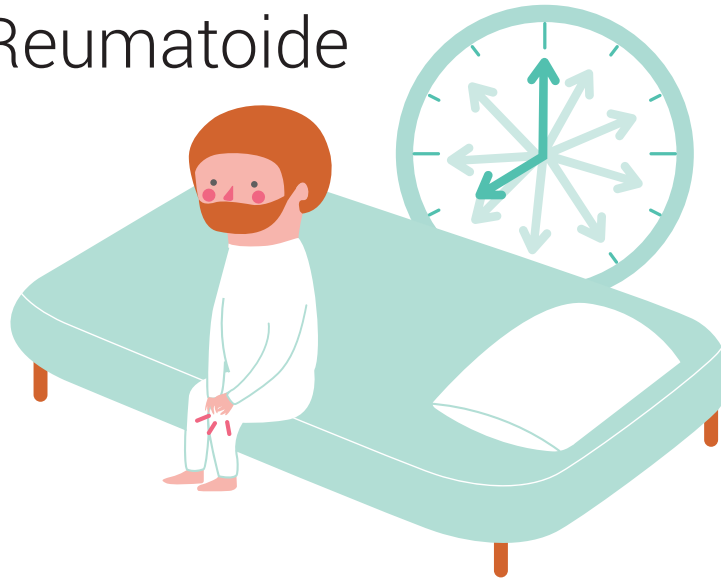
[2] Studies rated 1- or 2- should not be used for the development of recommendations used as evidence in the development of guidelines given the high risk of bias.

[3] On some occasions, the guideline development group identified important practical issues on which it wanted to place emphasis but related to which there was unlikely to be any supporting evidence. In general, these issues concern aspects of treatment considered good clinical practice and which are not commonly questioned. Such issues have been evaluated as questions of good clinical practice. Related recommendations are not an alternative to evidence-based recommendations, rather they should only be taken into account when there is no other way to highlight the corresponding issue.

Appendix 2. Information for patients

Está disponible también en formato electrónico en la página Web de la Sociedad Española de Reumatología (SER): www. ser.es.

Aprendiendo a convivir con la Artritis Reumatoide



Información para el paciente

Preguntas y respuestas para las personas que tienen artritis reumatoide, sus familiares y cuidadores.

Sociedad Española de Reumatología

Esta información ha sido realizada por la Unidad de Investigación de la Sociedad Española de Reumatología (SER) y el Grupo de trabajo de la Guía de Práctica Clínica para el Tratamiento de la Artritis Reumatoide. Está disponible también en formato electrónico en la página Web de la Sociedad Española de Reumatología (SER): www. ser.es. En esta página puede consultarse, además, la versión completa de la Guía.

Coordinación clínica
Dr. Alberto Cantabrana Alutiz
Coordinación desde la UI
Petra Díaz del Campo Fontecha
Agradecimientos
Al Dr. Federico Díaz González, la Dra. Sagrario Bustabad Reyes, Laly Alcaide y Gonzalo López Alonso por la revisión de esta información.

2ª Edición: Septiembre 2018
Ilustraciones: Lidia Lobato Álvarez
Maquetación: Álvaro Lobo Machín
Edita: Unidad de Investigación (UI).
Sociedad Española de Reumatología
Marqués del Duero, 5, 1ª planta. 28001, Madrid. España

04 A

00
Índice

01 Presentación 06

02 Diagnóstico de la enfermedad 08

¿Qué es la artritis reumatoide? 08
¿Cuáles son las causas que la producen? 09
¿Cuáles son los síntomas?
¿Qué articulaciones pueden verse afectadas? 11
¿Cómo se diagnostica? 15

03 Tratamiento y seguimiento de la artritis reumatoide 18

¿Cuáles son las opciones de tratamiento? 18
¿Cuál es la evolución de los pacientes que tienen artritis reumatoide? 30
¿Qué complicaciones pueden ocurrir? 31

04 Vivir con artritis reumatoide 33

¿Qué debo tener en cuenta cuando acuda al centro de salud o si voy al hospital? 33
¿Qué consejos sobre cuidados en la vida diaria debo seguir? 34
Reposo 34
Ejercicio 35
Alimentación: comida y dieta 36
Entorno familiar y laboral 38
Estados de ánimo 40
Controles clínicos 40
Dejar de fumar 42
Embarazo y consejo genético 42
Imagen corporal 44

05 Más información y recursos adicionales 47

¿Dónde puedo aprender más sobre la artritis reumatoide? 47

01
Presentación

Esta información está orientada a personas que tienen artritis reumatoide. También a sus familiares y cuidadores. Le podrá ayudar a conocer más esta enfermedad, para que pueda cuidarse mejor y aumentar así su calidad de vida. Puede que tenga que leerla varias veces o utilizar las diferentes secciones dependiendo de cuando necesite la información.

El documento recoge información sobre la enfermedad, el diagnóstico y el tratamiento; además incluye consejos sobre cómo puede manejar la enfermedad en su día a día y otros recursos de utilidad como los contactos de asociaciones de pacientes o recursos de Internet. Debe tener en cuenta que toda la información recogida aquí no sustituye la opinión ni los consejos de su médico o de otros profesionales como enfermeras especializadas. Se trata, más bien, de un documento que le ayudará a complementar la información ofrecida por el equipo sanitario que le atiende.

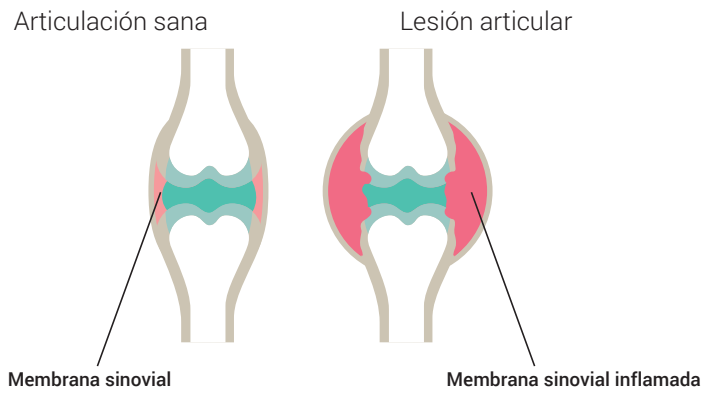
Este documento ha sido realizado por la Unidad de Investigación de la Sociedad Española de Reumatología (SER). Las recomendaciones que en él se recogen se han elaborado basándose en la literatura científica existente y en el consenso y experiencia del grupo de profesionales expertos en el tema (reumatología, enfermería

especializada). También se han tenido en cuenta otros materiales informativos sobre artritis reumatoide elaborados por sociedades científicas y organismos oficiales en España y en otros países. Además se ha utilizado la información derivada de un estudio de necesidades y preferencias de las personas con artritis reumatoide que ha elaborado la propia Unidad de Investigación.

02
Diagnóstico de la enfermedad

¿Qué es la artritis reumatoide?

La artritis es la inflamación de las articulaciones, que son las zonas del organismo donde se unen dos huesos, tales como los codos, los nudillos de las manos y las rodillas, y se caracteriza por dolor, hinchazón y sensación de entumecimiento o rigidez en ellas. Estos síntomas pueden durar solo unos días o semanas, es decir, tratarse de artritis aguda, o bien, durar meses o años, con lo que se hablaría de artritis crónica.



La artritis reumatoide (AR) es la forma de artritis crónica más frecuente, pudiendo afectar entre un 0,3% y 1% de la población mundial. Ocurre en todas las partes del mundo, independientemente de factores como la raza o el clima. En España afecta, aproximadamente, a unas 150.000 o 200.000 personas. La padecen más las mujeres (en una proporción de tres mujeres por cada hombre), y el número de casos aumenta con la edad, siendo más frecuentes entre los cuarenta y sesenta años, y también más en el medio urbano que en el rural.

¿Cuáles son las causas que la producen?

- **0,3% - 1% de la población mundial padece AR.**
- **España: 150.000 / 200.000 personas con AR.**
- **3 mujeres por cada hombre padecen AR.**
- **Es más frecuente entre los 40 y 60 años.**

No se conoce la causa de la enfermedad. Se sabe que es un proceso autoinmune. Esto quiere decir que la enfermedad se produce porque el sistema inmune, que en condiciones normales nos defiende de agentes externos como bacterias o virus y de células tumorales, ataca a las articulaciones, produciendo inflamación y daño en los componentes de las mismas. Se desconocen los motivos por los que esto ocurre así.
El hecho de que la padezcan más mujeres que hombres pone de relieve que los factores hormonales juegan un papel importante en la aparición de la enfermedad.

La artritis reumatoide no es una enfermedad infecciosa y no se puede contagiar de unas personas a otras, sin embargo, cabe la posibilidad de que algunos microorganismos, como ciertos virus, o los gérmenes causantes de la enfermedad periodontal (inflamación crónica de las encías), puedan jugar algún papel como desencadenantes de esa respuesta autoinmune.

El único factor ambiental conocido que puede contribuir a la aparición de la artritis reumatoide es el tabaco. Los fumadores tienen más riesgo de padecer la enfermedad. Esto puede deberse a que el tabaco puede modificar algunas proteínas humanas que, de esta manera, se convierten en objetivos que nuestro sistema inmune pretende eliminar, provocando esta respuesta autoinmune.

La artritis reumatoide es la consecuencia de modificaciones en el comportamiento del sistema inmune (autoinmunidad), que ocurren por la interacción entre una cierta predisposición genética, factores hormonales y factores del entorno (infecciones, tabaquismo....) a través de mecanismos que aún no se conocen por completo.

Consejo genético

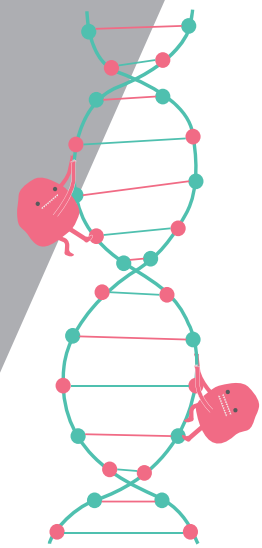
Existen algunos factores genéticos que favorecen el desarrollo de la AR y se han identificado algunas variantes genéticas (por ejemplo el alelo DRB1) que se asocian con formas más graves de la enfermedad, pero no se puede decir que sea una enfermedad hereditaria.

Solo el 20% de los gemelos monocigóticos (es decir, gemelos idénticos) padecen ambos una artritis reumatoide si uno de ellos la padece. Los familiares directos de una persona con artritis reumatoide (hijos, hermanos) tienen mayor probabilidad de tener la enfermedad, pero esta probabilidad sigue siendo baja. Es decir, si cualquier

10 D

persona tiene menos de un 1% de probabilidades de tener artritis reumatoide, los hijos de pacientes con la enfermedad tienen, en el peor de los casos, un 10% de probabilidades de tenerla o lo que es lo mismo, un 90% de probabilidades de no padecerla.

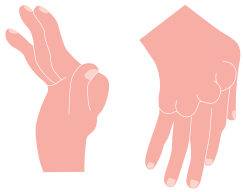
Un aspecto interesante de los estudios genéticos en artritis reumatoide es que, al igual que se han identificado variantes genéticas que confieren predisposición a padecer la enfermedad, e incluso orientan sobre su potencial gravedad, hay otras que permiten predecir la respuesta que se tendrá a determinados fármacos. Esta rama del conocimiento, actualmente en desarrollo, se conoce como farmacogenética y ayudará a diseñar tratamientos adaptados a las características de cada paciente. Ya se está aplicando en algunos tratamientos para el cáncer y se espera que en un futuro no muy lejano este conocimiento se pueda ampliar al tratamiento de la artritis reumatoide y permita realizar lo que se conoce como "medicina personalizada" o "medicina de precisión".



¿Cuáles son los síntomas? ¿Qué articulaciones pueden verse afectadas?

La artritis reumatoide es una enfermedad con manifestaciones clínicas muy amplias y variadas que abarca desde formas leves hasta formas graves que pueden llegar a acortar la esperanza de vida de los pacientes.

Articulaciones de la mano con AR agresiva.

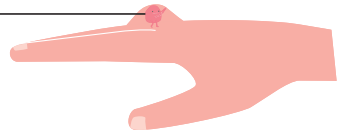


Febrícula.

Las manifestaciones principales de la enfermedad consisten en dolor e inflamación, es decir, hinchazón de las articulaciones. También es típica la rigidez o entumecimiento articular tras reposo prolongado, como por ejemplo, al levantarse de la cama por la mañana. A consecuencia de estos síntomas se produce dificultad para moverse y para desarrollar las actividades de la vida cotidiana. Las articulaciones que antes se afectan suelen ser los nudillos de las manos, las muñecas y los pies, con frecuencia de forma simétrica. También pueden afectarse otras zonas como rodillas, codos, hombros, tobillos, etc. A veces se afecta la columna vertebral, pero solo a nivel del cuello.

La artritis reumatoide puede producir síntomas fuera de las articulaciones. Muchos pacientes se quejan de cansancio, falta de apetito, pérdida de peso o incluso febrícula (sensación de fiebre leve). En ocasiones aparecen bultos o nódulos duros debajo de la piel en zonas próximas a las articulaciones, son los llamados nódulos reumatoides. Aparecen en una de cada tres a cinco personas con AR, su tamaño es variable (generalmente menores de 1-2 cm) y se localizan típicamente en áreas de presión como los codos, antebrazos, dedos de las manos y tendón de Aquiles. De forma más rara los nódulos reumatoides pueden aparecer en el interior del organismo, en los pulmones, en el corazón o los ojos.

Nódulos reumatoides



Síndrome de Sjögren secundario.

Sequedad de las mucosas del ojo (sensación de arenilla)

Sequedad vaginal

Sequedad bucal

Las personas con artritis reumatoide tienen, en general, un aumento de los problemas cardiovasculares que puede llevarles a que su esperanza de vida sea algo menor que la de otros miembros de su comunidad. Por este motivo, en muy importante que se controlen los factores de riesgo para padecer infartos o isquemia cerebral, la tensión arterial y el colesterol. No fumar y hacer ejercicios de forma regular son muy importantes en las personas con artritis reumatoide.

Con frecuencia las personas con artritis reumatoide padecen el llamado síndrome de Sjögren, una enfermedad que produce inflamación de las glándulas que lubrifican diversas partes del organismo como las lágrimas en los ojos, la saliva en la boca o las secreciones vaginales. La consecuencia de este proceso es conjuntivitis, sequedad ocular que se manifiesta como "sensación de arenilla en los ojos", sequedad bucal y vaginal.

Pero, como se ha dicho, la artritis reumatoide no es una enfermedad exclusivamente articular, sino que con el paso del tiempo, y en determinadas personas puede afectar a órganos y sistemas como los pulmones, el corazón, los ojos o los vasos y los nervios.

El pulmón se puede ver afectado por la AR de diversas maneras:

- El derrame pleural (acúmulo de líquido en la pleura, ese espacio que rodea los pulmones) es la manifestación pulmonar más frecuente; sin embargo, muchas veces pasa desapercibida y no suele ser grave.

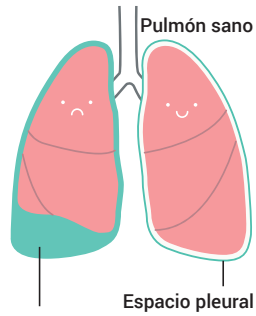
- La neumonitis, es decir la inflamación de los pulmones, es una complicación poco frecuente pero que puede ser seria. Se da con más frecuencia en fumadores, varones o personas con enfermedad más avanzada. Esta es otra de las razones importantes para que las personas con AR no fumen.

También, pero más raramente, las personas con AR pueden tener otras manifestaciones extraarticulares como problemas cardiacos (pe-

ricarditis o arritmias), oculares (epiescleritis), neurológicos (mononeuritis) o renales; en general ocurren en personas con enfermedad más grave y mal controlada.

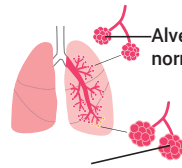
Por último, las personas con artritis reumatoide tienen, con mayor frecuencia que el resto de la población, otras enfermedades asociadas, como osteoporosis (descalcificación de los huesos) y problemas vasculares como la arteriosclerosis. Esta última puede suponer un problema de salud importante; de ahí que resulte esencial que las personas con artritis reumatoide controlen de forma estrecha, como ya se ha comentado, otros factores de riesgo cardiovascular como el fumar, el aumento de colesterol o la tensión arterial alta.

Derrame pleural



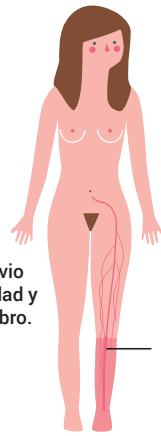
Derrame pleural

Neumonitis



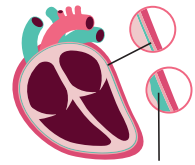
Alveólo con líquido dentro (neumonía)

Mononeuritis



Inflamación de un nervio que afecta a la motilidad y sensibilidad del miembro.

Pericaraditis

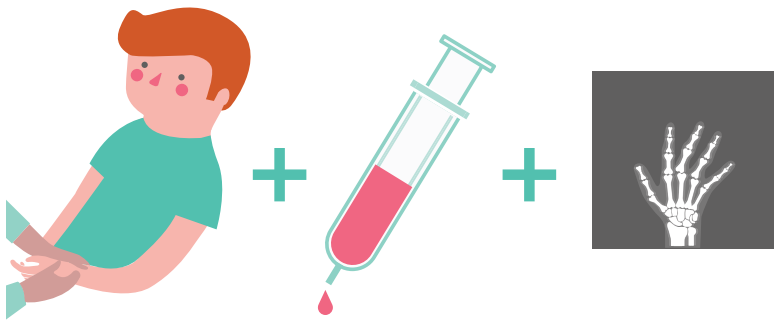


Exceso de fluído en la cavidad prericardial

¿Cómo se diagnostica?

La artritis reumatoide puede confundirse con otras enfermedades reumáticas como la artrosis, el lupus eritematoso, la artritis psoriásica, la gota, o algunas infecciones por virus. No existe una prueba diagnóstica única que nos indique la presencia o no de la enfermedad. El diagnóstico depende del estudio clínico minucioso del paciente por un médico que conozca en profundidad la enfermedad: el reumatólogo.

Lo fundamental para diagnosticar la artritis reumatoide es analizar los síntomas del paciente y los datos de la exploración física, con el fin de detectar la presencia de artritis y diferenciarla de otros procesos. Generalmente el reumatólogo le solicitará unos análisis de sangre y probablemente alguna radiografía. Sin embargo es importante señalar que ni los análisis, ni las radiografías, por sí solos, nos van a indicar el diagnóstico definitivo. Éste va a depender de la valoración global y conjunta de todos los datos anteriores.



D 15

Con frecuencia se habla de las pruebas reumáticas como análisis que nos van a confirmar si una persona tiene artritis reumatoide u otra enfermedad reumática. Es importante señalar que esta idea es errónea. No hay ninguna prueba reumática como tal. Es cierto que algunas determinaciones analíticas pueden ayudar en el diagnóstico, pero sólo ayudar. Por ejemplo, el factor reumatoide (FR) es una prueba analítica que es positiva en un 70-80 % de las personas con artritis reumatoide. Sin embargo, un 20-30 % de las personas con la misma enfermedad no lo tienen positivo. De ahí que un factor reumatoide negativo no excluye que alguien tenga la enfermedad. En sentido contrario, un factor reumatoide positivo puede verse en personas con otras enfermedades o incluso en un porcentaje no despreciable de gente sana. Por ello, un factor reumatoide positivo tampoco quiere decir, de ninguna manera, que alguien tenga artritis reumatoide. Se suele utilizar el término artritis reumatoide seropositiva para referirse a aquellas personas con artritis reumatoide que son factor reumatoide positivo. Esto no tiene nada que ver con el SIDA, donde el término seropositivo se refiere a las personas que han tenido contacto con el virus de la inmunodeficiencia humana.

Hay otras pruebas analíticas que también ayudan en el diagnóstico de la artritis reumatoide, como los anticuerpos péptido cíclico citrulinado (anti-PCC), la proteína C-reactiva (PCR) y la velocidad de sedimentación globular (VSG). De nuevo se habla de pruebas orientativas. En el caso de la PCR y la VSG se trata de dos análisis que ayudan a evaluar la actividad del proceso, pero que no son específicos de la artritis reumatoide y pueden aumentar por situaciones tan distintas

16 D

como una infección, un traumatismo o una enfermedad inflamatoria de cualquier órgano. El caso de los anticuerpos anti-PCC, es diferente. La positividad de este anticuerpo, en una persona con artritis, asegura el diagnóstico de artritis reumatoide en el 95% de los casos. Sin embargo, su negatividad no elimina el diagnóstico, ya que un 40 % de las artritis reumatoides son anti-PCC negativos.

LA IMPORTANCIA DE UN DIAGNÓSTICO PRECOZ

Es muy importante establecer lo antes posible el diagnóstico de la artritis reumatoide, ya que el tratamiento precoz aumenta la probabilidad de controlar la inflamación de las articulaciones y evitar el daño de las mismas, e incluso conseguir la remisión de la enfermedad (ausencia absoluta de síntomas de la enfermedad). Por ello, ante la aparición de síntomas como los descritos más arriba, se debe consultar con el médico de atención primaria, quien, si sospecha que Ud. puede padecer artritis reumatoide, deberá remitirle lo antes posible a su reumatólogo para confirmar el diagnóstico e iniciar el tratamiento.

03
Tratamiento y seguimiento de la artritis reumatoide

La meta del tratamiento en la artritis reumatoide es reducir el dolor articular y la inflamación y retrasar o prevenir el daño en las articulaciones. El tratamiento variará en cada paciente dependiendo de la intensidad y extensión de las articulaciones inflamadas y también de la presencia y gravedad de las manifestaciones en otros órganos, aparte de en las articulaciones.

¿Cuáles son las opciones de tratamiento?

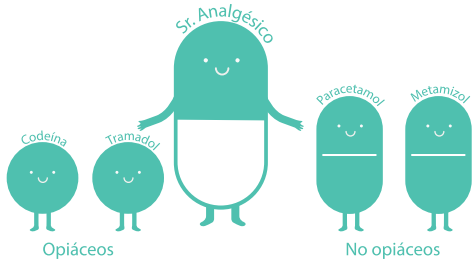
El tratamiento de la artritis reumatoide se basa en la utilización de fármacos que tienen diferentes misiones. De forma general se puede diferenciar entre los fármacos que controlan sólo los síntomas **–tratamientos sintomáticos–** y aquellos que tienen un efecto más profundo sobre los mecanismos de la enfermedad **–fármacos modificadores de la enfermedad o FAME-.** Los **corticoides** son otro grupo importante de medicamentos que están a mitad de camino entre los tratamientos sintomáticos y los FAME, pues comparten características de unos y otros. Los tres tipos de medicinas se combinan de di-

En la gran mayoría de los casos la artritis reumatoide se puede tratar de forma muy eficaz, permitiendo que los pacientes tengan una vida prácticamente normal. Esto es así a pesar de que no se dispone de tratamientos curativos, por lo que los pacientes necesitan recibir medicamentos durante largos periodos de tiempo o incluso durante toda la vida.

ferentes maneras en función de la gravedad de la enfermedad y las características particulares de cada paciente.

Tratamientos sintomáticos: Los constituyen los **analgésicos y los antiinflamatorios no esteroideos (AINE).** Estos medicamentos se suelen utilizar para completar el efecto de los FAME, sobre todo en épocas en las que hay mayor dolor por reactivación de la enfermedad o cuando existen síntomas de forma mantenida. Su acción es rápida, pero su efecto desaparece también rápidamente unas horas después de su administración.

De forma general se puede decir que los **analgésicos** son fármacos bastante bien tolerados y seguros. Ésta es su principal ventaja frente a otros medicamentos; sin embargo, su eficacia es menor y su efecto es sólo temporal, por lo que casi siempre se utilizan para complementar la acción de otros fármacos; además, no actúan sobre otras manifestaciones de las artritis crónicas como la inflamación y las deformidades articulares. Se pueden distinguir dos tipos de analgésicos: los opiáceos y los no opiáceos.



Los analgésicos no opiáceos más usados son: paracetamol y metamizol. Entre los opiáceos se pueden citar: codeína y tramadol. Los analgésicos opiáceos son más potentes pero pueden tener más efectos secundarios como estreñimiento, mareos o vómitos, por esta razón su uso sólo debe hacerse por indicación de un médico. Para disminuir los efectos secundarios de los opiáceos se debe comenzar usándolos a dosis bajas, que pueden incrementarse poco a poco en función de su tolerancia y eficacia. Existen medicamentos que combinan ambos tipos de analgésicos, opiáceos y no opiáceos.

Los **AINE** son el otro gran grupo de medicamentos para el tratamiento sintomático de la artritis reumatoide. Son de gran utilidad para mitigar el dolor de las enfermedades reumáticas. Suelen ser eficaces para reducir el tiempo de rigidez articular que padecen los pacientes después de un reposo prolongado. Existen múltiples antiinflamatorios: ibuprofeno, diclofenaco, naproxeno, aceclofenaco, ketoprofeno, meloxicam, indometacina, etc. En los últimos años se ha comercializado un nuevo tipo de antiinflamatorios, los coxibs, que tienen un riesgo menor de

problemas digestivos graves: celecoxib y etoricoxib. Los AINE no producen habituación (es decir, el paciente no se "acostumbra" a ellos), ni adicción. Al igual que cualquier medicamento, pueden tener efectos secundarios y las personas con antecedentes de úlcera de estómago o de duodeno (el principal efecto secundario de estos compuestos es la úlcera de estómago), con tensión arterial mal controlada, con antecedentes de infarto de miocardio, angina de pecho, con problemas de riñón, o que precisen anticoagulantes deberán tener más precaución o evitar su uso. Un factor muy importante a tener en cuenta es la dosis y el tiempo de utilización de un antiinflamatorio. Los efectos secundarios de los AINE son mucho menores cuando se utilizan a dosis bajas y durante periodos de tiempo limitados, lo que no significa que en algunos pacientes no puedan tomarse de manera prolongada. No se deben usar dos AINE a la vez.

Corticoides: **Los corticoides** son fármacos de gran utilidad en el tratamiento de la artritis reumatoide. Comparten acciones antiinflamatorias con otras más complejas similares a las de los FAME. Son los fármacos más eficaces para controlar la inflamación articular en muy poco tiempo, ya sea en forma de comprimidos, inyecciones o como tratamientos intra-articulares (infiltraciones) y se usan de diferentes formas en la artritis reumatoide:

1) Durante un tiempo largo, como complemento de otros tratamientos, generalmente a dosis bajas, por debajo de 7,5 mg. de prednisona al día.

2) Como tratamiento "de puente" hasta que empiezan a actuar los FAME, debido a la mayor rapidez de acción de los corticoides.

3) De forma intermitente, a dosis medias para controlar brotes de la enfermedad.

4) Puntualmente, por vía intra-articular (infiltraciones) para controlar la inflamación de alguna articulación aislada, como una rodilla o una muñeca.

Los corticoides son fármacos temidos por muchos pacientes debido a los efectos secundarios que pueden producir, que dependen fundamentalmente de la duración del tratamiento y de la dosis. Habitualmente, pautas de menos de dos a tres semanas a dosis medias o bajas (menos de 15 mg/día de prednisona) tienen muy pocos efectos adversos. Los problemas aparecen con el uso prolongado, de ahí que en estos casos suelan utilizarse dosis bajas (menos de 7,5 mg/día de prednisona) para minimizar sus consecuencias indeseables.

Entre los efectos adversos de los corticoides cabe mencionar: aumento de peso, fragilidad y hematomas en la piel, cataratas, osteoporosis, aumento de los niveles de glucosa en sangre y en raras ocasiones

necrosis (muerte de un fragmento de hueso) en caderas o rodillas. Sin embargo es preciso señalar que cuando un reumatólogo los recomienda para el tratamiento de un proceso reumático es porque ha analizado los posibles riesgos y beneficios, llegando a la conclusión de que los beneficios son muy superiores a los riesgos.

Los antiinflamatorios no esteroides (AINE) y los corticoides son fármacos muy útiles para reducir el dolor y la inflamación de las articulaciones.

Fármacos modificadores de la enfermedad (FAME): Aunque los tratamientos sintomáticos y los corticoides juegan un papel importante en el manejo de la artritis reumatoide, la base fundamental de la terapia de la AR la constituyen los tratamientos modificadores de la enfermedad o FAME. Estos fármacos son capaces de actuar sobre las células y las moléculas que participan en la inmunidad y por tanto sobre los mecanismos que dan lugar a los diferentes síntomas de la artritis reumatoide cambiando el curso natural de la enfermedad.

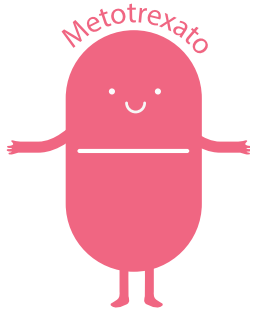
De forma general se pueden dividir los FAME en dos grandes grupos: **tradicionales y biológicos.**

Los **FAME tradicionales** han sido y continúan siendo en la actualidad el principal tratamiento de la artritis reumatoide. Los más utilizados son el metotrexato, la leflunomida y la sulfasalazina. También se incluyen en este grupo los antipa-

lúdicos como: cloroquina e hidroxicloroquina y, la ciclosporina, la azatioprina y la minociclina, aunque estos tres últimos se utilizan más raramente en la artritis reumatoide.

El metotrexato es el que se utiliza con más frecuencia. Es un medicamento que se empleó hace años a dosis muy altas en el tratamiento del cáncer, pero cuando se usa para tratar la artritis reumatoide se hace a dosis muy pequeñas que se incrementan de forma paulatina hasta conseguir el control de la enfermedad, lo que reduce muchísimo sus efectos secundarios y en general se tolera muy bien.

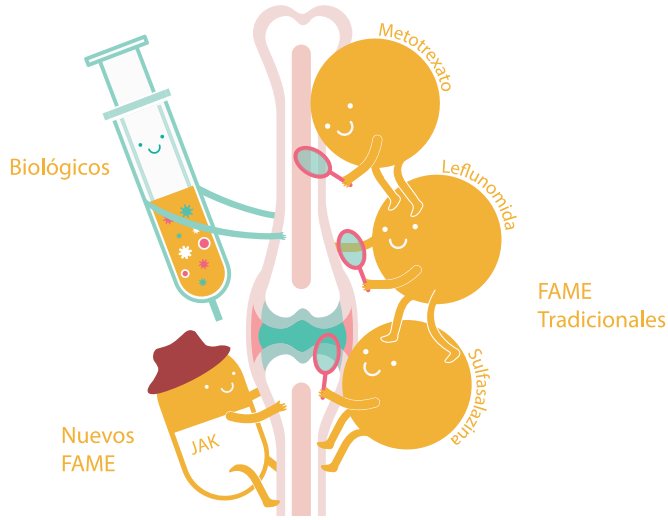
Estos fármacos han demostrado ser capaces de reducir y a veces suprimir completamente la actividad inflamatoria de la enfermedad, mejorando los síntomas articulares. Una característica común a todos ellos es que su acción es lenta, necesitándose habitualmente varias semanas o incluso meses de administración para que sean eficaces.



Son fármacos seguros, aunque como ocurre con todos los medicamentos pueden tener efectos secundarios. Por eso es necesario tomar una serie de precauciones cuando se utilicen. Lo más importante es cumplir con la dosis y pauta indicados y realizar los controles analíticos periódicos que su médico establezca para poder detectar con prontitud cualquier inconveniente como problemas de hígado, riñón o sobre el número de las células de la sangre.Debido a su carácter inmunosupresor, pueden aumentar algo el riesgo de infecciones, por lo que hay que comunicar la aparición de fiebre al médico responsable del tratamiento. Metotrexato y lefluno-

mida están contraindicados en mujeres embarazadas porque pueden causar daños al feto o producir abortos; para evitar esta complicación las mujeres con posibilidad de quedar embarazadas, deben utilizar un método anticonceptivo eficaz. Tampoco se debe beber alcohol, ni fumar si está tomando metotrexato.

Los **FAME biológicos** constituyen un importante avance en el tratamiento de las artritis. Son el resultado de la mejora que ha tenido lugar en el conocimiento de los mecanismos por los que



ocurren estas enfermedades. Los biológicos son proteínas que por su complejidad necesitan ser producidos en laboratorios usando generalmente células de mamíferos. Los biológicos que se usan en reumatología son anticuerpos monoclonales o proteínas de fusión que inhiben o bloquean la acción de alguna molécula o célula que juega un papel importante en la artritis. Por ser proteínas no se pueden ingerir en forma de comprimidos, ya que se degradan en el tubo digestivo y deben ser administradas por vía intravenosa o subcutánea. Los biológicos aprobados en España para el tratamiento de las artritis son: infliximab, etanercept, anakinra, adalimumab, golimumab, certolizumab pegol, rituximab, abatacept y tocilizumab.

Desde hace poco han comenzado a comercializarse productos biosimilares del infliximab y del etanercept, y muy pronto estará también disponible un biosimilar del adalimumab. Un fármaco biosimilar es un fármaco biológico que es producido según las exigencias específicas de la Agencia Europea del Medicamento y debe demostrar similitud con su fármaco de referencia en cuanto a calidad, actividad biológica, seguridad y eficacia, mediante ensayos clínicos de comparación directa. Dado su menor precio, probablemente, la llegada de los fármacos biosimilares va a mejorar el acceso de los pacientes reumáticos a las terapias biológicas. Pero los fármacos biosimilares no son genéricos de sus fármacos de referencia por lo que no son sustituibles, es decir, que no pueden ser reemplazados por el farmacéutico. El intercambio de un biológico por su biosimilar es un acto médico que debe ser realizado por el médico prescriptor, con el consentimiento del paciente.

FÁRMACOS BIOLÓGICOS Y BIOSIMILARES

Principio activo
Adalimumab
Certolizumab pegol
Etanercept y su biosimilar
Golimumab
Infliximab y sus biosimilares
Abatacept
Anakinra
Rituximab
Tocilizumab

Recientemente se ha aprobado en algunos países un nuevo FAME para el tratamiento de la AR, el tofacitinib, que forma parte de una nueva subcategoría de FAME, aunque se le compara a los biológicos. Se les llama inhibidores JAK, pues bloquean la vía de una enzima que se encuentra dentro de la células llamada Janus cinasa (JAK), involucrada en la respuesta inmunológica. Otro compuesto de este nuevo grupo de fármacos inhibidores de la JAK es el baricitinib que ha presentado prometedores datos de seguridad y eficacia. A diferencia de los agentes biológicos tradicionales, estos compuestos se pueden tomar en comprimidos.

Los FAME biológicos, al afectar al sistema inmunológico pueden ocasionar la reactivación de infecciones latentes como hepatitis o tuberculosis. Su reumatólogo antes de prescribirlos hará un estudio para excluirlas. Para evitar la aparición de nuevas infecciones se le recomendará la vacunación, habitualmente contra la gripe y el neumococo. También se le informará de que no debería recibir vacunas con virus vivos atenuados tales como polio oral, varicela, sarampión, paperas y rubeola. Para evitar el desarrollo de infecciones serias, mientras se encuentre en tratamiento con un FAME biológico, puede tomar medidas de precaución, como el evitar iniciar la terapia si tuviese alguna infección o modificar la dosis del agente biológico si desarrolla una después de iniciado el tratamiento. Y deberá ponerse en contacto con su médico si presenta síntomas de infección al usar un biológico.

Si ha tenido una enfermedad que ataca la mielina, tal como esclerosis múltiple, o si ha tenido una insuficiencia cardíaca congestiva, no se de-

ben usar los FAME biológicos que pertenecen al grupo de los anti-factor de necrosis tumoral (TNF), como etanercept, infliximab, adalimumab, golimumab o certolizumab pegol.

También existe el riesgo teórico de desarrollar cáncer, particularmente linfoma, con el uso a largo plazo de algunos biológicos. Hasta la fecha, sin embargo, los casos reportados de cáncer causados por el uso de cualquier medicamento están dentro de la frecuencia y tipos de cáncer esperados para personass con AR que no reciben ningún biológico. Como medida adicional de seguridad se tiende a quitar el uso de los biológicos a los pacientes que han tenido algún cáncer.

Papel de las terapias alternativas: Algunos pacientes muestran interés o solicitan información sobre el papel de las terapias alternativas, - las no recogidas por la práctica médica habitual u ortodoxa-, y de algunas dietas en el tratamiento de la artritis reumatoide. A continuación se comentan algunas de las terapias alternativas más

28 T

usuales. Las intervenciones dietéticas se tratarán **más adelante.**

Acupuntura: La acupuntura es una práctica china tradicional mediante la cual se insertan agujas delgadas pequeñas en la piel en puntos específicos del cuerpo. La posición y la profundidad exactas de las agujas están determinadas por un diagnóstico altamente individualizado. Aparentemente, la acupuntura promueve la producción de unas sustancias analgésicas llamadas endorfinas. Los estudios clínicos realizados no han mostrado resultados claros sobre la acupuntura como tratamiento de la artritis. En este momento, la acupuntura aún se considera un tratamiento experimental.

Tratamiento Quiropráctico: El tratamiento quiropráctico se centra en el ajuste o la manipulación manual de la columna vertebral con el fin de aliviar el dolor muscular y calmar el dolor en la espalda. El tratamiento quiropráctico puede ser potencialmente nocivo en personas con articulaciones inflamadas, osteoporosis o una forma de artritis que afecte la columna vertebral.

Homeopatía: Fue desarrollada en el siglo XVIII por el doctor alemán Samuel Hahnemann. Él creía que las sustancias que causan enfermedad podrían, administrándose en pequeñas cantidades, provocar una respuesta curativa. La homeopatía se basa en la idea de que cantidades diluidas de un veneno o sustancia causante de enfermedad puede aliviar sus mismos síntomas. Para la mayoría de los científicos, esto no tiene sentido. Se venden productos homeopáticos en farmacias y tiendas naturistas en forma de cremas, soluciones, y como pequeñas tabletas que se disuelven en la lengua. Sin embargo, no hay evidencia científica de que la homeopatía pueda aliviar, retrasar o detener el progreso de la artritis reumatoide.

Muchos de estos tratamientos son inocuos, pero puede que no se hayan evaluado lo suficiente o que en realidad no tengan ningún beneficio. Se debe tener siempre presente que las terapias alternativas y complementarias no reemplazan a los medicamentos recetados por su médico y que por tanto no debe abandonarlos

¿Cuál es la evolución de los pacientes que tienen artritis reumatoide?

La artritis reumatoide sin tratamiento, tiene a evolucionar mal y puede acabar produciendo el deterioro de las articulaciones afectadas llevando a los pacientes a sufrir incapacidades. Sin embargo, el diagnóstico precoz y la utilización de los nuevos fármacos, junto con los FAME tradicionales, ha dispuesto que la gran mayoría de las personas con artritis reumatoide puedan llevar una vida prácticamente normal.

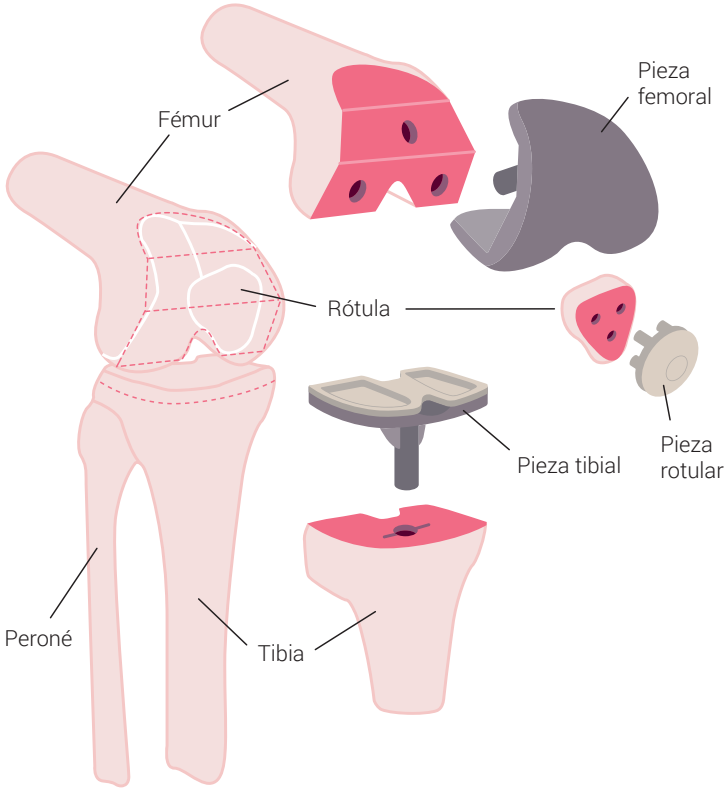
Es muy importante para una buena evolución de la artritis reumatoide la realización de un **diagnóstico precoz** de cara a iniciar el tratamiento lo antes posible, ya que los dos primeros años del curso de la enfermedad son claves para mejorar el pronóstico funcional de los pacientes. De hecho, uno de los mejores indicadores de daño articular futuro es la limitación para desarrollar las actividades normales de la vida diaria (limitación funcional) en estos dos primeros años. Existen otros indicadores: la presencia de FR o anti-PCC ayudan a predecir si la AR llevará un curso más serio y los casos más graves de AR se asocian con la presencia de ambos anticuer-

pos. Los signos radiológicos tempranos de daño articular también predicen una AR más grave.

¿Qué complicaciones pueden ocurrir?

A veces, aunque cada vez con menos frecuencia, se acaba produciendo un deterioro tan importante de una o varias articulaciones que da lugar a la aparición de dolor y/o discapacidad no controlables con el tratamiento médico. En ese caso su médico podría sugerirle el reemplazo total de la articulación (es decir, poner una prótesis; llamado también artroplastia total de la articulación), o la corrección quirúrgica de algunas deformidades en las manos o en los pies. Los cirujanos ortopédicos son quienes llevan a cabo estos procedimientos que implican, en el caso de la artroplastia, el reemplazo de las partes dañadas de las articulaciones con componentes metálicos y plásticos. Los reemplazos totales de cadera y de rodilla son los que se realizan con mayor frecuencia y con mejores resultados.

Artroplastia de
la rodilla



32 T

04
Vivir con artritis reumatoide

¿Qué debo tener en cuenta cuando acuda al centro de salud o si voy al hospital?

Durante el proceso de diagnóstico, tratamiento y seguimiento de su enfermedad va a encontrar distintos profesionales sanitarios. Lo habitual es que en primer lugar consulte con su médico de familia los síntomas que presente. En caso de que éste sospeche la existencia de una artritis es muy probable que lo remita al especialista (reumatólogo), para su valoración y tratamiento.

También es posible que desee que le acompañe un familiar o un amigo. A veces es difícil recordar todo o que se le olvide contestar algo referido a algunas de estas preguntas y así su acompañante puede completar la información que a usted se le haya pasado.

No tenga reparo en preguntar por aquellas cuestiones que no le han quedado claras, o comente que le expliquen las cosas en un lenguaje sencillo y comprensible. También puede tomar notas o solicitar alguna información por escrito.

Antes de su cita médica con el especialista prepare brevemente lo que quiere decir o consultar. En su primera visita al reumatólogo es conveniente que, de antemano, prepare algunas respuestas a posibles preguntas que le van a realizar y que van a ser importantes para su diagnóstico y tratamiento, como:

¿Qué tipos de síntomas tiene? ¿Cuándo empezaron? ¿Qué articulaciones se nota dolorosas o limitadas? ¿Hay alguna actividad o posiciones que hacen que sus síntomas mejoren o empeoren? ¿Alguno de sus familiares cercanos (padres, hijos, hermanos) tiene problemas articulares? ¿Qué medicamentos toma usted? ¿Ha probado ya algún tratamiento para los síntomas articulares? ¿Ha sido eficaz alguno de ellos?

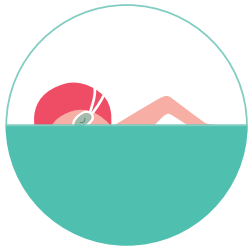
Lo más positivo es que pueda expresar sus necesidades y preferencias tanto con el diagnóstico como con las diferentes opciones de tratamiento.

¿Qué consejos sobre cuidados en la vida diaria debo seguir?

Es importante que las personas con artritis reumatoide se mantengan en las mejores condiciones de salud posible. La siguiente información puede ayudarle en aspectos que contribuirán a mejorar su calidad de vida.

Reposo

El descanso, con un número adecuado de horas de sueño, mejora la sensación de cansancio y fatiga que suele producir la enfermedad. En algunas personas el cansancio puede ser muy intenso y ser el síntoma predominante, incluso más que el dolor. Si esto sucede, quizá sea necesario aumentar las horas de descanso y aprender a regular mejor el ritmo de sus actividades. En las fases de reagudización de la enfermedad es importante el reposo de las articulaciones inflamadas.



Ejercicio

La actividad física es una parte importante de su tratamiento. Estudios científicos han demostrado que el ejercicio puede reducir el dolor y mejorar la funcionalidad, el estado de ánimo y la calidad de vida de los adultos con artritis y puede ayudar a controlar otras afecciones crónicas comunes, como diabetes, enfermedades cardiovasculares y obesidad.

El ejercicio mejora la rigidez y la limitación de los movimientos causados por la artritis. También puede mejorar la flexibilidad, fortalecer los músculos, mejorar el sueño, fortalecer el corazón, ayudar a adelgazar y mejorar la apariencia física. Es por tanto fundamental hacer ejercicio, incluso desde el inicio de la enfermedad, con el fin de mantener la movilidad completa de las articulaciones.

Puntos importantes para recordar:

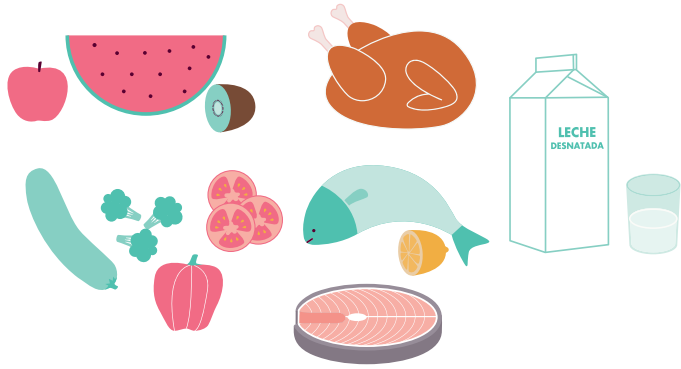
- *Es mejor hacer algo de ejercicio que nada. El ejercicio físico moderado no representa ningún riesgo para las personas con artritis.*
- *Se deben evitar los deportes que requieren contacto físico como futbol, baloncesto, balonmano…*
- *El ejercicio debe hacerse además de las actividades diarias. Se puede realizar durante el día, con sesiones de 10 minutos como mínimo.*
- *Siempre comenzar lentamente y con poca actividad y modificar la actividad si los síntomas de artritis aumentan.*

• *Los ejercicios dentro del agua (natación, acuagym, etc.) son una buena opción, porque ejercen menos tensión en las articulaciones que el ejercicio que se practica en tierra, especialmente cuando ya existe daño en las articulaciones que soportan el peso del cuerpo.*

Alimentación: comida y dieta

Existe mucha información sobre dietas y suplementos nutricionales que supuestamente son capaces de ejercer un efecto beneficioso sobre diversos tipos de enfermedades reumáticas, incluyendo a la artritis reumatoide. La mayor parte de esta información es confusa y no está basada en estudios realizados con el rigor científico adecuado.

Como norma general debe seguirse una dieta variada que consiste en comer de todo en cantidades moderadas. Una alimentación variada y equilibrada aporta la gran mayoría de las vitaminas y minerales que el organismo necesita.



Un buen ejemplo de dieta saludable, es la dieta mediterránea. En esta dieta se debe aumentar el consumo de verduras y frutas intentando consumir dos raciones de verdura y tres piezas de fruta al día. Una ración de verdura corresponde a medio plato de vegetales aproximadamente. Es preferible el pescado sobre la carne, aunque es importante el comer ambas cosas. Con respecto a las carnes, son preferibles las carnes magras (sin grasa), o las de aves (como el pollo o el pavo). Dentro de las grasas insaturadas (grasas líquidas a temperatura ambiente), es beneficioso utilizar aceite de oliva en las comidas, aunque su consumo debe ser moderado debido a su importante aporte calórico.

Es importante el consumo de leche y derivados lácteos por su aporte de calcio. Una vez finalizado el periodo de crecimiento, estos productos deben tomarse desnatados o semi-desnatados para evitar el aporte excesivo de grasas.

Un ejemplo de suplementos nutricionales que pueden tener alguna utilidad son los ácidos grasos poli-insaturados Omega-3, que se encuentran comúnmente en los pescados grasos frescos como el salmón, el atún, la caballa y la sardina. En los últimos cien años, la dieta occidental ha cambiado radicalmente hasta incluir cada vez menos pescado, y por ende, menos ácido graso Omega 3. Diversos datos experimentales atribuyen a los ácidos grasos Omega-3 actividad antiinflamatoria. La ingestión de cantidades razonables de este tipo de ácidos grasos (2-3 gr/día) puede ser beneficiosa en personas con artritis reumatoide, al reducir la necesidad de tomar fármacos antiinflamatorios no esteroideos. Sin embargo, estos compues-

tos no han demostrado una reducción de la actividad de la enfermedad.

En pacientes con niveles elevados de colesterol se debe restringir la ingesta de embutidos, mantequillas, quesos grasos, bollería y demás productos procesados industrialmente.

En pacientes con hipertensión arterial debe reducirse o evitarse el consumo de sal o productos ricos en sal (conservas, salazones, quesos curados, etc.), así como de las bebidas gaseosas.

En general, la mayoría de las recomendaciones generales sobre alimentación y hábitos de vida saludables que se aplican a la población general, son de utilidad para las personas con enfermedades reumáticas. Las modificaciones en la dieta y los suplementos nutricionales van a tener un impacto mínimo en la mayoría de los pacientes con artritis, y no deben de sustituir nunca al tratamiento farmacológico que le prescribe su médico.

Entorno familiar y laboral

Las repercusiones físicas y emocionales de la AR son distintas en cada paciente y dependen de la gravedad de la enfermedad, de su actitud ante la misma, de la disposición para intentar adaptarse a su vida cotidiana y del apoyo de su entorno.

Sus amigos y familiares pueden ayudarle con apoyo emocional, comprendiendo y aceptando sus limitaciones y prestándole ayuda física.

Es importante tener a alguien con quien hablar sobre los problemas que ocasiona la enfermedad y que le anime a vencerlos: el contacto con otros enfermos de AR y las asociaciones de pacientes, le puede ser de gran ayuda para afrontarla.

En cuanto a su actividad laboral, asesórese sobre sus derechos y las opciones para adaptar su puesto de trabajo a sus necesidades.

No se aísle y salga con sus amigos y familiares. Busque el apoyo de sus seres queridos. También puede apuntarse a una asociación de pacientes. Compartir las dificultades con otras personas con AR es de gran apoyo psicológico y es la mejor manera de estar informado.

Estados de ánimo

El impacto psicológico o emocional a causa del dolor y las limitaciones por los problemas articulares pueden alterar la vida personal, familiar, laboral y social del paciente e incidir de forma negativa en su calidad de vida. Los efectos emocionales graves pueden provocar que la persona caiga en una profunda depresión, se aísle de sus familiares, amigos o compañeros o sufra ataques de ansiedad. La afectación psicológica puede favorecer que las personas con artritis fumen y beban más, con las repercusiones negativas que esto tiene para su salud y el curso de su enfermedad.

También es conocido que el estrés emocional puede empeorar la artritis. Por este motivo, junto a un tratamiento efectivo para reducir la inflamación y mejorar los síntomas de la enfermedad, es necesario intentar lograr un bienestar mental para sobrellevar mejor la enfermedad.

En algunos pacientes puede ser necesario un apoyo psicológico o psiquiátrico para mejorar el estado de ánimo y la desmotivación ocasionados por la enfermedad.

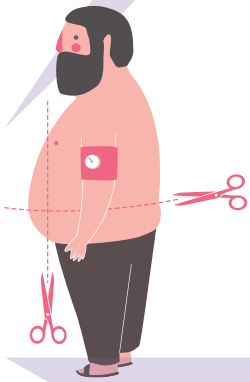
Aprenda a afrontar su enfermedad. Los pensamientos positivos pueden ayudarle a mejorar el estado de ánimo.

Controles clínicos

Las personas con artritis reumatoide y, sobre todo, los que tienen una enfermedad mal contro-

lada y con importante inflamación, tienen más riesgo de que se dañen sus vasos sanguíneos y una mayor predisposición a presentar complicaciones cardiovasculares (infartos cardiacos o cerebrales). *Por este motivo es muy importante intentar que la enfermedad esté bien controlada, además de controlar también otros factores que predisponen a dañar los vasos sanguíneos como son:*

- *Obesidad central, es decir, un exceso de grasa en la zona abdominal.*
- *Diabetes*
- *Niveles elevados de triglicéridos y niveles bajos de lipoproteínas de alta densidad (HDL o "colesterol bueno") en la sangre.*
- *Presión arterial alta (hipertensión arterial).*



Así que es muy importante tomarse periódicamente la tensión arterial y hacerse algún análisis de control. En caso de que en uno o más controles exista una alteración de alguno de estos factores es importante iniciar un tratamiento para normalizarlo.

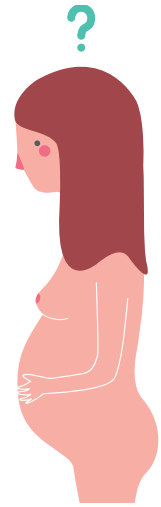
Acuda a las revisiones. Realice los análisis y pruebas que se le indiquen. Aproveche para consultar a su médico las dudas que tenga sobre la enfermedad o su tratamiento.

Dejar de fumar

El consumo de tabaco es otro factor muy conocido que perjudica a la salud, pero en el caso de las personas con artritis reumatoide se ha confirmado que el tabaco, además de incrementar de forma importante el riesgo de dañar las arterias del cuerpo (arteriosclerosis), también favorece que la enfermedad sea más grave y difícil de tratar.

Haga una vida sana. Dejar de fumar mejorará su enfermedad y por tanto su calidad de vida, aunque sea algo que le resulte difícil de conseguir, tiene que lograrlo.

Embarazo



Con frecuencia, la artritis reumatoide afecta a mujeres en edad reproductiva, por lo que el embarazo debe considerarse como un acontecimiento habitual en estas pacientes.

En la actualidad, se sabe que con un cuidado médico y obstétrico adecuado, la mayoría de estas personas pueden tener un embarazo con éxito, lo que no significa que esté libre de posibles complicaciones, por lo que los posibles riesgos para la madre y para el feto deben ser discutidos previamente entre el médico y la paciente.

Hay cuatro aspectos fundamentales que deben considerarse en las personas con artritis reumatoide durante la preconcepción y el embarazo:

1. Efecto de la enfermedad reumática sobre el embarazo: *como norma general, se debe recomendar el embarazo a las mujeres con AR durante las fases inactivas de la enfermedad. Los efectos de la inflamación junto con la necesidad de utilizar más medicación para el control de la enfermedad pueden causar problemas durante el embarazo. Por lo tanto es deseable intentar la concepción después de al menos un periodo de 6 meses de enfermedad inactiva.*

2. Efecto del embarazo sobre la enfermedad reumática: *en muchas mujeres con AR, la enfermedad va a mejorar, e incluso entrar en remisión clínica durante la gestación. Sin embargo, debe tenerse en cuenta, que la práctica totalidad de las pacientes van a tener una reactivación de la sintomatología durante el post-parto.*

3. Efecto del tratamiento sobre el embarazo y la lactancia: *lo deseable, como en todo embarazo normal, es que la paciente no necesite tomar ninguna medicación durante el embarazo y la lactancia. Desgraciadamente la mayoría de las mujeres con AR van a necesitar continuar con su tratamiento de base, ya que la suspensión de la medicación conlleva el riesgo de reactivación de la enfermedad. Si la paciente estaba tomado medicación contraindicada en el embarazo (como por ejemplo el metotrexato), esta deberá ser retirada entre 3 y 4 meses antes de la concepción y sustituida por otra que no lo esté. En caso de estar tomando medicación no contraindicada formalmente, el tratamiento no debe modificarse.*

4. Efecto del tratamiento en los varones: *ante el deseo de ser padres, deberían consultar con su reumatólogo para la planificación del embarazo, ya que sería prudente estar sin tratamiento con metotrexato como mínimo los tres meses previos.*

Su reumatólogo le informará sobre los fármacos que pueden emplearse en estas situaciones.

Imagen corporal

La imagen personal, la representación que de sí misma tiene cualquier persona, es una imagen mental que engloba la imagen corporal y psicológica (género, peso, talla, color de piel ojos y cabello, capacidad intelectual y emocional,...,), forjada por la propia persona y por la mirada de los otros, y es vulnerable a los cambios de los componentes que la integran (aspecto e integridad física y psicológica).

Algunos tratamientos farmacológicos pueden afectar al aspecto físico de los pacientes. El caso más común ocurre con la toma prolongada o a dosis elevadas de corticoides, que pueden ocasionar un aspecto cushingoide, llamado así por su similitud con el que presentan las personas con hiperfunción de las glándulas suprarrenales (enfermedad de Cushing), e incluye manifestaciones como aumento de peso, cara redonda (faz de "luna llena"), acúmulo de grasa en la parte alta de la espalda y la base del cuello ("morrillo"), hirsutismo (aparición o aumento de vello facial y en las extremidades), acné y estrías cutáneas

de color violáceo en el abdomen, los pechos y la raíz de los miembros. Estas anomalías pueden aparecer de forma aislada o en diversas combinaciones. También, el uso prolongado de corticoides, incluso a dosis bajas, produce fragilidad capilar que facilita la aparición de manchas violáceas en la piel ("púrpura" esteroidea). Su reumatólogo intentará evitar o minimizar estos efectos indeseables aconsejándole que vigile su alimentación para evitar el sobrepeso y limitando las dosis y el tiempo de administración de corticoides al mínimo imprescindible.

La toma prolongada de antipalúdicos (cloroquina e hidroxicloroquina) puede ocasionar la aparición de manchas en la piel de color pardo-grisáceo. El metotrexato y la leflunomida pueden provocar caída del pelo de intensidad variable, y algunos fármacos biológicos pueden, paradójicamente, provocar la aparición de psoriasis y otras lesiones de la piel. En estos casos puede discutir con su reumatólogo un cambio de fármaco.

Al hablar de las manifestaciones extrarticulares de la artritis reumatoide se mencionan los nódulos reumatoides, que pueden aparecer en el curso de la enfermedad y suelen hacerlo en zonas de fricción: codos, nudillos,.... A veces desaparecen espontáneamente, pero en ocasiones son persistentes o aparecen en forma abundante en codos, manos, pies y otras localizaciones (nodulosis reumatoide) pudiendo ocasionar alguna limitación en la funcionalidad y cambios en el aspecto físico que pueden repercutir negativamente en el ánimo del paciente, por lo que estaría indicado considerar su extirpación quirúrgica.

Las formas más agresivas o muy evolucionadas de artritis reumatoide pueden dañar de forma irreversible las articulaciones y ocasionar importantes deformidades, tanto en las grandes articulaciones como en las manos y los pies. En esta situación, a las limitaciones funcionales que ocasionan dichas deformidades, puede añadirse en algunos pacientes un sufrimiento psicológico ligado a hechos como el no poder usar un calzado no ortopédico, o por el propio deterioro de la imagen corporal. Para evitar llegar a dicha situación es fundamental un diagnóstico precoz y un tratamiento enérgico de la artritis reumatoide y la colaboración de reumatólogo, ortopeda y terapeuta ocupacional en el manejo de la enfermedad.

Derivado de la propia enfermedad o de los efectos de los tratamientos farmacológicos que usted necesita, su imagen física puede experimentar cambios que le afecten negativamente. Si aprende a reconocer su nueva imagen y a aceptarla se facilitará todo el proceso.

46 V

05
Más información y recursos adicionales

¿Dónde puedo aprender más sobre la artritis reumatoide?

Además de la información que le pueden ofrecer en su centro de salud u hospital, existen algunas asociaciones de pacientes con las que puede ponerse en contacto y donde encontrará más pacientes como usted y familias que pueden proporcionarle consejo y ayuda.

Del mismo modo hay páginas en internet y libros que puede consultar y en los que puede encontrar información adicional sobre la artritis reumatoide.

Asociaciones de pacientes

- ConArtritis. Coordinadora Nacional de Artritis: http://www.conartritis.org/
- LIRE. Liga Reumatológica Española: http://www.lire.es/

Algunos libros

Miller M. Miller D. Mi Sueño Americano: el viaje de una mujer viviendo con una enfermedad crónica. AuthorHouse, 2010

Leong A. Layder J. ¡Supérate! Testimonio de cómo abordar el problema de vivir con artritis. Barcelona, Grupo Aula Médica; 2004.

Paso a Paso. Diario de la Artritis Reumatoide. Coordinadora Nacional de Artritis (ConArtritis). 2012.

Recursos de internet

http://www.ser.es/pacientes/enfermedades-reumaticas/artritis-reumatoide/

http://www.conartritis.org/todo-sobre-artritis/que-es-la-ar/

http://www.rheumatology.org/I-Am-A/Patient-Caregiver/Enfermedades-y-Condiciones/Artritis-Reumatoide

https://medlineplus.gov/spanish/rheumatoidarthritis.html

http://espanol.arthritis.org/espanol/disease-center/artritis-reumatoide/

Términos médicos

- Anticuerpos anti-péptidos citrulinados cíclicos: la presencia de estos anticuerpos en sangre de personas con artritis se relaciona con el diagnóstico de artritis reumatoide y con una enfermedad más grave.

- Arritmias: es una alteración en la sucesión de los latidos cardiacos. Puede presentarse como cambios en la frecuencia cardíaca, tanto porque se acelere o disminuya (taquicardia o bradicardia), en la regularidad de los latidos, o como una combinación de ambas anomalías. Algunas arritmias favorecen la formación de coágulos en

la sangre, como la fibrilación auricular y otros. Puede llegar a producir pérdida de conocimiento o incluso la parada cardiaca.

• Arteriosclerosis: endurecimiento de las arterias. La arteriosclerosis por lo general causa estrechamiento de las arterias que puede progresar hasta la obstrucción del vaso impidiendo el flujo de la sangre por la arteria afectada.

• Artritis: es la inflamación de una o más articulaciones. Una articulación es la zona donde dos huesos se encuentran.

• Artritis aguda: la inflamación de las articulaciones aparece bruscamente y en la mayoría de los casos dura unos días, desapareciendo después de que la causa desaparezca o se reciba tratamiento. Se caracteriza por hinchazón, calor, enrojecimiento, dolor e incapacidad para movilizar la articulación.

• Artritis crónica: la inflamación aparece lentamente, se mantiene durante mucho tiempo y suele provocar alteraciones de la articulación. Se acompaña de síntomas leves de dolor articular, por lo que la persona frecuentemente no sabe precisar cuando comenzaron los síntomas. Con el tiempo aparecen secuelas por la destrucción de los tejidos y las cicatrices resultantes de su reparación.

• Capacidad funcional: concepto que hace referencia a la capacidad para desarrollar las actividades normales de la vida diaria.

• Efectos secundarios: los tratamientos farmacológicos a veces conllevan efectos desagra-

dables o reacciones no deseadas para el enfermo, que se conocen como efectos secundarios. Pueden depender del tratamiento recibido, de las dosis administradas, del estado general del paciente o de otros factores relacionados.

- Enfermedades autoinmunes: trastornos que causan que el sistema inmunitario ataque por error a nuestras propias células y órganos. Las enfermedades autoinmunes pueden afectar muchas partes del organismo.

- Epiescleritis: enfermedad del ojo que consiste en la inflamación de una estructura membranosa situada en la porción anterior del globo ocular que se llama epiesclera y es la porción más superficial de la esclera o esclerótica (el blanco del ojo). Los síntomas principales son enrojecimiento de la porción anterior del ojo, lagrimeo constante, sensación de irritación y fotofobia (molestia o sensibilidad ante la luz brillante). En los casos graves se puede perforar liberando el líquido interno del ojo y causando ceguera.

- Factor reumatoide: es un autoanticuerpo que se encuentra en la sangre. Está también presente en ciertas enfermedades reumáticas y en algunas infecciones crónicas.

- Farmacogenética: es el estudio del papel de la herencia en la variación individual de la respuesta farmacológica tanto en lo que se refiere a eficacia en la respuesta como a efectos adversos.

- Mononeuritis: inflamación de un nervio. Puede afectar a nervios de las extremidades superiores o inferiores o a alguno de los nervios craneales (ej. neuritis del nervio óptico).

• Osteoporosis: es un proceso asociado con la menopausia y el envejecimiento que consiste en la disminución de la resistencia de los huesos, e implica un incremento del riesgo de fracturas. La resistencia del hueso depende tanto de la cantidad (masa ósea) como de la calidad del mismo.

• Pericarditis: es la inflamación de la capa externa del corazón, el pericardio, en el que se produce acúmulo de líquido pudiendo llegar a disminuir la capacidad del corazón de bombear la sangre.

• Predisposición genética: es la probabilidad de padecer una enfermedad en particular. Genético no es sinónimo de hereditario, ya que solo los genes de espermatozoides y óvulos participan de la herencia.

• Pronóstico: resultado que se espera respecto al futuro desarrollo de la salud de una persona, basándose en análisis y en consideraciones de juicio clínico.

• Síndrome de Sjögren: es un trastorno autoinmune en el cual se destruyen las glándulas que producen las lágrimas y la saliva, lo que causa resequedad en la boca y en los ojos. Este trastorno puede afectar a otras partes del cuerpo, incluso los riñones y los pulmones.

• Sistema inmunitario: es una red compleja de células, tejidos y órganos que funcionan en equipo para defendernos de los gérmenes y de las células tumorales. Ayuda a nuestro cuerpo a reconocer estos "invasores" y a mantenerlos

fuera de nuestro organismo y, si no puede, encontrarlos y deshacerse de ellos. Si nuestro sistema inmune no funciona bien, puede causar serios problemas, con tendencia a las infecciones o a atacar a los tejidos y órganos generando enfermedades autoinmunes.

Aprendiendo a convivir con la **Artritis Reumatoide**

Información para pacientes, familiares y cuidadores sobre artritis reumatoide

La información contenida en este documento pretende ofrecer consejos y pautas prácticas y sencillas a personas que tienen artritis reumatoide, a sus familiares y cuidadores. Es una ayuda para conocer mejor la enfermedad y de este modo aprender a cuidarse mejor y mejorar la calidad de vida. Le ayudará a complementar la información ofrecida por el equipo sanitario que le atiende.

También se recogen otros recursos, como libros de consulta, asociaciones de pacientes y páginas disponibles en Internet, que les puedan ayudar igualmente con información adicional en el manejo de la artritis reumatoide.

Disponible en: www.ser.es

Appendix 3. Glossary and abbreviations

Glossary

Burden of disease: indicator that allows us to measure the loss of health due to the fatal and non-fatal consequences of a disease (mortality and morbidity) in a population. It is measured in disability-adjusted life years (DALYs).

Case series: an analysis of series of patients with a given condition.

Case-control study: a study that identifies people with a disease (cases), for example, lung cancer, and compares them with a group of people without the disease (controls).

The relationship between one or various disease-related factors (for example, smoking) is assessed by comparing the rate of exposure to these or other factors between cases and controls.

Clinical practice guideline: set of recommendations based on a systematic review of the evidence and the assessment of the risks and benefits of the different options, seeking to optimize the healthcare provided to patients.

Cohort study: consists of following up of one or more cohorts of individuals with different levels of exposure to a risk factor and assessing the development of the disease or condition of interest.

Confidence interval: is the range in which the true magnitude of the effect (never accurately known) lies with a given level of certainty or confidence. It is common to talk about "a 95% confidence interval". This means that the true value of the study effect will lie in this interval in 95% of trials. Note: the confidence interval reflects the likelihood of random errors, but not of systematic errors (bias).

Cross-sectional descriptive study: describes the rates of an event or exposure at a specific time (single measurement). It allows us to examine the relationship between a risk factor (or exposure) and an effect (or outcome) in a given population at a given time (cut-off point). This is also called a prevalence study.

Discussion group: qualitative research technique enabling the identification of attitudes, opinions, appraisals or perceptions regarding something or someone among a group of individuals.

Efficacy: the degree to which an intervention produces a beneficial outcome under ideal circumstances.

Heterogeneity: In meta-analyses, heterogeneity refers to variability or differences between studies in the estimates of effects. It is important to differentiate between

"statistical heterogeneity", that is, differences between the claimed effects, and "clinical heterogeneity", that is, differences between studies in the main characteristics of participants, interventions or outcome measures. Statistical tests for heterogeneity are used to assess whether the variability observed in results is greater than that which would be expected due to chance alone.

In-depth interview: is a qualitative research technique to obtain data through a conversation between an informant who has pre-established characteristics and a skilled interviewer.

Indirect evidence: the information available is indirect when direct comparisons between the interventions of interest are not available, or when there are major differences between the populations in the studies available and the population, interventions or outcomes considered in the question of interest.

MEDLINE/PubMed: PubMed is a search engine that accesses the references and abstracts of the biomedical literature in the MEDLINE database maintained by the US National Library of Medicine.

Meta-analysis: is a statistical approach that makes it possible to combine the results of different studies (diagnostic test studies, clinical trials, cohort studies, etc.) to evaluate the heterogeneity and obtain overall results. This term is also used to refer to systematic reviews that include meta-analysis.

Morbidity: refers to having an illness or the symptoms of an illness or medical problems associated with a treatment and also to the amount of illness (incidence or prevalence) in a given population.

Mortality: refers to the rate or proportion of people in a given population that die from a given disease in a given period of time.

Odds ratio (OR): can be used as a measure of the efficacy of a treatment. If the OR is 1, the effect of the treatment is not different from that observed in the control group. If the OR is above (or below) 1, the effect of treatment is higher (or lower) than that observed in the control group. It should be noted that the effect being measured may be negative (e.g., death or disability) or positive (e.g., smoking cessation).

Open trial: 1. Clinical trial in which the researcher knows details about the intervention given to the participant. 2. Clinical trial with an open sequential design.

Placebo: inactive substance or procedure administered to a participant, to compare its effects with those of the intervention under study. Placebo is used in clinical trials to blind participants to their treatment allocation. To ensure appropriate

blinding, the placebo should not be distinguishable from the intervention substance or procedure.

Prevalence: refers to the rate or proportion of people in a given population who have a given condition or finding at a given time.

Primary research: refers to the type of research that collects original data. Primary studies are different from reviews or syntheses, these being based on data from individual primary studies. They also differ from systematic reviews that summarise the results of a set of primary studies.

Qualitative research: is a concept that covers a wide range of theoretical, methodological and technical approaches and is characterised by studying phenomena in their natural context, attempting to make sense of, or interpret, them based on the meanings people attach to them. This type of research is based on the types of empirical material (interviews, observations, texts, etc.) that best describe both routine and problematic situations, and what they mean in the lives of individuals.

Randomised clinical trial: an experimental study in which subjects are assigned randomly (at random) to a specific treatment or intervention among two or more possible options. One of the groups tends to receive the conventional treatment (control group), for comparison purposes, while the other group receives the treatment under study (experimental group). Both groups are monitored to assess any potential differences in outcomes.

SIGN: Scottish Intercollegiate Guidelines Network. A multidisciplinary Scottish group that develops clinical practice guidelines with recommendations based on the best available scientific evidence, as well as documents concerning the methods used to develop the guidelines.

Single- or double-blind trial: a clinical trial in which the participants (single blind) or neither the participants nor the clinicians involved (double blind) know which intervention each individual is receiving.

Systematic review: is a summary of the evidence on a specific question gathering the results of relevant studies, using explicit and systematic methods for identifying, critically appraising and synthesising the scientific literature. It may or may not include meta-analysis.

Abbreviations

ABA: abatacept

ACPA: anti-citrullinated protein antibody

ACR: American College of Rheumatology

ADA: adalimumab

AMI: acute myocardial infarction

ANAK: anakinra

AZA: azathioprine

BARI: baricitinib

bDMARD: biologic disease-modifying anti-rheumatic drug

CDAI: Clinical Disease Activity Index

CI: confidence Interval

cIMT: carotid intima-media thickness

CINAHL: Cumulative Index to Nursing & Allied Health Literature

CP: cyclophosphamide

CPG: clinical practice guideline

CRP: C-reactive protein

csDMARD: conventional synthetic disease-modifying anti-rheumatic drug

CZP: certolizumab pegol

DALYs: disability-adjusted life years

DAS: Disease Activity Score

DLCO: diffusing capacity of the lungs for carbon monoxide

DMARD: disease-modifying anti-rheumatic drug

EMA: European Medicines Agency

ESR: erythrocyte sedimentation rate

ETN: etanercept

EULAR: European League Against Rheumatism

FDA: Food and Drug Administration

FVC: forced vital capacity

GDG: guideline development group

GH: growth hormone

GM-CSF: granulocyte-macrophage colony-stimulating factor

GOL: golimumab

HAQ: Health Assessment Questionnaire

HAQ-DI: Health Assessment Questionnaire – Disability Index

HBV: hepatitis B virus

HCQ: hydroxychloroquine

HCV: hepatitis C virus

HIV: human immunodeficiency virus

HLA: human leukocyte antigen

HLA B27: human leukocyte antigen B27

HR: hazard ratio

HRCT: high-resolution computed tomography

IFX: infliximab

ILD: interstitial lung disease

LEF: leflunomide

MMF: mycophenolate mofetil

MRI: magnetic resonance imaging

MTX: methotrexate

NSAID: nonsteroidal anti-inflammatory drug

NSIP: nonspecific interstitial pneumonia

OR: odds ratio

PASI: Psoriasis Area and Severity Index

PFT: pulmonary function tests

PH: pulmonary hypertension

PICO: Patient/Intervention/Comparison/Outcome

PRO: patient-reported outcome

RA: rheumatoid arthritis

RCT: randomised clinical trial

RF: rheumatoid factor

RR: relative risk

RTX: rituximab

SDAI: Simple Disease Activity Index

SEPAR: Spanish Society of Pulmonology and Thoracic Surgery (Sociedad Española de Neumología y Cirugía Torácica)

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

SF-36: Short Form Health Survey

SIGN: Scottish Intercollegiate Guidelines Network

SMD: standardised mean difference

SORCOM: Rheumatology Society of the Autonomous Region of Madrid (Sociedad de Reumatología de la Comunidad de Madrid)

SSZ: sulfasalazine

T2T: treat-to-target

TB: Tuberculosis

TCZ: tocilizumab

TNF: tumour necrosis factor

TNFi: Tumour necrosis factor inhibitors

TOFA: tofacitinib

tsDMARD: targeted synthetic disease-modifying anti-rheumatic drug

UIP: usual interstitial pneumonia

YLD: years lived with disability or poor health

YLL: years of life lost

Appendix 4. Declarations of interest

Alejandro Balsa Criado and/or members of his family (up to first degree relatives) have received funding (hereon, personal funding) from Pfizer, Roche, Abbott–Abbvie, Bristol-Myers Squibb (BMS), UCB, MSD, Janssen and Novartis for attending courses/conferences and for giving talks and consultancy work for pharmaceutical and tech companies; funding from Pfizer, Abbott–Abbvie and UCB for running educational programmes and courses, and economic support from Pfizer and Roche for participating in a research study. Further, a department, unit or research group (or similar) he leads has also received economic support from Pfizer for funding a research study, and from Pfizer, Roche, BMS and UCB for educational programmes or courses.

Petra Díaz del Campo works at the SER Research Unit developing clinical practice guidelines with multiple sources of funding from the pharmaceutical industry.

Jose María Álvaro-Gracia Álvaro has received personal funding from Roche, Pfizer and UCB for attending courses/conferences; fees from Abbvie, BMS, Janssen, MSD, Novartis, Pfizer, Tigenix, Roche and UCB for giving talks; and economic support from BMS, Tigenix, Roche and UCB for consultancy work for pharmaceutical and other tech companies. Further, a department, unit or research group (or similar) he leads has also received economic support from Abbvie, BMS, MSD, Novartis, Pfizer, Tigenix, Roche and UCB for funding a research study.

José Luis Andreu Sánchez has received personal funding from Abbvie, Gebro, Janssen, MSD, Novartis and Pfizer for attending conferences/symposia; fees from Abbvie, Antares, GSK, MSD, Nordic, Novartis, Sanofi and UCB for giving talks; and economic support from Abbvie, Amgen, AstraZeneca, Biogen, Cellgene, Celltrion, Fresenius Kabi, Gebro, Pfizer and Regeneron for participating in a research study and consultancy work for pharmaceutical and tech companies.

Francisco Javier Blanco García has received personal funding from Pfizer for attending courses/conferences; fees from Bioibérica for giving talks; funding from UCB and BMS for running educational programmes and courses; and economic support from Gebro, Hospira and Pfizer for consultancy work for pharmaceutical and tech companies. Further, a department, unit or research group (or similar) he leads has also received economic support from Roche, Pfizer, Abbvie, Grünenthal, Wyeth, Celltrion, Cellerix, Sanofi-Aventis, BMS, Celgene, Flexion, UCB, Novartis, Ardea Biosciences, MSD, Janssen, Amgen, Tedec Meiji, Boehringer, AB Science, Ablynx N.V., Archigen Biotech Limited, Galapagos, Gedeon, Genentech, Gilead Sciences, GSK, INC Research UK Ltd., Inventiv Health Clinical, Nichi-IKO Pharmaceutical,

ONO Pharmaceutical, Regeneron and TRB Chemedica for funding a research study.

Laura Cano García has received personal funding from Pfizer and Roche for attending courses/conferences; fees from Roche, Sandoz, Novartis, MSD, Lilly and BMS for giving talks; and economic support from Roche and Sanofi for consultancy work for pharmaceutical and tech companies.

Esmeralda Delgado Frías has received personal funding from Abbvie for attending courses/conferences; and fees from UCB, Pfizer and Actelion for giving talks.

José Federico Díaz González has received personal funding from MSD, Pfizer, Celgene, Abbvie and Janssen for attending courses/conferences; fees from BMS, Janssen, Abbvie and Roche for giving talks; funding from MSD, Abbvie and Roche for running educational programmes and courses and for participating in a research project; and economic support from Hospira, Abbvie, and Biogen for consultancy work for pharmaceutical and tech companies. Further, a department, unit or research group (or similar) he leads has also received economic support from MSD, Abbvie and Roche for contracting staff and for funding a research project.

Ana Mª Fernández Ortiz has received personal funding from Lilly, Gebro, Abbvie, Pfizer, MSD, Roche and BMS for attending courses/conferences; fees from Pfizer, Roche, UCB, Lilly, GSK, BMS and Abbvie for giving talks, as well as funding from BMS for participating in a research project.

Blanca García Magallón has received personal funding from MSD, Menarini, Roche, Pfizer, Abbvie, Novartis, Lilly and Janssen for attending courses/conferences; fees from MSD, Menarini, Gebro and Amgen for giving talks; and funding from MSD for participating in a research project.

Luis Gómez Carrera has received personal funding from Boerhinger-Ingelheim and Roche for attending courses/conferences and fees from Esteve, Roche and Boerhinger-Ingelheim for giving talks. Further, a department, unit or research group (or similar) he leads has also received economic support from Boerhinger-Ingelheim for funding a research project.

Carlos González Juanatey has received personal funding from Boerhinger-Ingelheim, Sanofi, Bayer, Pfizer, Astra, Abbott and Medtronic for attending courses/conferences; fees from Boerhinger-Ingelheim, Sanofi, Bayer, Pfizer, Astra, Abbott, Medtronic, Novartis and Rovi for giving talks; funding from Abbott, Novartis, Bayer, Boerhinger-Ingelheim and Sanofi for participating in a research project; and economic support from Sanofi for consultancy work for pharmaceutical and tech companies. Further, a department, unit or research group (or similar) he leads has

also received economic support from Medtronic and Menarini for purchasing equipment; support from Medtronic from contracting staff and from Boerhinger-Ingelheim, Sanofi, Astra, Abbott, Novartis and Rovi for funding educational programmes or courses.

M. Vanesa Hernández Hernández has personal received funding from GSK for attending courses/conferences; and fees from Menarini, Ferrer, Abbvie, Ferrer, Pfizer, Ferrer, UCB and Esteve for giving talks.

Antonio Juan Mas has received personal funding from Pfizer, Novartis, MSD, Abbvie, Roche and Lilly for attending courses/conferences; fees from Roche, Pfizer, Novartis and MSD for giving talks; and funding from Novartis for participating in a research project.

Francisco Javier Narváez García has personal received funding from Pfizer for attending courses/conferences; fees from Abbvie, BMS and Roche for giving talks; and economic support from Lilly for consultancy work for pharmaceutical and tech companies.

Ana Ortiz García has received personal funding from Janssen, Lilly, Novartis, Pfizer, Roche, Sandoz and UCB for attending courses/conferences; fees from Lilly, MSD, Roche and UCB for consultancy work for pharmaceutical and tech companies; and funding from BMS, MSD and Roche for participating in a research project.

Lucía Silva Fernández has received personal funding from Sandoz, Lilly and Amgem for attending courses/conferences; and fees from UCB, Novartis, Lilly, Sanofi and BMS for consultancy work/talks.

Alejandro Tejedor Varillas has received personal fees from MSD, Esteve and Grünenthal for giving talks.

Appendix 5. Drugs for rheumatoid arthritis. Pregnancy and breastfeeding

Table 15. Main drugs employed in rheumatoid arthritis and their use during pregnancy

Drug	FDA Classification	Risk to the mother	Risk to the foetus	Information in the Summary of Product Characteristics (SmPC)	Observations
Acetylsalicylic acid and nonsteroidal anti-inflammatory drugs	C	Used during the menstrual cycle, they may reduce fertility	Possible increase in miscarriages (nonsteroidal anti-inflammatory drugs)	• Acetylsalicylic acid: Do not give during the third trimester of pregnancy. During the first and second trimester, acetylsalicylic acid should not be given unless strictly necessary. Salicylates must only be used during pregnancy after carefully assessing the risk-benefit ratio. • Ibuprofen: During the first and second trimester of pregnancy, ibuprofen should not be given unless strictly necessary. It is contraindicated during the third trimester of pregnancy.	
Glucocorticoids	Prednisone: B Others: C	• Premature rupture of membranes • High blood pressure • Gestational diabetes	• Used after week 30 of pregnancy, they may cause premature rupture of membranes • Intrauterine growth	During pregnancy or when there is a risk of pregnancy, they should only be used when absolutely necessary.	
Methotrexate	X	Used to induce therapeutic abortion in cases of ectopic pregnancy	Craniofacial abnormalities, short limbs and mental retardation	This drug may cause foetal death, embryotoxicity, miscarriage or teratogenic effects when administered to pregnant women. It is contraindicated during pregnancy. Pregnancy should be avoided if either member of the couple is taking this drug. The optimal interval between the end of treatment with this drug and pregnancy has not been clearly established. The interval recommended in the literature varies between 3 months and 1 year.	

Table 15. Main drugs employed in rheumatoid arthritis and their use during pregnancy

Drug	FDA Classification	Risk to the mother	Risk to the foetus	Information in the Summary of Product Characteristics (SmPC)	Observations
Leflunomide	X	No	Abortion inducer, craniofacial abnormalities, mental retardation	Contraindicated during pregnancy Women of childbearing age should use effective contraceptives during treatment and for 2 years after the last dose or until after an 11-day after wash-out with cholestyramine.	Male patients should be warned about potential male-mediated foetal toxicity. During treatment with this drug, effective contraception should be used.
Antimalarials	C	No	No	ESome data on pregnant women (from 300-1000 pregnancies) indicate that hydroxychloroquine does not cause malformations or foetal/neonatal toxicity. As a precautionary measure, it is preferable to avoid its use during pregnancy.	Despite the US Food and Drug Administration category, numerous studies support their use during pregnancy.
Sulfasalazine	C	No	Intrauterine growth restriction, prematurity	Data published on the use of this drug in pregnant women do not show adverse effects on pregnancy, or foetal or newborn health.	Treatment with this drug inhibits the absorption and metabolism of folic acid. Folic acid deficiency may cause serious blood disorders. Intake of folic/folinic acid is required.

Table 15. Main drugs employed in rheumatoid arthritis and their use during pregnancy

Drug	FDA Classification	Risk to the mother	Risk to the foetus	Information in the Summary of Product Characteristics (SmPC)	Observations
Anti-TNF agents	B	Insufficient data in humans	Possible link to VACTERL association	• Infliximab: Not recommended during pregnancy. Women of childbearing age should use effective contraception during treatment and for at least 6 months after the last dose. • Etanercept: Not recommended during pregnancy or breastfeeding. Women of childbearing age must be advised to avoid becoming pregnant. • Adalimumab: Due to the TNF-inhibitory activity of this drug, its use during pregnancy may affect the immune response of the newborn. Adalimumab should only be used during pregnancy when considered clearly necessary. • Certolizumab pegol: It has been approved for potential use during pregnancy and breastfeeding in women with chronic inflammatory rheumatic diseases. • Golimumab: Not recommended during pregnancy; only use if strictly necessary.	In men, although a potential link with asthenozoospermia and a reduction in sperm motility was initially suggested in men, there are no conclusive data indicating that these drugs reduce male fertility. • They are among the drugs for which there is the most experience of their use during pregnancy, and according to expert opinion, they do not seem to cause an unreasonable level of problems. • Recently, the SmPC has included mention of an observational study that found a higher rate of major birth defects in pregnancies exposed to etanercept than those not exposed to this drug or other TNF inhibitors (adjusted OR 2.4; 95% CI: 1 to 5.5). The types of important congenital defects were consistent with those most commonly reported in the general population, and no particular patterns of abnormalities were observed. No changes have been reported in the rates of miscarriage, stillbirth or minor malformations.
Rituximab	C	Immunoglobulins G cross the placental barrier	Low or undetectable levels of CD19+ B cells in newborn infants of mothers treated with this drug	• B-cell levels in newborn infants of mothers exposed to this drug have not been assessed in clinical trials. There are insufficient data and non-controlled studies in pregnant women. • They should not be given to pregnant women unless the expected benefit exceeds the potential risk.	

Table 15. Main drugs employed in rheumatoid arthritis and their use during pregnancy

Drug	FDA Classification	Risk to the mother	Risk to the foetus	Information in the Summary of Product Characteristics (SmPC)	Observations
Tocilizumab	C	Its effects in humans are not known	Its effects in humans are not known	Unknown potential risk in humans. This drug should not be used during pregnancy, unless strictly necessary.	
Abatacept	C	Its effects in humans are not known	Its effects in humans are not known	The use of this drug is not recommended in pregnant women unless strictly necessary.	In a case series, it seemed to increase the risk of congenital malformations compared to rates in the general population.
Anakinra	B	Its effects in humans are not known	Its effects in humans are not known	This drug is not recommended during pregnancy, or in women of childbearing age who are not using contraceptives.	
Tofacitinib	X	Its effects in humans are not known	Its effects in humans are not known	Contraindicated during pregnancy.	There are case series of patients with rheumatoid arthritis, psoriatic arthritis or ulcerative colitis in pharmacovigilance reports.
Baricitinib	X	No hay datos suficientes acerca del uso de baricitinib en mujeres embarazadas.	Insufficient data on the use of this drug in pregnant women	Contraindicated during pregnancy.	There is educational material, available including alert cards for patients to underline this contraindication and what to do if they were to become pregnant while on this drug.

Category	Safety	Description
A	Controlled studies have not demonstrated an increased risk It is unlikely to harm the foetus.	Studies in pregnant women have not found evidence of an associated risk during the first trimester of pregnancy and there is no evidence for the other trimesters.
B	No increased risk described in humans. Its use during pregnancy is considered acceptable.	Animal studies have not found an associated risk, but there are no appropriate studies on pregnant women or there are animal studies that have reported adverse effects but which have not been confirmed in pregnant women.
C	Harm to the foetus cannot be ruled out. Its use should be based on a risk- benefit assessment.	Animal studies have demonstrated adverse effects, but it has not been studied in pregnant women, or it has not been studied in either pregnant women or animals.
D	There is evidence of risk to the foetus. It should only be used if there are no other options.	Studies in pregnant women have demonstrated an increased risk of adverse events, but in some cases, the benefits may exceed these risks.
X	It is contraindicated during pregnancy.	Studies in pregnant women as well as in animals have demonstrated that the potential risks are clearly greater than the potential benefits.

Table 16. Main drugs employed in rheumatoid arthritis and their use during breastfeeding

Drug	Levels in maternal breast milk	Levels in breastfed infant	Risk	Observations
Nonsteroidal anti-inflammatory drugs	Low	None or low	Very low or low	• Avoid those with a long half-life or with enterohepatic circulation. • Avoid therapeutic doses of acetylsalicylic acid. • Summary of product characteristics (SmPC) for ibuprofen: The use of ibuprofen during breastfeeding is not recommended due to the potential risk of inhibition of the synthesis of prostaglandins in the newborn. • Despite the specifications in the SmPC, numerous publications endorse its use during breastfeeding.
Prednisone and prednisolone	Low	None or low	Very low or low	• If taken long term or at high doses, avoid breastfeeding for 3 to 4 hours after the dose. • Intraarticular corticosteroids (methylprednisolone, triamcinolone) may affect milk production in the short term. • Corticosteroids during the prenatal period can lead to delay in lactogenesis II (onset of copious milk production), reducing the quantity of milk produced in the first week • Use of dexamethasone has been associated with a reduction in prolactin levels. • SmPC: Prednisone is excreted in breast milk in very small amounts. There are no reports of any harm to breastfed babies. Nonetheless, long-term use of high doses may affect the adrenal function of the infant, and hence, this should be monitored. If the patient needs very high doses, breastfeeding should be discontinued.
Methotrexate	Low	No data	High	• No or negligible transfer to breast milk when used at low weekly doses during maintenance therapy for rheumatoid arthritis and other autoimmune diseases. Nonetheless, its use is not recommended due to potential accumulation in the infant's tissues. • It is cleared from the body after six elimination half-lives of the drug. It is prudent to wait 4 days after the last dose before breastfeeding. In the meantime, breast milk should be regularly expressed and discarded. • SmPC: Contraindicated during breastfeeding. If its use is necessary, breastfeeding should be suspended before starting treatment.
Leflunomide	No data	No data	Very high	• Given the lack of data and long half-life of this drug, its use is not recommended. • SmPC: Breastfeeding women should not be treated with this drug.

Table 16. Main drugs employed in rheumatoid arthritis and their use during breastfeeding

Drug	Levels in maternal breast milk	Levels in breastfed infant	Risk	Observations
Antimalarials	Low	No data	Low	• SmPC: Excreted in breast milk but at therapeutic doses no adverse effects are expected in breastfed infants.
Sulfasalazine	Moderate (metabolite)	Variable (metabolite)	Low risk	• Caution in full-term neonates who develop diarrhoea. • Should be avoided in patients with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency. • SmPC: Sulfasalazine and sulfapyridine are found at low concentrations in breast milk, meaning that there is a theoretical risk of kernicterus in neonates. Despite this, the risk can be considered negligible if the maternal dose does not exceed 2-3 g/day. Precautions should be taken, especially in the case of infants born prematurely or with glucose-6-phosphate dehydrogenase deficiency.
Anti-TNF agents	Low	Detected due to residues of what passes through the placental barrier	Low risk	• It has been reported that etanercept is excreted in breast milk after subcutaneous administration. No other anti-TNFs have been detected in infant blood, except in the case of infants whose mothers were treated during pregnancy. • SmPC: Given that immunoglobulins are excreted in breast milk, a risk to breastfed infants cannot be ruled out.
Rituximab	No data	No data	Unknown	• SmPC: Breastfeeding should be avoided during treatment and up to 12 months after the last dose.
Tocilizumab	No data	No data	Unknown	• SmPC: It is not known whether this drug is excreted in breast milk. A decision must be taken about whether to continue breastfeeding and suspend the treatment or vice versa.
Abatacept	No data	No data	Unknown	• SmPC: Women should not breastfeed while on this drug or for 14 weeks after the last dose.
Anakinra	No data	No data	Unknown	• SmPC: It is not known whether this drug or its metabolites are excreted in breast milk. A risk for newborns/infants cannot be ruled out. Breastfeeding should be suspended while on this drug.
Tofacitinib	Unknown	Unknown	Risk for breastfed infants cannot be ruled out	• SmPC: Excreted in rat breast milk. This drug is contraindicated during breastfeeding.

Table 16. Main drugs employed in rheumatoid arthritis and their use during breastfeeding

Drug	Levels in maternal breast milk	Levels in breastfed infant	Risk	Observations
Baricitinib	Unknown	Unknown	Risk for newborn/ breastfed infant cannot be ruled out	• SmPC: It is not known whether this drug or its metabolites are excreted in human breast milk. Pharmacological/toxicological data from animal studies have shown its excretion in breast milk. • The decision about whether to stop breastfeeding or discontinue this drug must be taken weighing up the benefits of breastfeeding for the infant and benefits of the therapy for the mother.

References

1. Firestein GS, Budd, R., Gabriel, S. E., McInnes, I. B., & O'Dell, J. R. Kelley and Firestein's Tex book of Rheumatology E-Book. 2016. Elsevier Health Sciences.
2. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205-19.
3. Library of Clinical Practice Guidelines of the Spanish National Health Service, Catálogo de Guías de Práctica Clínica en el Sistema Nacional de Salud (SNS) https://portal.guiasalud.es/gpc/?_sfm_wpcf-estado=1
4. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, *et al.* 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res. 2016;68:1-26.
5. GUIPCAR. Guía de Práctica Clínica para el manejo de la Artritis Reumatoide en España. 2011. Madrid: Sociedad Española de Reumatología.
6. Gibofsky A. Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am J Manag Care. 2012;18(13 Suppl):S295-302.
7. Carmona L, Villaverde V, Hernandez-Garcia C, Ballina J, Gabriel R, Laffon A. The prevalence of rheumatoid arthritis in the general population of Spain. Rheumatology (Oxford). 2002;41(1):88-95.
8. Vandenbroucke JP, Hazevoet HM, Cats A. Survival and cause of death in rheumatoid arthritis: a 25-year prospective followup. J Rheumatol. 1984;11(2):158-61.
9. López de Argumedo M RE, Gutiérrez A, Bayón JC. Actualización del Sistema de Trabajo Compartido para Revisiones Sistemáticas de la Evidencia Científica y Lectura Crítica (Plataforma FLC 3.0). Spanish Ministry of Health, Social Services and Equality. Basque Office for Health Technology Assessment (OSTEBA); 2017. Informes de Evaluación de Tecnologías Sanitarias: OSTEBA.
10. Grupo de trabajo sobre GPC. Elaboración de Guías de Práctica Clínica en el Sistema Nacional de Salud. Manual Metodológico. Madrid: Plan Nacional para el SNS del MSC. Instituto Aragonés de Ciencias de la Salud-I+CS; 2007. Guías de Práctica Clínica en el SNS: I+CS Nº 2006/0I.
11. M11.Murray CJL. The Global Burden of Disease. Harvard University Press-World Health Organization, 1996.
12. Pereira J, Cañon 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.
13. Murray CJ, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, *et al.* GBD 2010: design, definitions, and metrics. Lancet. 2012;380(9859):2063-6.
14. Murray CJL, Lopez AD. Measuring global health: motivation and evolution of the Global Burden of Disease Study. Lancet. 2017;390(10100):1460-4.
15. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1260-344.

16. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211-59.
17. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151-210.
18. Cross M, Smith E, Hoy D, Carmona L. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. 2014;73(7):1316-22.
19. Kiadaliri AA, Kristensen LE, Englund M. Burden of rheumatoid arthritis in the Nordic region, 1990-2015: a comparative analysis using the Global Burden of Disease Study 2015. Scand J Rheumatol. 2018;47(2):1-101.
20. Moradi-Lakeh M, Forouzanfar MH, Vollset SE, El Bcheraoui C, Daoud F, Afshin A, *et al.* Burden of musculoskeletal disorders in the Eastern Mediterranean Region, 1990-2013: findings from the Global Burden of Disease Study 2013. Ann Rheum Dis. 2017;76(8):1365-73.
21. Gerlag DM, Raza K, van Baarsen LG, Brouwer E, Buckley CD, Burmester GR, *et al.* EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. Ann Rheum Dis. 2012;71(5):638-41.
22. John S, Myerscough A, Marlow A, Hajeer A, Silman A, Ollier W, *et al.* Linkage of cytokine genes to rheumatoid arthritis. Evidence of genetic heterogeneity. Ann Rheum Dis. 1998;57(6):361-5.
23. Kallberg H, Padyukov L, Plenge RM, Ronnelid J, Gregersen PK, van der Helm-van Mil AH, *et al.* Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. Am J Hum Genet. 2007;80(5):867-75.
24. Alpizar-Rodriguez D, Finckh A. Environmental factors and hormones in the development of rheumatoid arthritis. Semin Immunopathol. 2017;39(4):461-8.
25. Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, *et al.* Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum. 2004;50(2):380-6.
26. Rantapaa-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, *et al.* Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum. 2003;48(10):2741-9.
27. Bos WH, Wolbink GJ, Boers M, Tijhuis GJ, de Vries N, van der Horst-Bruinsma IE, *et al.* Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. Ann Rheum Dis. 2010;69(3):490-4.
28. van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJ, Brouwer E, Codreanu C, Combe B, *et al.* EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. Ann Rheum Dis. 2017;76(3):491-6.
29. Olivieri I, Sarzi-Puttini P, Bugatti S, Atzeni F, d'Angelo S, Caporali R. Early treatment in early undifferentiated arthritis. Autoimmun Rev. 2012;11(8):589-92.
30. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, *et al.* 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69(9):1580-8.

31. van Nies JA, Krabben A, Schoones JW, Huizinga TW, Kloppenburg M, van der Helm-van Mil AH. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. Ann Rheum Dis. 2014;73(5):861-70.
32. Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. Clin Exp Rheumatol. 2003;21(5 Suppl 31):S154-7.
33. Biliavska I, Stamm TA, Martinez-Avila J, Huizinga TW, Landewe RB, Steiner G, *et al.* Application of the 2010 ACR/EULAR classification criteria in patients with very early inflammatory arthritis: analysis of sensitivity, specificity and predictive values in the SAVE study cohort. Ann Rheum Dis. 2013;72(8):1335-41.
34. Berglin E, Dahlqvist SR. Comparison of the 1987 ACR and 2010 ACR/EULAR classification criteria for rheumatoid arthritis in clinical practice: a prospective cohort study. Scand J Rheumatol. 2013;42(5):362-8.
35. Reneses S, Pestana L, Garcia A. Comparison of the 1987 ACR criteria and the 2010 ACR/EULAR criteria in an inception cohort of patients with recent-onset inflammatory polyarthritis. Clin Exp Rheumatol. 2012;30(3):417-20.
36. Britsemmer K, Ursum J, Gerritsen M, van Tuyl LH, van Schaardenburg D. Validation of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: slight improvement over the 1987 ACR criteria. Ann Rheum Dis. 2011;70(8):1468-70.
37. Cader MZ, Filer A, Hazlehurst J, de Pablo P, Buckley CD, Raza K. Performance of the 2010 ACR/EULAR criteria for rheumatoid arthritis: comparison with 1987 ACR criteria in a very early synovitis cohort. Ann Rheum Dis. 2011;70(6):949-55.
38. Le Loet X, Nicolau J, Boumier P, Daragon A, Mejjad O, Pouplin S, *et al.* Validation of the 2010-ACR/EULAR -classification criteria using newly EULAR-defined erosion for rheumatoid arthritis on the very early arthritis community-based (VErA) cohort. Joint Bone Spine. 2015;82(1):38-41.
39. Ye H, Su Y, Li R, Zhao J, Liu X, Mei Y, *et al.* Comparison of three classification criteria of rheumatoid arthritis in an inception early arthritis cohort. Clin Rheumatol. 2016;35(10):2397-401.
40. Zhao J, Li G, Xu J, Zhang X, Zhang Z. Performance of the American College of Rheumatology/European League Against Rheumatism 2010 criteria for the diagnosis of rheumatoid arthritis in Chinese patients. Joint Bone Spine. 2013;80(5):482-7.
41. Kennish L, Labitigan M, Budoff S, Filopoulos MT, McCracken WA, Swearingen CJ, *et al.* Utility of the new rheumatoid arthritis 2010 ACR/EULAR classification criteria in routine clinical care. BMJ Open. 2012;2(5).
42. van der Linden MP, Knevel R, Huizinga TW, van der Helm-van Mil AH. Classification of rheumatoid arthritis: comparison of the 1987 American College of Rheumatology criteria and the 2010 American College of Rheumatology/European League Against Rheumatism criteria. Arthritis Rheum. 2011;63(1):37-42.
43. Kaneko Y, Kuwana M, Kameda H, Takeuchi T. Sensitivity and specificity of 2010 rheumatoid arthritis classification criteria. Rheumatology (Oxford). 2011;50(7):1268-74.
44. de Hair MJ, Lehmann KA, van de Sande MG, Maijer KI, Gerlag DM, Tak PP. The clinical picture of rheumatoid arthritis according to the 2010 American College of Rheumatology/European League Against Rheumatism criteria: is this still the same disease? Arthritis Rheum. 2012;64(2):389-93.

45. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315-24.
46. Zhao J, Su Y, Li R, Ye H, Zou Q, Fang Y, *et al.* Classification criteria of early rheumatoid arthritis and validation of its performance in a multi-centre cohort. Clin Exp Rheumatol. 2014;32(5):667-73.
47. Makinen H, Kaarela K, Huhtala H, Hannonen PJ, Korpela M, Sokka T. Do the 2010 ACR/EULAR or ACR 1987 classification criteria predict erosive disease in early arthritis? Ann Rheum Dis. 2013;72(5):745-7.
48. Varache S, Cornec D, Morvan J, Devauchelle-Pensec V, Berthelot JM, Le Henaff-Bourhis C, *et al.* Diagnostic accuracy of ACR/EULAR 2010 criteria for rheumatoid arthritis in a 2-year cohort. J Rheumatol. 2011;38(7):1250-7.
49. Cornec D, Varache S, Morvan J, Devauchelle-Pensec V, Berthelot JM, Le Henaff-Bourhis C, *et al.* Comparison of ACR 1987 and ACR/EULAR 2010 criteria for predicting a 10-year diagnosis of rheumatoid arthritis. Joint Bone Spine. 2012;79(6):581-5.
50. Kasturi S, Goldstein BL, Malspeis S, Karlson EW, Costenbader KH. Comparison of the 1987 American College of Rheumatology and the 2010 American College of Rheumatology/European League against Rheumatism criteria for classification of rheumatoid arthritis in the Nurses' Health Study cohorts. Rheumatol Int. 2014;34(3):407-11.
51. Ravindran V, Abdulaziz A, Bhargavan PV. Performance of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis in a prospective early arthritis cohort in Kerala, India. 2014;9(3):107-11.
52. Aken J, Heimans L, Gillet-van Dongen H, Visser K, Ronday HK, Speyer I, *et al.* Five-year outcomes of probable rheumatoid arthritis treated with methotrexate or placebo during the first year (the PROMPT study). Annals of the Rheumatic Diseases [Internet]. 2014; 73(2):[396-400 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/462/CN-00959462/frame.html.
53. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, *et al.* Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med. 2001;111(6):446-51.
54. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76(6):960-77.
55. Tornero Molina J, Ballina Garcia FJ, Calvo Alen J, Caracuel Ruiz MA, Carbonell Abello J, Lopez Meseguer A, *et al.* Recommendations for the use of methotrexate in rheumatoid arthritis: up and down scaling of the dose and administration routes. Reumatol Clin. 2015;11(1):3-8.
56. 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. Reumatol Clin. 2015;11(5):279-94.
57. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, *et al.* Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet. 2004;364(9430):263-9.

58. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, *et al.* Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis. 2007;66(11):1443-9.
59. Corominas H, Narvaez J, Diaz-Torne C, Salvador G, Gomez-Caballero ME, de la Fuente D, *et al.* Diagnostic and therapeutic delay of rheumatoid arthritis and its relationship with health care devices in Catalonia. The AUDIT study. Reumatol Clin. 2016;12(3):146-50.
60. Clemente D, Hernandez-Garcia C, Abasolo L, Villaverde V, Lajas C, Loza E, *et al.* [Reduction in time until first treatment with disease modifying treatment in patients with rheumatoid arthritis]. Reumatol Clin. 2007;3(6):245-50.
61. Raza K, Stack R, Kumar K, Filer A, Detert J, Bastian H, *et al.* Delays in assessment of patients with rheumatoid arthritis: variations across Europe. Ann Rheum Dis. 2011;70(10):1822-5.
62. Kumar K, Daley E, Carruthers DM, Situnayake D, Gordon C, Grindulis K, *et al.* Delay in presentation to primary care physicians is the main reason why patients with rheumatoid arthritis are seen late by rheumatologists. Rheumatology (Oxford). 2007;46(9):1438-40.
63. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, *et al.* Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. 2016;75(1):3-15.
64. Tejera Segura B, Bustabad S. A new form of communication between rheumatology and primary care: The virtual consultation. Reumatol Clin. 2016;12(1):11-4.
65. Rheumatology Society of the Autonomous Region of Madrid (SORCOM). Panel of experts recommended by SORCOM. Criterios de calidad para la asistencia reumatológica. (Recomendaciones oficiales de la Sociedad de Reumatología de la Comunidad de Madrid). 2002. Rev Esp Reumatol; 29:155–7.
66. Alonso Ruiz A VFJ, Tornero Molina J, Carbonell Abelló J, Lázaro P, Mercado D, *et al.* Estándares de calidad asistencial en reumatología. Reumatol Clin. 2007; 3:218–25.
67. Nolla JM, Martínez C, García-Vicuña R, Seoane-Mato D, Rosario Lozano MP, Alonso A *et al.* Quality standards for rheumatology outpatient clinic. The EXTRELLA project. Reumatol Clin 2016; 12:248-55.
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. Ann Rheum Dis. 2015;74(5):806-12.
69. Blanco FJ, Ballina J, Carbonell J, Martin-Mola E, Tornero J, Ramirez E, *et al.* [Descriptive study of the use of DMARD in patients with rheumatoid arthritis or persistent arthritis who start drug treatment in Spain (FIRST)]. Reumatol Clin. 2011;7(2):88-93.
70. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, *et al.* EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2007;66(1):34-45.
71. Combe B, Landewe R, Daien CI, Hua C, Aletaha D, Alvaro-Gracia JM, *et al.* 2016 update of the EULAR recommendations for the management of early arthritis. 2017;76(6):948-59.

72. Hua C, Daien CI, Combe B, Landewe R. Diagnosis, prognosis and classification of early arthritis: results of a systematic review informing the 2016 update of the EULAR recommendations for the management of early arthritis. RMD Open. 2017;3(1):e000406.
73. Almoallim H, Janoudi N, Attar SM, Garout M, Algohary S, Siddiqui MI, *et al.* Determining early referral criteria for patients with suspected inflammatory arthritis presenting to primary care physicians: a cross-sectional study. Open Access Rheumatol. 2017;9:81-90.
74. Meyfroidt S, Stevens J, De Lepeleire J, Westhovens R, De Cock D, Van der Elst K, *et al.* A general practice perspective on early rheumatoid arthritis management: A qualitative study from Flanders. Eur J Gen Pract. 2015;21(4):231-7.
75. Akesson K, Dreinhofer KE, Woolf AD. Improved education in musculoskeletal conditions is necessary for all doctors. Bull World Health Organ. 2003;81(9):677-83.
76. van den Bosch WB, Mangnus L, Reijnierse M, Huizinga TW, van der Helm-van Mil AH. The diagnostic accuracy of the squeeze test to identify arthritis: a cross-sectional cohort study. Ann Rheum Dis. 2015;74(10):1886-9.
77. Barra L, Bykerk V, Pope JE, Haraoui BP, Hitchon CA, Thorne JC, *et al.* Anticitrullinated protein antibodies and rheumatoid factor fluctuate in early inflammatory arthritis and do not predict clinical outcomes. J Rheumatol. 2013;40(8):1259-67.
78. Colebatch AN, Edwards CJ, Ostergaard M, van der Heijde D, Balint PV, D'Agostino MA, *et al.* EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis. 2013;72(6):804-14.
79. Duer-Jensen A, Horslev-Petersen K, Hetland ML, Bak L, Ejbjerg BJ, Hansen MS, *et al.* Bone edema on magnetic resonance imaging is an independent predictor of rheumatoid arthritis development in patients with early undifferentiated arthritis. Arthritis Rheum. 2011;63(8):2192-202.
80. Nieuwenhuis WP, Krabben A, Stomp W, Huizinga TW, van der Heijde D, Bloem JL, *et al.* Evaluation of magnetic resonance imaging-detected tenosynovitis in the hand and wrist in early arthritis. Arthritis Rheumatol. 2015;67(4):869-76.
81. Nieuwenhuis WP NE, van Steenbergen HW, Mangnus L, Huizinga TWJ, Reijnierse M, van der Helm- van Mil AHM. Is MRI of Use in Identifying Which Undifferentiated Arthritis Patients Will Develop RA? [abstract]. Arthritis Rheumatol. 2015; 67 (suppl 10). Available from: http://acrabstracts.org/abstract/is-mri-of-use-in-identifying-which-undifferentiated-arthritis-patients-will-develop-ra/.
82. Sahbudin I PL, Cader Z, *et al.* OP0015 Ultrasound-Defined Tenosynovitis is a Strong Predictor of Early Rheumatoid Arthritis Annals of the Rheumatic Diseases 2015;74:69-70.
83. Narvaez Garcia JA. [Evaluation through imaging of early rheumatoid arthritis]. Reumatol Clin. 2010;6(2):111-4.
84. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. Ann Rheum Dis. 2002;61(4):290-7.
85. Bruschi E, Casu C, Filippini D, Pisoni L, Schito E, Zahalkova L, *et al.* Improving diagnosis of early inflammatory arthritis: results of a novel triage system. Clin Exp Rheumatol. 2013;31(4):606-9.
86. Tavares R, Wells GA, Bykerk VP, Guillemin F, Tugwell P, Bell MJ. Validation of a self-administered inflammatory arthritis detection tool for rheumatology triage. J Rheumatol. 2013;40(4):417-24.

87. Bell MJ, Tavares R, Guillemin F, Bykerk VP, Tugwell P, Wells GA. Development of a self-administered early inflammatory arthritis detection tool. BMC Musculoskelet Disord. 2010;11:50.
88. Callahan LF, Pincus T. A clue from a self-report questionnaire to distinguish rheumatoid arthritis from noninflammatory diffuse musculoskeletal pain. The P-VAS:D-ADL ratio. Arthritis Rheum. 1990;33(9):1317-22.
89. van Aken J, Lard LR, le Cessie S, Hazes JM, Breedveld FC, Huizinga TW. Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. Ann Rheum Dis. 2004;63(3):274-9.
90. 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). 2004;43(7):906-14.
91. 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). 2011;50(6):1106-10.
92. Kavanaugh A, Fleischmann RM, Emery P, Kupper H, Redden L, Guerette B, *et al.* Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. Ann Rheum Dis. 2013;72(1):64-71.
93. Ruyssen-Witrand A, Guernec G, Nigon D, Tobon G, Jamard B, Rat AC, *et al.* Aiming for SDAI remission versus low disease activity at 1 year after inclusion in ESPOIR cohort is associated with better 3-year structural outcomes. Ann Rheum Dis. 2015;74(9):1676-83.
94. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, *et al.* American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011;70(3):404-13.
95. Sakellariou G, Scire CA, Verstappen SM, Montecucco C, Caporali R. In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. Ann Rheum Dis. 2013;72(2):245-9.
96. Ranganath VK, Motamedi K, Haavardsholm EA, Maranian P, Elashoff D, McQueen F, *et al.* Comprehensive appraisal of magnetic resonance imaging findings in sustained rheumatoid arthritis remission: a substudy. Arthritis Care Res (Hoboken). 2015;67(7):929-39.
97. Dale J, Stirling A, Zhang R, Purves D, Foley J, Sambrook M, *et al.* Targeting ultrasound remission in early rheumatoid arthritis: The results of the TaSER study, a randomised clinical trial. Annals of the Rheumatic Diseases. 2016;75(6):1043-50.
98. Haavardsholm EA, Aga AB, Olsen IC, Lillegraven S, Hammer HB, Uhlig T, *et al.* Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. Bmj. 2016;354:i4205.
99. Widdifield J, Bernatsky S, Paterson JM, Thorne JC, Cividino A, Pope J, *et al.* Quality care in seniors with new-onset rheumatoid arthritis: a Canadian perspective. Arthritis Care Res (Hoboken). 2011;63(1):53-7.
100. Feldman DE, Bernatsky S, Houde M, Beauchamp ME, Abrahamowicz M. Early consultation with a rheumatologist for RA: does it reduce subsequent use of orthopaedic surgery? Rheumatology (Oxford). 2013;52(3):452-9.

101. Ferraz-Amaro I D-GF. NSAIDs and peptic ulcer disease. In: Jianyuan Chai (Eds.), Peptic Ulcer Disease. Rijeka: Intechweb; 2011:75-92
102. Antman EM. Evaluating the Cardiovascular Safety of Nonsteroidal Anti-Inflammatory Drugs. Circulation. 2017;135(21):2062-72.
103. Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R, *et al.* Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis. 2009;68(7):1119-24.
104. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum. 2006;54(2):628-34.
105. Martin-Martinez MA, Andreu-Sanchez JL, Sanchez-Alonso F, Corominas H, Perez-Venegas JJ, Roman-Ivorra JA, *et al.* A composite indicator to assess the quality of care in the management of patients with rheumatoid arthritis in outpatient rheumatology clinics. Reumatol Clin. 2017.
106. Buttgereit F, da Silva JA, Boers M, Burmester GR, Cutolo M, Jacobs J, *et al.* Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis. 2002;61(8):718-22.
107. Da Silva JA, Jacobs JW, Kirwan JR, Boers M, Saag KG, Ines LB, *et al.* Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis. 2006;65(3):285-93.
108. Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW, Van der Heijden GJ. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis. 2009;68(12):1833-8.
109. van der Goes MC, Jacobs JW, Boers M, Andrews T, Blom-Bakkers MA, Buttgereit F, *et al.* Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice. Ann Rheum Dis. 2010;69(11):1913-9.
110. Vainchenker W, Dusa A, Constantinescu SN. JAKs in pathology: role of Janus kinases in hematopoietic malignancies and immunodeficiencies. Semin Cell Dev Biol. 2008;19(4):385-93.
111. Lacronique V, Boureux A, Valle VD, Poirel H, Quang CT, Mauchauffe M, *et al.* A TEL-JAK2 fusion protein with constitutive kinase activity in human leukemia. Science. 1997;278(5341):1309-12.
112. Kralovics R, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR, *et al.* A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med. 2005;352(17):1779-90.
113. Borie DC, O'Shea JJ, Changelian PS. JAK3 inhibition, a viable new modality of immunosuppression for solid organ transplants. Trends Mol Med. 2004;10(11):532-41.
114. Levy DE, Loomis CA. STAT3 signaling and the hyper-IgE syndrome. N Engl J Med. 2007;357(16):1655-8.
115. Kisseleva T, Bhattacharya S, Braunstein J, Schindler CW. Signaling through the JAK/STAT pathway, recent advances and future challenges. Gene. 2002;285(1-2):1-24.
116. Laurence A, Pesu M, Silvennoinen O, O'Shea J. JAK Kinases in Health and Disease: An Update. Open Rheumatol J. 2012;6:232-44.
117. Johnston JA, Bacon CM, Riedy MC, O'Shea JJ. Signaling by IL-2 and related cytokines: JAKs, STATs, and relationship to immunodeficiency. J Leukoc Biol. 1996;60(4):441-52.

118. Conklyn M, Andresen C, Changelian P, Kudlacz E. The JAK3 inhibitor CP-690550 selectively reduces NK and CD8+ cell numbers in cynomolgus monkey blood following chronic oral dosing. J Leukoc Biol. 2004;76(6):1248-55.
119. Changelian PS, Moshinsky D, Kuhn CF, Flanagan ME, Munchhof MJ, Harris TM, *et al.* The specificity of JAK3 kinase inhibitors. Blood. 2008;111(4):2155-7.
120. Changelian PS, Flanagan ME, Ball DJ, Kent CR, Magnuson KS, Martin WH, *et al.* Prevention of organ allograft rejection by a specific Janus kinase 3 inhibitor. Science. 2003;302(5646):875-8.
121. Milici AJ, Kudlacz EM, Audoly L, Zwillich S, Changelian P. Cartilage preservation by inhibition of Janus kinase 3 in two rodent models of rheumatoid arthritis. Arthritis Res Ther. 2008;10(1):R14.
122. Ghoreschi K, Jesson MI, Li X, Lee JL, Ghosh S, Alsup JW, *et al.* Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). J Immunol. 2011;186(7):4234-43.
123. Emery P TP, Weinblatt M, Tanaka Y, Keystone EC, Dow ER, Higgs R, Macias WL, Rocha G, Rooney TP, Schlichting DE, Zuckerman SH, McInnes IB. Microarray pathway analysis comparing baricitinib and adalimumab in moderate to severe rheumatoid arthritis patients, from a phase 3 study [abstract]. Arthritis Rheumatol. 2017; 69 (suppl 10). Available from: http://acrabstracts.org/abstract/microarray-pathway-analysis-comparing-baricitinib-and-adalimumab-in-moderate-to-severe-rheumatoid-arthritis-patients-from-a-phase-3-study/.
124. WHO Expert Committee on Biological Standardization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). Geneva; 2009. Available from: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf.
125. Dorner T, Strand V, Cornes P, Goncalves J, Gulacsi L, Kay J. The changing landscape of biosimilars in rheumatology. 2016;75(6):974-82.
126. Kay J. Editorial: Biosimilars: New or Deja Vu? Arthritis Rheumatol. 2016;68(5):1049-52.
127. Chingcuanco F, Segal JB, Kim SC, Alexander GC. Bioequivalence of biosimilar tumor necrosis factor-alpha inhibitors compared with their reference biologics: A systematic review. Ann Intern Med. 2016;165(8):565-74.
128. Park W, Hrycaj P, Jeka S, Kovalenko V, Lysenko G, Miranda P, *et al.* A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis. 2013;72(10):1605-12.
129. Yoo DH, Hrycaj P, Miranda P, Ramiterre E, Piotrowski M, Shevchuk S, *et al.* A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis. 2013;72(10):1613-20.
130. Jorgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, *et al.* Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017;389(10086):2304-16.
131. Glintborg B, Sorensen IJ, Loft AG, Lindegaard H, Linauskas A, Hendricks O, *et al.* A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 pa-

tients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis. 2017;76(8):1426-31.

132. Smolen JS, Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, *et al.* Comparing biosimilar SB2 with reference infliximab after 54 weeks of a double-blind trial: clinical, structural and safety results. Rheumatology (Oxford). 2017;56(10):1771-9.
133. Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, Baranauskaite A, *et al.* A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2017;76(1):58-64.
134. European Medicines Agency: Inflectra (infliximab). Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002778/human_med_001677.jsp&mid=WC0b01ac058001d124.
135. FDA News Release: FDA approves Inflectra, a biosimilar to Remicade. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm.
136. European Medicines Agency: Flixabi (infliximab). Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004020/human_med_001980.jsp&mid=WC0b01ac058001d124.
137. FDA. Drugs@FDA: FDA Approved Drug Products. Renflexis. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=761054.
138. Emery P, Vencovsky J, Sylwestrzak A, Leszczynski P, Porawska W, Baranauskaite A, *et al.* A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2017;76(1):51-7.
139. Griffiths CEM, Thaci D, Gerdes S, Arenberger P, Pulka G, Kingo K, *et al.* The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. Br J Dermatol. 2017;176(4):928-38.
140. Yoo DH, Suh CH, Shim SC, Jeka S, Molina FFC, Hrycaj P, *et al.* Efficacy, safety and pharmacokinetics of up to two courses of the rituximab biosimilar CT-P10 versus innovator rituximab in patients with rheumatoid arthritis: Results up to week 72 of a phase I randomized controlled trial. BioDrugs. 2017;31(4):357-67.
141. Boers M, Verhoeven AC, Markusse HM, Laar MA, Westhovens R, Denderen JC, *et al.* Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet (London, England) [Internet]. 1997; 350(9074):[309-18 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/381/CN-00142381/frame.html.
142. van Tuyl LH, Boers M, Lems WF, Landewe RB, Han H, van der Linden S, *et al.* Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. Ann Rheum Dis. 2010;69(5):807-12.
143. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, *et al.* Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum. 2005;52(11):3381-90.

144. de Jong PH, Hazes JM, Han HK, Huisman M, van Zeben D, van der Lubbe PA, *et al.* Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. Ann Rheum Dis. 2014;73(7):1331-9.
145. Rasch LA, van Tuyl LH, Lems WF, Boers M. Initial high-dose prednisolone combination therapy using COBRA and COBRA-light in early rheumatoid arthritis. Neuroimmunomodulation. 2015;22(1-2):51-6.
146. den Uyl D, ter Wee M, Boers M, Kerstens P, Voskuyl A, Nurmohamed M, *et al.* A non-inferiority trial of an attenuated combination strategy ('COBRA-light') compared to the original COBRA strategy: clinical results after 26 weeks. Ann Rheum Dis. 2014;73(6):1071-8.
147. Verschueren P, De Cock D, Corluy L, Joos R, Langenaken C, Taelman V, *et al.* Effectiveness of methotrexate with step-down glucocorticoid remission induction (COBRA Slim) versus other intensive treatment strategies for early rheumatoid arthritis in a treat-to-target approach: 1-year results of CareRA, a randomised pragmatic open-label superiority trial. Ann Rheum Dis. 2017;76(3):511-20.
148. ter Wee MM, den Uyl D, Boers M, Kerstens P, Nurmohamed M, van Schaardenburg D, *et al.* Intensive combination treatment regimens, including prednisolone, are effective in treating patients with early rheumatoid arthritis regardless of additional etanercept: 1-year results of the COBRA-light open-label, randomised, non-inferiority trial. Ann Rheum Dis. 2015;74(6):1233-40.
149. Safy M JJ, IJff ND, Bijlsma JWJ, van Laar JM, deHair MJH *et al.* Long-term outcome is better when a methotrexate-based treatment strategy is combined with 10 mg prednisone daily: follow-up after the second Computer-Assisted Management in Early Rheumatoid Arthritis trial. Ann Rheum Dis 2017; in press.
150. Landewe RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, *et al.* COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum. 2002;46(2):347-56.
151. Korthals-de Bos I, Van Tulder M, Boers M, Verhoeven AC, Ader HJ, Bibo J, *et al.* Indirect and total costs of early rheumatoid arthritis: a randomized comparison of combined step-down prednisolone, methotrexate, and sulfasalazine with sulfasalazine alone. J Rheumatol. 2004;31(9):1709-16.
152. Verschueren P, De Cock D, Corluy L, Joos R, Langenaken C, Taelman V, *et al.* Patients lacking classical poor prognostic markers might also benefit from a step-down glucocorticoid bridging scheme in early rheumatoid arthritis: week 16 results from the randomized multicenter CareRA trial. Arthritis Res Ther. 2015;17:97.
153. van Tuyl LH, Plass AM, Lems WF, Voskuyl AE, Kerstens PJ, Dijkmans BA, *et al.* Discordant perspectives of rheumatologists and patients on COBRA combination therapy in rheumatoid arthritis. Rheumatology (Oxford). 2008;47(10):1571-6.
154. Choy EH, Smith CM, Farewell V, Walker D, Hassell A, Chau L, *et al.* Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. Ann Rheum Dis. 2008;67(5):656-63.
155. Bakker MF, Jacobs JW, Welsing PM, Verstappen SM, Tekstra J, Ton E, *et al.* Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2012;156(5):329-39.

156. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M, *et al.* Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet. 1999;353(9164):1568-73.
157. Rantalaiho V, Korpela M, Laasonen L, Kautiainen H, Jarvenpaa S, Hannonen P, *et al.* Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. Arthritis Res Ther. 2010;12(3):R122.
158. Calguneri M, Pay S, Caliskaner Z, Apras S, Kiraz S, Ertenli I, *et al.* Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. Clin Exp Rheumatol. 1999;17(6):699-704.
159. Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe D, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying antirheumatic drugs for rheumatoid arthritis: abridged Cochrane systematic review and network meta-analysis. Bmj. 2016;353:i1777.
160. O'Dell JR, Leff R, Paulsen G, Haire C, Mallek J, Eckhoff PJ, *et al.* Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002;46(5):1164-70.
161. Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, *et al.* A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. Arthritis Rheum. 2012;64(9):2824-35.
162. van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF, *et al.* Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet. 2012;379(9827):1712-20.
163. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, *et al.* Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med. 2013;369(4):307-18.
164. McInnes IB, O'Dell JR. State-of-the-art: rheumatoid arthritis. Ann Rheum Dis. 2010;69(11):1898-906.
165. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HL, *et al.* Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Arthritis Rheum. 2011;63(10):2865-72.
166. Weinblatt ME. The role of current strategies in the future treatment of rheumatoid arthritis. Rheumatology (Oxford). 1999;38 Suppl 2:19-23.
167. Lie E, van der Heijde D, Uhlig T, Mikkelsen K, Kalstad S, Kaufmann C, *et al.* Treatment strategies in patients with rheumatoid arthritis for whom methotrexate monotherapy has failed: data from the NOR-DMARD register. Ann Rheum Dis. 2011;70(12):2103-10.
168. Heimans L, Wevers-de Boer KV, Visser K, Goekoop RJ, van Oosterhout M, Harbers JB, *et al.* A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. Ann Rheum Dis. 2014;73(7):1356-61.

169. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, *et al.* Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. N Engl J Med. 2017;376(7):652-62.
170. Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, *et al.* Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet. 2017;390(10093):457-68.
171. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, *et al.* Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-19.
172. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, *et al.* Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum. 2012;64(3):617-29.
173. Keystone EC, Taylor PC, Tanaka Y, Gaich C, DeLozier AM, Dudek A, *et al.* Patient-reported outcomes from a phase 3 study of baricitinib versus placebo or adalimumab in rheumatoid arthritis: secondary analyses from the RA-BEAM study. Ann Rheum Dis. 2017;76(11):1853-61.
174. Tanaka Y, Atsumi T, Amano K, Harigai M, Ishii T, Kawaguchi O, *et al.* Efficacy and safety of baricitinib in Japanese patients with rheumatoid arthritis: Subgroup analyses of four multinational phase 3 randomized trials. Mod Rheumatol. 2017:1-9.
175.Finckh A, Dehler S, Gabay C. The effectiveness of leflunomide as a co-therapy of tumour necrosis factor inhibitors in rheumatoid arthritis: a population-based study. Ann Rheum Dis. 2009;68(1):33-9.
176. Stefano R, Frati E, Nargi F, Baldi C, Menza L, Hammoud M, *et al.* Comparison of combination therapies in the treatment of rheumatoid arthritis: leflunomide-anti-TNF-alpha versus methotrexate-anti-TNF-alpha. Clinical rheumatology [Internet]. 2010; 29(5):[517-24 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/160/CN-00763160/frame.html.
177. Strangfeld A, Hierse F, Kekow J, von Hinueber U, Tony HP, Dockhorn R, *et al.* Comparative effectiveness of tumour necrosis factor alpha inhibitors in combination with either methotrexate or leflunomide. Ann Rheum Dis. 2009;68(12):1856-62.
178. Hyrich KL, Symmons DP, Watson KD, Silman AJ. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006;54(6):1786-94.
179. Manders SH, Kievit W, Jansen TL, Stolk JN, Visser H, Schilder AM, *et al.* Effectiveness of Tumor Necrosis Factor Inhibitors in Combination with Various csDMARD in the Treatment of Rheumatoid Arthritis: Data from the DREAM Registry. J Rheumatol. 2016;43(10):1787-94.
180. Chatzidionysiou K, Lie E, Nasonov E, Lukina G, Hetland ML, Tarp U, *et al.* Effectiveness of disease-modifying antirheumatic drug co-therapy with methotrexate and lefluno-

mide in rituximab-treated rheumatoid arthritis patients: results of a 1-year follow-up study from the CERERRA collaboration. Ann Rheum Dis. 2012;71(3):374-7.

181. Narvaez J, Diaz-Torne C, Magallares B, Hernandez MV, Reina D, Corominas H, *et al.* Comparative effectiveness of tocilizumab with either methotrexate or leflunomide in the treatment of rheumatoid arthritis. PLoS One. 2015;10(4):e0123392.
182. Richter A, Strangfeld A, Herzer P, Wilden E, Bussmann A, Listing J, *et al.* Sustainability of rituximab therapy in different treatment strategies: results of a 3-year followup of a German biologics register. Arthritis Care Res (Hoboken). 2014;66(11):1627-33.
183. Burmester GR, Kivitz AJ, Kupper H, Arulmani U, Florentinus S, Goss SL, *et al.* Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. Annals of the Rheumatic Diseases [Internet]. 2015; 74(6):[1037-44 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/356/CN-01083356/frame.html.
184. Kaeley GS, Evangelisto AM, Nishio MJ, Goss SL, Liu S, Kalabic J, *et al.* Methotrexate Dosage Reduction Upon Adalimumab Initiation: Clinical and Ultrasonographic Outcomes from the Randomized Noninferiority MUSICA Trial. J Rheumatol. 2016;43(8):1480-9.
185. Combe B, Furst DE, Keystone EC, van der Heijde D, Luijtens K, Ionescu L, *et al.* Certolizumab Pegol Efficacy Across Methotrexate Regimens: A Pre-Specified Analysis of Two Phase III Trials. Arthritis Care Res (Hoboken). 2016;68(3):299-307.
186. Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. Ann Rheum Dis. 2012;71(11):1914-5.
187. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, *et al.* Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998;41(9):1552-63.
188. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, *et al.* Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004;363(9410):675-81.
189. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, *et al.* The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54(1):26-37.
190. Nam JL, Ramiro S, Gaujoux-Viala C, Takase K, Leon-Garcia M, Emery P, *et al.* Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2014;73(3):516-28.
191. Burmester GR, Mariette X, Montecucco C, Monteagudo-Saez I, Malaise M, Tzioufas AG, *et al.* Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis. 2007;66(6):732-9.
192. Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg PA, Lems WF, Twisk JW, *et al.* Development of antidrug antibodies against adalimumab and asso-

ciation with disease activity and treatment failure during long-term follow-up. Jama. 2011;305(14):1460-8.

193. Combe B, Dasgupta B, Louw I, Pal S, Wollenhaupt J, Zerbini CA, *et al.* Efficacy and safety of golimumab as add-on therapy to disease-modifying antirheumatic drugs: results of the GO-MORE study. Ann Rheum Dis. 2014;73(8):1477-86.
194. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, *et al.* Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013;381(9877):1541-50.
195. Burmester GR, Lin Y, Patel R, van Adelsberg J, Mangan EK, Graham NM, *et al.* Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis. 2016;76(5):840-7.
196. Smolen JS, Burmester GR, Combe B, Curtis JR, Hall S, Haraoui B, *et al.* Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. Lancet. 2016;388(10061):2763-74.
197. Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, *et al.* Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum. 2013;65(1):28-38.
198. Fleischmann R, Weinblatt ME, Schiff M, Khanna D, Maldonado MA, Nadkarni A, *et al.* Patient-Reported Outcomes From a Two-Year Head-to-Head Comparison of Subcutaneous Abatacept and Adalimumab for Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016;68(7):907-13.
199. Jobanputra P, Maggs F, Deeming A, Carruthers D, Rankin E, Jordan AC, *et al.* A randomised efficacy and discontinuation study of etanercept versus adalimumab (RED SEA) for rheumatoid arthritis: a pragmatic, unblinded, non-inferiority study of first TNF inhibitor use: outcomes over 2 years. BMJ Open. 2012;12;2(6).
200. Porter D, van Melckebeke J, Dale J, Messow CM, McConnachie A, Walker A, *et al.* Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial. Lancet. 2016;388(10041):239-47.
201. Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, *et al.* Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. Arthritis Rheumatol. 2017;69(3):506-17.
202. Schiff M, Takeuchi T, Fleischmann R, Gaich CL, DeLozier AM, Schlichting D, *et al.* Patient-reported outcomes of baricitinib in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. Arthritis Res Ther. 2017;19(1):208.
203. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, *et al.* Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med. 2014;370(25):2377-86.

204. Strand V, Lee EB, Fleischmann R, Alten RE. Tofacitinib versus methotrexate in rheumatoid arthritis: patient-reported outcomes from the randomised phase III ORAL Start trial. 2016;2(2):e000308.
205. Conaghan PG, Ostergaard M, Bowes MA, Wu C, Fuerst T, van der Heijde D. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema, synovitis and bone erosion in methotrexate-naive, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. 2016;75(6):1024-33.
206. Colmegna I, Ohata BR, Menard HA. Current understanding of rheumatoid arthritis therapy. Clin Pharmacol Ther. 2012;91(4):607-20.
207. Fatimah N, Salim B, Nasim A, Hussain K, Gul H, Niazi S. Frequency of methotrexate intolerance in rheumatoid arthritis patients using methotrexate intolerance severity score (MISS questionnaire). Clinical Rheumatology. 2016;35(5):1341-5.
208. Nikiphorou E, Negoescu A, Fitzpatrick JD, Goudie CT, Badcock A, Ostor AJ, *et al.* Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort. Clin Rheumatol. 2014;33(5):609-14.
209. Gottenberg JE, Brocq O, Perdriger A, Lassoued S, Berthelot JM, Wendling D, *et al.* Non-TNF-Targeted Biologic vs a Second Anti-TNF Drug to Treat Rheumatoid Arthritis in Patients With Insufficient Response to a First Anti-TNF Drug: A Randomized Clinical Trial. Jama. 2016;316(11):1172-80.
210. Hirabara S, Takahashi N, Fukaya N, Miyake H, Yabe Y, Kaneko A, *et al.* Clinical efficacy of abatacept, tocilizumab, and etanercept in Japanese rheumatoid arthritis patients with inadequate response to anti-TNF monoclonal antibodies. Clin Rheumatol. 2014;33(9):1247-54.
211. Torrente-Segarra V, Acosta Pereira A, Morla R, Ruiz JM, Clavaguera T, Figuls R, *et al.* VARIAR Study: Assessment of short-term efficacy and safety of rituximab compared to an tumor necrosis factor alpha antagonists as second-line drug therapy in patients with rheumatoid arthritis refractory to a first tumor necrosis factor alpha antagonist. Reumatol Clin. 2016;12:319-22.
212. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010;376(9746):1094-108.
213. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, *et al.* Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum. 2010;62(1):22-32.
214. Schiff MH, Kempis J, Goldblum R, Tesser JR, Mueller RB. Rheumatoid arthritis secondary non-responders to TNF can attain an efficacious and safe response by switching to certolizumab pegol: a phase IV, randomised, multicentre, double-blind, 12-week study, followed by a 12-week open-label phase. Annals of the Rheumatic Diseases [Internet]. 2014; 73(12):[2174-7 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/018/CN-01048018/frame.html.
215. Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J, *et al.* Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis fac-

tor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009;374(9685):210-21.

216. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, *et al.* Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54(9):2793-806.
217. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, *et al.* IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67(11):1516-23.
218. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, *et al.* Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005;353(11):1114-23.
219. Chatzidionysiou K, van Vollenhoven RF. Rituximab versus anti-TNF in patients who previously failed one TNF inhibitor in an observational cohort. Scand J Rheumatol. 2013;42(3):190-5.
220. Emery P, Gottenberg JE, Rubbert-Roth A, Sarzi-Puttini P, Choquette D, Taboada VM, *et al.* Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. Ann Rheum Dis. 2015;74(6):979-84.
221. Harrold LR, Reed GW, Kremer JM, Curtis JR, Solomon DH, Hochberg MC, *et al.* The comparative effectiveness of abatacept versus anti-tumour necrosis factor switching for rheumatoid arthritis patients previously treated with an anti-tumour necrosis factor. Ann Rheum Dis. 2015;74(2):430-6.
222. Manders SH, Kievit W, Adang E, Brus HL, Moens HJ, Hartkamp A, *et al.* Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. Arthritis Res Ther. 2015;17:134.
223. Soliman MM, Hyrich KL, Lunt M, Watson KD, Symmons DP, Ashcroft DM. Rituximab or a second anti-tumor necrosis factor therapy for rheumatoid arthritis patients who have failed their first anti-tumor necrosis factor therapy? Comparative analysis from the British Society for Rheumatology Biologics Register. Arthritis Care Res (Hoboken). 2012;64(8):1108-15.
224. Finckh A, Ciurea A, Brulhart L, Kyburz D, Moller B, Dehler S, *et al.* B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum. 2007;56(5):1417-23.
225. Finckh A, Ciurea A, Brulhart L, Moller B, Walker UA, Courvoisier D, *et al.* Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis. 2010;69(2):387-93.
226. Finckh A, Moller B, Dudler J, Walker UA, Kyburz D, Gabay C. Evolution of radiographic joint damage in rituximab-treated versus TNF-treated rheumatoid arthritis cases with inadequate response to TNF antagonists. Ann Rheum Dis. 2012;71(10):1680-5.

227. Gomez-Reino JJ, Maneiro JR, Ruiz J, Rosello R, Sanmarti R, Romero AB. Comparative effectiveness of switching to alternative tumour necrosis factor (TNF) antagonists versus switching to rituximab in patients with rheumatoid arthritis who failed previous TNF antagonists: the MIRAR Study. Ann Rheum Dis. 2012;71(11):1861-4.
228. Harrold LR, Reed GW, Magner R, Shewade A, John A, Greenberg JD, *et al.* Comparative effectiveness and safety of rituximab versus subsequent anti-tumor necrosis factor therapy in patients with rheumatoid arthritis with prior exposure to anti-tumor necrosis factor therapies in the United States Corrona registry. Arthritis Res Ther. 2015;17:256.
229. Chatzidionysiou K, Askling J, Eriksson J, Kristensen LE, van Vollenhoven R. Effectiveness of TNF inhibitor switch in RA: results from the national Swedish register. Ann Rheum Dis. 2015;74(5):890-6.
230. Lee YH, Bae SC. Comparative efficacy and safety of tocilizumab, rituximab, abatacept and tofacitinib in patients with active rheumatoid arthritis that inadequately responds to tumor necrosis factor inhibitors: A Bayesian network meta-analysis of randomized controlled trials. International Journal of Rheumatic Diseases. 2016.
231. Singh JA, Hossain A, Tanjong Ghogomu E, Mudano AS, Maxwell LJ, Buchbinder R, *et al.* Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics: a systematic review and network meta-analysis. Cochrane Database Syst Rev. 2017;3:Cd012591.
232. Vieira MC, Zwillich SH, Jansen JP, Smiechowski B, Spurden D, Wallenstein GV. Tofacitinib versus biologic treatments in patients with active rheumatoid arthritis who have had an inadequate response to tumor necrosis factor inhibitors: results from a network meta-analysis. Clinical Therapeutics. 2016;38(12):2628-41.e5.
233. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, *et al.* Baricitinib in Patients with Refractory Rheumatoid Arthritis. N Engl J Med. 2016;374(13):1243-52.
234. Spanish Society of Rehabilitation and Physical Medicine (SERMEF). Manual SERMEF de Rehabilitación y Medicina Física. 1º Edición. Spain: Panamericana; 2006. Capítulo 19. p 263-271.
235. Cramp F, Hewlett S, Almeida C, Kirwan JR, Choy EH, Chalder T, *et al.* Non-pharmacological interventions for fatigue in rheumatoid arthritis. Cochrane Database Syst Rev. 2013(8):Cd008322.
236. Robinson V, Brosseau L, Casimiro L, Judd M, Shea B, Wells G, *et al.* Thermotherapy for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2002(2):Cd002826.
237. Brosseau L, Judd MG, Marchand S, Robinson VA, Tugwell P, Wells G, *et al.* Transcutaneous electrical nerve stimulation (TENS) for the treatment of rheumatoid arthritis in the hand. Cochrane Database Syst Rev. 2003(3):Cd004377.
238. Brosseau L, Robinson V, Wells G, Debie R, Gam A, Harman K, *et al.* Low level laser therapy (Classes I, II and III) for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2005(4):Cd002049.
239. Steultjens EM, Dekker J, Bouter LM, van Schaardenburg D, van Kuyk MA, van den Ende CH. Occupational therapy for rheumatoid arthritis. Cochrane Database Syst Rev. 2004(1):Cd003114.
240. Macedo AM, Oakley SP, Panayi GS, Kirkham BW. Functional and work outcomes improve in patients with rheumatoid arthritis who receive targeted, comprehensive occupational therapy. Arthritis Rheum. 2009;61(11):1522-30.

241. Chalmers AC, Busby C, Goyert J, Porter B, Schulzer M. Metatarsalgia and rheumatoid arthritis--a randomized, single blind, sequential trial comparing 2 types of foot orthoses and supportive shoes. J Rheumatol. 2000;27(7):1643-7.
242. Lamb SE, Williamson EM, Heine PJ, Adams J, Dosanjh S, Dritsaki M, *et al.* Exercises to improve function of the rheumatoid hand (SARAH): a randomised controlled trial. Lancet. 2015;385(9966):421-9.
243. Hollander JL, Jessar RA, Brown EM, Jr. Intra-synovial corticosteroid therapy: a decade of use. Bull Rheum Dis. 1961;11:239-40.
244. Naredo E, Cabero F, Beneyto P, Cruz A, Mondejar B, Uson J, *et al.* A randomized comparative study of short term response to blind injection versus sonographic-guided injection of local corticosteroids in patients with painful shoulder. J Rheumatol. 2004;31(2):308-14.
245. McCarty DJ, Harman JG, Grassanovich JL, Qian C. Treatment of rheumatoid joint inflammation with intrasynovial triamcinolone hexacetonide. J Rheumatol. 1995;22(9):1631-5.
246. Blyth T, Hunter JA, Stirling A. Pain relief in the rheumatoid knee after steroid injection. A single-blind comparison of hydrocortisone succinate, and triamcinolone acetonide or hexacetonide. Br J Rheumatol. 1994;33(5):461-3.
247. Chakravarty K, Pharoah PD, Scott DG. A randomized controlled study of post-injection rest following intra-articular steroid therapy for knee synovitis. Br J Rheumatol. 1994;33(5):464-8.
248. Guillen Astete C, Boteanu A, Medina Quinones C, Garcia Montes N, Roldan Moll F, Carballo Carmano C, *et al.* Is it safe to perform joint infiltrations or aspirations in patients anticoagulated with acenocoumarol? Reumatol Clin. 2015;11(1):9-11.
249. Thumboo J, O'Duffy JD. A prospective study of the safety of joint and soft tissue aspirations and injections in patients taking warfarin sodium. Arthritis Rheum. 1998;41(4):736-9.
250. Slotkoff A, Clauw D, Nashel D. Effects of soft tissue corticosteroid injection on glucose control in diabetes. Arthritis Rheum 1994; 34 (Supl 6): 347. 1994.
251. Hartmann H. [Arthrocentesis in rheumatology practice]. Tidsskr Nor Laegeforen. 2000;120(7):800-2.
252. Seror P, Pluvinage P, d'Andre FL, Benamou P, Attuil G. Frequency of sepsis after local corticosteroid injection (an inquiry on 1160000 injections in rheumatological private practice in France). Rheumatology (Oxford). 1999;38(12):1272-4.
253. Owen D. Aspiration and injection of joint and soft tissues. In: Kelly W, Harris E, Ruddy S, Sledge C, editors. Textbook of Rheumatology: Philadelphia: WB Saunders Company, 1997; 591-608.; 1997.
254. Bessant R, Steuer A, Rigby S, Gumpel M. Osmic acid revisited: factors that predict a favourable response. Rheumatology (Oxford). 2003;42(9):1036-43.
255. Jahangier ZN, Jacobs JW, Lafeber FP, Moolenburgh JD, Swen WA, Bruyn GA, *et al.* Is radiation synovectomy for arthritis of the knee more effective than intraarticular treatment with glucocorticoids? Results of an eighteen-month, randomized, double-blind, placebo-controlled, crossover trial. Arthritis Rheum. 2005;52(11):3391-402.
256. Liepe K, Zaknun JJ, Padhy A, Barrenechea E, Soroa V, Shrikant S, *et al.* Radiosynovectomy using yttrium-90, phosphorus-32 or rhenium-188 radiocolloids versus corticoid instillation for rheumatoid arthritis of the knee. Ann Nucl Med. 2011;25(5):317-23.

257. Kapetanovic MC, Lindqvist E, Saxne T, Eberhardt K. Orthopaedic surgery in patients with rheumatoid arthritis over 20 years: prevalence and predictive factors of large joint replacement. Ann Rheum Dis. 2008;67(10):1412-6.
258. Louie GH, Ward MM. Changes in the rates of joint surgery among patients with rheumatoid arthritis in California, 1983-2007. Ann Rheum Dis. 2010;69(5):868-71.
259. Creighton MG, Callaghan JJ, Olejniczak JP, Johnston RC. Total hip arthroplasty with cement in patients who have rheumatoid arthritis. A minimum ten-year follow-up study. J Bone Joint Surg Am. 1998;80(10):1439-46.
260. Grauer JN, Tingstad EM, Rand N, Christie MJ, Hilibrand AS. Predictors of paralysis in the rheumatoid cervical spine in patients undergoing total joint arthroplasty. J Bone Joint Surg Am. 2004;86-a(7):1420-4.
261. Luessenhop CP, Higgins LD, Brause BD, Ranawat CS. Multiple prosthetic infections after total joint arthroplasty. Risk factor analysis. J Arthroplasty. 1996;11(7):862-8.
262. Ravi B, Croxford R, Hollands S, Paterson JM, Bogoch E, Kreder H, *et al.* Increased risk of complications following total joint arthroplasty in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014;66(2):254-63.
263. Schrama JC, Espehaug B, Hallan G, Engesaeter LB, Furnes O, Havelin LI, *et al.* Risk of revision for infection in primary total hip and knee arthroplasty in patients with rheumatoid arthritis compared with osteoarthritis: a prospective, population-based study on 108,786 hip and knee joint arthroplasties from the Norwegian Arthroplasty Register. Arthritis Care Res (Hoboken). 2010;62(4):473-9.
264. Ogilvie-Harris DJ, Basinski A. Arthroscopic synovectomy of the knee for rheumatoid arthritis. Arthroscopy. 1991;7(1):91-7.
265. Ishikawa H, Ohno O, Hirohata K. Long-term results of synovectomy in rheumatoid patients. J Bone Joint Surg Am. 1986;68(2):198-205.
266. Doets HC, Bierman BT, von Soesbergen RM. Synovectomy of the rheumatoid knee does not prevent deterioration. 7-year follow-up of 83 cases. Acta Orthop Scand. 1989;60(5):523-5.
267. Zwartele RE, Witjes S, Doets HC, Stijnen T, Poll RG. Cementless total hip arthroplasty in rheumatoid arthritis: a systematic review of the literature. Arch Orthop Trauma Surg. 2012;132(4):535-46.
268. Loza E, Lajas C, Andreu JL, Balsa A, Gonzalez-Alvaro I, Illera O, *et al.* Consensus statement on a framework for the management of comorbidity and extra-articular manifestations in rheumatoid arthritis. Rheumatol Int. 2015;35(3):445-58.
269. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, *et al.* Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Ann Rheum Dis. 2014;73(1):62-8.
270. Theander L, Nyhall-Wahlin BM, Nilsson JA, Willim M, Jacobsson LTH, Petersson IF, *et al.* Severe extraarticular manifestations in a community-based cohort of patients with rheumatoid arthritis: Risk factors and incidence in relation to treatment with tumor necrosis factor inhibitors. J Rheumatol. 2017;44(7):981-7.
271. Haga HJ, Naderi Y, Moreno AM, Peen E. A study of the prevalence of sicca symptoms and secondary Sjogren's syndrome in patients with rheumatoid arthritis, and its association to disease activity and treatment profile. Int J Rheum Dis. 2012;15(3):284-8.

272. Santosh K, Dhir V, Singh S, Sood A, Gupta A, Sharma A, *et al.* Prevalence of secondary Sjogren's syndrome in Indian patients with rheumatoid arthritis: a single-center study. Int J Rheum Dis. 2017;20(7):870-4.
273. Moller B, Scherer A, Forger F, Villiger PM, Finckh A. Anaemia may add information to standardised disease activity assessment to predict radiographic damage in rheumatoid arthritis: a prospective cohort study. Ann Rheum Dis. 2014;73(4):691-6.
274. Ayvaz OC, Yavasoglu I, Kadikoylu G, Bozkurt G, Bolaman Z. Thrombocytosis in rheumatoid arthritis: JAK2V617F-positive essential thrombocythemia. Rheumatol Int. 2012;32(1):269-71.
275. Narvaez J, Domingo-Domenech E, Gomez-Vaquero C, Lopez-Vives L, Estrada P, Aparicio M, *et al.* Biological agents in the management of Felty's syndrome: a systematic review. Semin Arthritis Rheum. 2012;41(5):658-68.
276. Kelly C, Iqbal K, Iman-Gutierrez L, Evans P, Manchegowda K. Lung involvement in inflammatory rheumatic diseases. Best Pract Res Clin Rheumatol. 2016;30(5):870-88.
277. Mavrogeni S, Dimitroulas T, Sfikakis PP, Kitas GD. Heart involvement in rheumatoid arthritis: multimodality imaging and the emerging role of cardiac magnetic resonance. Semin Arthritis Rheum. 2013;43(3):314-24.
278. Tong L, Thumboo J, Tan YK, Wong TY, Albani S. The eye: a window of opportunity in rheumatoid arthritis? Nat Rev Rheumatol. 2014;10(9):552-60.
279. Murray PI, Rauz S. The eye and inflammatory rheumatic diseases: The eye and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis. Best Pract Res Clin Rheumatol. 2016;30(5):802-25.
280. Couderc M, Tatar Z, Pereira B, Tiple A, Gilson M, Fautrel B, *et al.* Prevalence of Renal Impairment in Patients with Rheumatoid Arthritis: Results from a Cross-Sectional Multicenter Study. Arthritis Care and Research. 2016;68(5):638-44.
281. Mori S, Yoshitama T, Hirakata N, Ueki Y. Prevalence of and factors associated with renal dysfunction in rheumatoid arthritis patients: a cross-sectional study in community hospitals. Clin Rheumatol. 2017;36(12):2673-82.
282. Radic M, Martinovic Kaliterna D, Radic J. Overview of vasculitis and vasculopathy in rheumatoid arthritis--something to think about. Clin Rheumatol. 2013;32(7):937-42.
283. Pamuk ÖN, Kalyoncu U, Aksu K, Omma A, Pehlivan Y, Çağatay Y, *et al.* A multicenter report of biologic agents for the treatment of secondary amyloidosis in Turkish rheumatoid arthritis and ankylosing spondylitis patients. Rheumatology International. 2016;36(7):945-53.
284. Balsa A, Lojo-Oliveira L, Alperi-Lopez M, Garcia-Manrique M, Ordonez-Canizares C, Perez L, *et al.* Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring in clinical practice: The Spanish Cohort of the COMORA Study. Reumatol Clin. 2017.
285. Ranganath VK, Maranian P, Elashoff DA, Woodworth T, Khanna D, Hahn T, *et al.* Comorbidities are associated with poorer outcomes in community patients with rheumatoid arthritis. Rheumatology (Oxford). 2013;52(10):1809-17.
286. Aurrecoechea E, Llorca Diaz J, Diez Lizuain ML, McGwin G, Jr., Calvo-Alen J. Gender-associated comorbidities in rheumatoid arthritis and their impact on outcome: data from GENIRA. Rheumatol Int. 2017;37(4):479-85.

287. Radner H, Yoshida K, Hmamouchi I, Dougados M, Smolen JS, Solomon DH. Treatment patterns of multimorbid patients with rheumatoid arthritis: Results from an international cross-sectional study. J Rheumatol. 2015;42(7):1099-104.
288. van den Hoek J, Boshuizen HC, Roorda LD, Tijhuis GJ, Nurmohamed MT, Dekker J, *et al.* Association of somatic comorbidities and comorbid depression with mortality in patients with rheumatoid arthritis: A 14-Year prospective cohort study. Arthritis Care Res (Hoboken). 2016;68(8):1055-60.
289. Baillet A, Gossec L, Carmona L, Wit M, van Eijk-Hustings Y, Bertheussen H, *et al.* Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Ann Rheum Dis. 2016;75(6):965-73.
290. Gossec L, Baillet A, Dadoun S, Daien C, Berenbaum F, Dernis E, *et al.* Collection and management of selected comorbidities and their risk factors in chronic inflammatory rheumatic diseases in daily practice in France. Joint Bone Spine. 2016;83(5):501-9.
291. Chen DY, Chen YM, Hsieh TY, Hung WT, Hsieh CW, Chen HH, *et al.* Drug trough levels predict therapeutic responses to dose reduction of adalimumab for rheumatoid arthritis patients during 24 weeks of follow-up. Rheumatology (Oxford). 2016;55(1):143-8.
292. Plasencia C, Wolbink G, Krieckaert CL, Kneepkens EL, Turk S, Jurado T, *et al.* Comparing a tapering strategy to the standard dosing regimen of TNF inhibitors in rheumatoid arthritis patients with low disease activity. Clin Exp Rheumatol. 2016;34(4):655-62.
293. Fautrel B, Pham T, Alfaiate T, Gandjbakhch F, Foltz V, Morel J, *et al.* Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: Results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study). Annals of the Rheumatic Diseases [Internet]. 2016; 75(1):[59-67 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/209/CN-01134209/frame.html.
294. van Herwaarden N, van der Maas A, Minten MJ, van den Hoogen FH, Kievit W, van Vollenhoven RF, *et al.* Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. BMJ. 2015;350:h1389.
295. van Herwaarden N, Herfkens-Hol S, van der Maas A, van den Bemt BJ, van Vollenhoven RF, Bijlsma JW, *et al.* Dose reduction of tocilizumab in rheumatoid arthritis patients with low disease activity. Clin Exp Rheumatol. 2014;32(3):390-4.
296. Westhovens R, Robles M, Ximenes AC, Wollenhaupt J, Durez P, Gomez-Reino J, *et al.* Maintenance of remission following 2 years of standard treatment then dose reduction with abatacept in patients with early rheumatoid arthritis and poor prognosis. Annals of the Rheumatic Diseases [Internet]. 2015; 74(3):[564-8 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/730/CN-01047730/frame.html.
297. González-Álvaro I, Martínez-Fernández C, Dorantes-Calderón B, García-Vicuña R, Hernández-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 (United Kingdom). 2015;54(7):1200-9.

298. Emery P, Hammoudeh M, FitzGerald O, Combe B, Martin-Mola E, Buch MH, *et al.* Sustained remission with etanercept tapering in early rheumatoid arthritis. N Engl J Med. 2014;371(19):1781-92.
299. Wiland P, Dudler J, Veale D, Tahir H, Pedersen R, Bukowski J, *et al.* The Effect of Reduced or Withdrawn Etanercept-methotrexate Therapy on Patient-reported Outcomes in Patients with Early Rheumatoid Arthritis. J Rheumatol. 2016;43(7):1268-77.
300. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, *et al.* Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet. 2013;381(9870):918-29.
301. Pavelka K, Burgos-Vargas R, Miranda P, Guzman R, Yen JH, Izzi MA, *et al.* Etanercept in moderate rheumatoid arthritis: PRESERVE study results from central/eastern Europe, Latin America and Asia. International Journal of Clinical Rheumatology [Internet]. 2014; 9(5)(5):[415-30 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/470/CN-01037470/frame.html.
302. van Vollenhoven RF, Ostergaard M, Leirisalo-Repo M, Uhlig T, Jansson M, Larsson E, *et al.* Full dose, reduced dose or discontinuation of etanercept in rheumatoid arthritis. Ann Rheum Dis. 2016;75(1):52-8.
303. Raffeiner B, Botsios C, Ometto F, Bernardi L, Stramare R, Todesco S, *et al.* Effects of half dose etanercept (25 mg once a week) on clinical remission and radiographic progression in patients with rheumatoid arthritis in clinical remission achieved with standard dose. Clinical and Experimental Rheumatology [Internet]. 2015; 33(1):[63-8 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/487/CN-01090487/frame.html.
304. Marks JL, Holroyd CR, Dimitrov BD, Armstrong RD, Calogeras A, Cooper C, *et al.* Does combined clinical and ultrasound assessment allow selection of individuals with rheumatoid arthritis for sustained reduction of anti-tumor necrosis factor therapy? Arthritis Care Res (Hoboken). 2015;67(6):746-53.
305. Epis O, Casu C, Belloli L, Schito E, Filippini D, Muscara M, *et al.* Reduced dose of tocilizumab for the maintenance of remission in patients with rheumatoid arthritis: a clinical experience. Rheumatol Int. 2015;35(9):1569-70.
306. Haschka J, Englbrecht M, Hueber AJ, Manger B, Kleyer A, Reiser M, *et al.* Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping antirheumatic therapy: Interim results from the prospective randomised controlled RETRO study. Annals of the Rheumatic Diseases [Internet]. 2016; 75(1):[45-51 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/127/CN-01134127/frame.html.
307. Inciarte-Mundo J, Hernandez MV, Rosario V, Ruiz-Esquide V, Cabrera-Villalba S, Ramirez J, *et al.* Reduction of biological agent dose in rheumatic diseases: descriptive analysis of 153 patients in clinical practice conditions. Reumatol Clin. 2014;10(1):10-6.
308. Maneiro JR, Perez-Pampin E, Salgado E, Carmona L, Gomez-Reino JJ. Observational study of optimization of biologic therapies in rheumatoid arthritis: a single-centre experience. Rheumatol Int. 2014;34(8):1059-63.
309. Naredo E, Valor L, De la Torre I, Montoro M, Bello N, Martinez-Barrio J, *et al.* Predictive value of Doppler ultrasound-detected synovitis in relation to failed tapering of biologic therapy in patients with rheumatoid arthritis. Rheumatology (Oxford). 2015;54(8):1408-14.

310. Rodriguez-Rodriguez L, Leon L, Lamas JR, Gomez A, Vadillo C, Blanco M, *et al.* Dose down-titration of biological DMARDs in patients with rheumatoid arthritis over time and in daily clinical practice. Clin Exp Rheumatol. 2016;34(5):872-9.
311. Bredemeier M, de Oliveira FK, Rocha CM. Low- versus high-dose rituximab for rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2014;66(2):228-35.
312. Bredemeier M, Campos GG, de Oliveira FK. Updated systematic review and meta-analysis of randomized controlled trials comparing low- versus high-dose rituximab for rheumatoid arthritis. Clin Rheumatol. 2015;34(10):1801-5.
313. Lopez-Olivo MA, Amezaga Urruela M, McGahan L, Pollono EN, Suarez-Almazor ME. Rituximab for rheumatoid arthritis. Cochrane Database Syst Rev. 2015;1:Cd007356.
314. Teng YK, Tekstra J, Breedveld FC, Lafeber F, Bijlsma JW, van Laar JM. Rituximab fixed retreatment versus on-demand retreatment in refractory rheumatoid arthritis: comparison of two B cell depleting treatment strategies. Ann Rheum Dis. 2009;68(6):1075-7.
315. Chatzidionysiou K, Lie E, Lukina G, Hetland ML, Hauge EM, Pavelka K, *et al.* Rituximab Retreatment in Rheumatoid Arthritis in a Real-life Cohort: Data from the CERERRA Collaboration. J Rheumatol. 2017;44(2):162-9.
316. Emery P, Mease PJ, Rubbert-Roth A, Curtis JR, ller-Ladner U, Gaylis NB, *et al.* Retreatment with rituximab based on a treatment-to-target approach provides better disease control than treatment as needed in patients with rheumatoid arthritis: a retrospective pooled analysis. Rheumatology (Oxford, England) [Internet]. 2011; 50(12):[2223-32 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/786/CN-00805786/frame.html.
317. Goodson N, Marks J, Lunt M, Symmons D. Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. Ann Rheum Dis. 2005;64(11):1595-601.
318. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, *et al.* Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation. 2003;107(9):1303-7.
319. Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid arthritis: a disease associated with accelerated atherogenesis. Semin Arthritis Rheum. 2005;35(1):8-17.
320. del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum. 2001;44(12):2737-45.
321. Gonzalez-Gay MA, Gonzalez-Juanatey C, Lopez-Diaz MJ, Pineiro A, Garcia-Porrua C, Miranda-Filloy JA, *et al.* HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. Arthritis Rheum. 2007;57(1):125-32.
322. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, *et al.* The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum. 2005;52(2):412-20.
323. Gonzalez-Gay MA, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Martin J, Llorca J. Endothelial dysfunction, carotid intima-media thickness, and accelerated atherosclerosis in rheumatoid arthritis. Semin Arthritis Rheum. 2008;38(2):67-70.

324. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, Garcia-Porrua C, Llorca J, Ollier WE, *et al.* Echocardiographic and Doppler findings in long-term treated rheumatoid arthritis patients without clinically evident cardiovascular disease. Semin Arthritis Rheum. 2004;33(4):231-8.
325. Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Inflammation and endothelial dysfunction in rheumatoid arthritis. Clin Exp Rheumatol. 2006;24(2):115-7.
326. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, Garcia-Porrua C, Llorca J, Vidan J, *et al.* HLA-DRB1 status affects endothelial function in treated patients with rheumatoid arthritis. Am J Med. 2003;114(8):647-52.
327. Vaudo G, Marchesi S, Gerli R, Allegrucci R, Giordano A, Siepi D, *et al.* Endothelial dysfunction in young patients with rheumatoid arthritis and low disease activity. Ann Rheum Dis. 2004;63(1):31-5.
328. Gonzalez-Juanatey C, Llorca J, Testa A, Revuelta J, Garcia-Porrua C, Gonzalez-Gay MA. Increased prevalence of severe subclinical atherosclerotic findings in long-term treated rheumatoid arthritis patients without clinically evident atherosclerotic disease. Medicine (Baltimore). 2003;82(6):407-13.
329. Gonzalez-Gay MA, Gonzalez-Juanatey C, Pineiro A, Garcia-Porrua C, Testa A, Llorca J. High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. J Rheumatol. 2005;32(7):1219-23.
330. Gonzalez-Juanatey C, Llorca J, Martin J, Gonzalez-Gay MA. Carotid intima-media thickness predicts the development of cardiovascular events in patients with rheumatoid arthritis. Semin Arthritis Rheum. 2009;38(5):366-71.
331. Evans MR, Escalante A, Battafarano DF, Freeman GL, O'Leary DH, del Rincon I. Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. Arthritis Rheum. 2011;63(5):1211-20.
332. Chung CP, Oeser A, Raggi P, Gebretsadik T, Shintani AK, Sokka T, *et al.* Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. Arthritis Rheum. 2005;52(10):3045-53.
333. Krishnan E, Lingala VB, Singh G. Declines in mortality from acute myocardial infarction in successive incidence and birth cohorts of patients with rheumatoid arthritis. Circulation. 2004;110(13):1774-9.
334. Krause D, Schleusser B, Herborn G, Rau R. Response to methotrexate treatment is associated with reduced mortality in patients with severe rheumatoid arthritis. Arthritis Rheum. 2000;43(1):14-21.
335. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. Lancet. 2002;359(9313):1173-7.
336. Carmona L, Descalzo MA, Perez-Pampin E, Ruiz-Montesinos D, Erra A, Cobo T, *et al.* All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Ann Rheum Dis. 2007;66(7):880-5.
337. Hurlimann D, Forster A, Noll G, Enseleit F, Chenevard R, Distler O, *et al.* Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. Circulation. 2002;106(17):2184-7.
338. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, Garcia-Porrua C, Llorca J, Gonzalez-Gay MA. Active but transient improvement of endothelial function in rheumatoid arthritis

patients undergoing long-term treatment with anti-tumor necrosis factor alpha antibody. Arthritis Rheum. 2004;51(3):447-50.

339. Gonzalez-Juanatey C, Llorca J, Sanchez-Andrade A, Garcia-Porrua C, Martin J, Gonzalez-Gay MA. Short-term adalimumab therapy improves endo-thelial function in patients with rheumatoid arthritis refractory to infliximab. Clin Exp Rheumatol. 2006;24(3):309-12.
340. Gonzalez-Juanatey C, Llorca J, Vazquez-Rodriguez TR, Diaz-Varela N, Garcia-Quiroga H, Gonzalez-Gay MA. Short-term improvement of endothelial function in rituximab-treated rheumatoid arthritis patients refractory to tumor necrosis factor alpha blocker therapy. Arthritis Rheum. 2008;59(12):1821-4.
341. Gonzalez-Juanatey C, Llorca J, Garcia-Porrua C, Martin J, Gonzalez-Gay MA. Effect of anti-tumor necrosis factor alpha therapy on the progression of subclinical atherosclerosis in severe rheumatoid arthritis. Arthritis Rheum. 2006;55(1):150-3.
342. Del Porto F, Lagana B, Lai S, Nofroni I, Tinti F, Vitale M, *et al.* Response to anti-tumour necrosis factor alpha blockade is associated with reduction of carotid intima-media thickness in patients with active rheumatoid arthritis. Rheumatology (Oxford). 2007;46(7):1111-5.
343. Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor alpha therapy and cardiovascular events in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2011;63(4):522-9.
344. Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, Tsao P, *et al.* Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70(4):576-82.
345. Ruiz-Limon P, Ortega R, Arias de la Rosa I, Abalos-Aguilera MDC, Perez-Sanchez C, Jimenez-Gomez Y, *et al.* Tocilizumab improves the proatherothrombotic profile of rheumatoid arthritis patients modulating endothelial dysfunction, NETosis, and inflammation. Transl Res. 2017;183:87-103.
346. Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, *et al.* Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis. 2017;76(7):1253-62.
347. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, *et al.* EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis. 2017;76(1):17-28.
348. Avina-Zubieta JA, Abrahamowicz M, De Vera MA, Choi HK, Sayre EC, Rahman MM, *et al.* Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study. Rheumatology (Oxford). 2013;52(1):68-75.
349. McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakov O, Ford I, *et al.* Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet. 2004;363(9426):2015-21.
350. Hermann F, Forster A, Chenevard R, Enseleit F, Hurlimann D, Corti R, *et al.* Simvastatin improves endothelial function in patients with rheumatoid arthritis. J Am Coll Cardiol. 2005;45(3):461-4.

351. Rollefstad S, Ikdahl E, Hisdal J, Olsen IC, Holme I, Hammer HB, *et al.* Rosuvastatin-induced carotid plaque regression in patients with inflammatory joint diseases: The Rosuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and Other Inflammatory Joint Diseases Study. Arthritis Rheumatol. 2015;67(7):1718-28.
352. Gil-Guillen V, Orozco-Beltran D, Maiques-Galan A, Aznar-Vicente J, Navarro J, Cea-Calvo L, *et al.* [Agreement between REGICOR and SCORE scales in identifying high cardiovascular risk in the Spanish population]. Rev Esp Cardiol. 2007;60(10):1042-50.
353. van Halm VP, Peters MJ, Voskuyl AE, Boers M, Lems WF, Visser M, *et al.* Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease: a cross-sectional study, the CARRE Investigation. Ann Rheum Dis. 2009;68(9):1395-400.
354. Sihvonen S, Korpela M, Mustila A, Mustonen J. The predictive value of rheumatoid factor isotypes, anti-cyclic citrullinated peptide antibodies, and antineutrophil cytoplasmic antibodies for mortality in patients with rheumatoid arthritis. J Rheumatol. 2005;32(11):2089-94.
355. Snir O, Widhe M, von Spee C, Lindberg J, Padyukov L, Lundberg K, *et al.* Multiple antibody reactivities to citrullinated antigens in sera from patients with rheumatoid arthritis: association with HLA-DRB1 alleles. Ann Rheum Dis. 2009;68(5):736-43.
356. Gomez-Vaquero C, Corrales A, Zacarias A, Rueda-Gotor J, Blanco R, Gonzalez-Juanatey C, *et al.* SCORE and REGICOR function charts underestimate the cardiovascular risk in Spanish patients with rheumatoid arthritis. Arthritis Res Ther. 2013;15(4):R91.
357. Corrales A, Dessein PH, Tsang L, Pina T, Blanco R, Gonzalez-Juanatey C, *et al.* Carotid artery plaque in women with rheumatoid arthritis and low estimated cardiovascular disease risk: a cross-sectional study. Arthritis Res Ther. 2015;17:55.
358. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, *et al.* 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J. 2016;37(39):2999-3058.
359. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, *et al.* Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2010;62(6):1583-91.
360. Koduri G, Norton S, Young A, Cox N, Davies P, Devlin J, *et al.* Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. Rheumatology (Oxford). 2010;49(8):1483-9.
361. Sokka T, Kautiainen H, Toloza S, Makinen H, Verstappen SM, Lund Hetland M, *et al.* QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Ann Rheum Dis. 2007;66(11):1491-6.
362. Habib HM, Eisa AA, Arafat WR, Marie MA. Pulmonary involvement in early rheumatoid arthritis patients. Clin Rheumatol. 2011;30(2):217-21.
363. Wilsher M, Voight L, Milne D, Teh M, Good N, Kolbe J, *et al.* Prevalence of airway and parenchymal abnormalities in newly diagnosed rheumatoid arthritis. Respir Med. 2012;106(10):1441-6.
364. Gabbay E, Tarala R, Will R, Carroll G, Adler B, Cameron D, *et al.* Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med. 1997;156(2 Pt 1):528-35.
365. Robles-Perez A, Luburich P, Rodriguez-Sanchon B, Dorca J, Nolla JM, Molina-Molina M, *et al.* Preclinical lung disease in early rheumatoid arthritis. Chron Respir Dis. 2016;13(1):75-81.

366. Yunt ZX, Solomon JJ. Lung disease in rheumatoid arthritis. Rheum Dis Clin North Am. 2015;41(2):225-36.
367. Kelly CA, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN, *et al.* Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics--a large multicentre UK study. Rheumatology (Oxford). 2014;53(9):1676-82.
368. Zhu J, Zhou Y, Chen X, Li J. A metaanalysis of the increased risk of rheumatoid arthritis-related pulmonary disease as a result of serum anticitrullinated protein antibody positivity. J Rheumatol. 2014;41(7):1282-9.
369. Lee YS, Kim HC, Lee BY, Lee CK, Kim MY, Jang SJ, *et al.* The Value of Biomarkers as Predictors of Outcome in Patients with Rheumatoid Arthritis-Associated Usual Interstitial Pneumonia. Sarcoidosis Vasc Diffuse Lung Dis. 2016;33(3):216-23.
370. Mink SN, Maycher B. Comparative manifestations and diagnostic accuracy of high-resolution computed tomography in usual interstitial pneumonia and nonspecific interstitial pneumonia. Curr Opin Pulm Med. 2012;18(5):530-4.
371. Solomon JJ, Chung JH, Cosgrove GP, Demoruelle MK, Fernandez-Perez ER, Fischer A, *et al.* Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2016;47(2):588-96.
372. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Patterns of interstitial lung disease and mortality in rheumatoid arthritis. Rheumatology (Oxford). 2017;56(3):344-50.
373. Olson AL, Swigris JJ, Sprunger DB, Fischer A, Fernandez-Perez ER, Solomon J, *et al.* Rheumatoid arthritis-interstitial lung disease-associated mortality. Am J Respir Crit Care Med. 2011;183(3):372-8.
374. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Progressive decline of lung function in rheumatoid arthritis-associated interstitial lung disease. Arthritis Rheumatol. 2017;69(3):542-9.
375. Xaubet A, Ancochea J, Bollo E, Fernandez-Fabrellas E, Franquet T, Molina-Molina M, *et al.* Guidelines for the diagnosis and treatment of idiopathic pulmonary fibrosis. Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) Research Group on Diffuse Pulmonary Diseases. Arch Bronconeumol. 2013;49(8):343-53.
376. Morisset J, Vittinghoff E, Lee BY, Tonelli R, Hu X, Elicker BM, *et al.* The performance of the GAP model in patients with rheumatoid arthritis associated interstitial lung disease. Respir Med. 2017;127:51-6.
377. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Methotrexate and lung disease in rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis Rheumatol. 2014;66(4):803-12.
378. Conway R, Carey JJ. Methotrexate and lung disease in rheumatoid arthritis. Panminerva Med. 2017;59(1):33-46.
379. Kremer JM, Alarcon GS, Weinblatt ME, Kaymakcian MV, Macaluso M, Cannon GW, *et al.* Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: a multicenter study with literature review. Arthritis Rheum. 1997;40(10):1829-37.
380. Searles G, McKendry RJ. Methotrexate pneumonitis in rheumatoid arthritis: potential risk factors. Four case reports and a review of the literature. J Rheumatol. 1987;14(6):1164-71.

381. Alarcon GS, Kremer JM, Macaluso M, Weinblatt ME, Cannon GW, Palmer WR, *et al.* Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. Methotrexate-Lung Study Group. Ann Intern Med. 1997;127(5):356-64.
382. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Methotrexate use and risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomised controlled trials. BMJ. 2015;350:h1269.
383. Sawada T, Inokuma S, Sato T, Otsuka T, Saeki Y, Takeuchi T, *et al.* Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis. Rheumatology (Oxford). 2009;48(9):1069-72.
384. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Leflunomide Use and Risk of Lung Disease in Rheumatoid Arthritis: A Systematic Literature Review and Metaanalysis of Randomized Controlled Trials. J Rheumatol. 2016;43(5):855-60.
385. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum. 2014;43(5):613-26.
386. Nakashita T, Ando K, Kaneko N, Takahashi K, Motojima S. Potential risk of TNF inhibitors on the progression of interstitial lung disease in patients with rheumatoid arthritis. BMJ Open. 2014;4(8):e005615.
387. Koo BS, Hong S, Kim YJ, Kim YG, Lee CK, Yoo B. Mortality in patients with rheumatoid arthritis-associated interstitial lung disease treated with an anti-tumor necrosis factor agent. Korean Journal of Internal Medicine. 2015;30(1):104-9.
388. Mera-Varela A, Perez-Pampin E. Abatacept therapy in rheumatoid arthritis with interstitial lung disease. J Clin Rheumatol. 2014;20(8):445-6.
389. Akiyama M, Kaneko Y, Yamaoka K, Kondo H, Takeuchi T. Association of disease activity with acute exacerbation of interstitial lung disease during tocilizumab treatment in patients with rheumatoid arthritis: a retrospective, case-control study. Rheumatol Int. 2016;36(6):881-9.
390. Chartrand S, Swigris JJ, Peykova L, Fischer A. Rituximab for the treatment of connective tissue disease-associated interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis. 2015;32(4):296-304.
391. Jani M, Hirani N, Matteson EL, Dixon WG. The safety of biologic therapies in RA-associated interstitial lung disease. Nat Rev Rheumatol. 2014;10(5):284-94.
392. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, *et al.* Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. Semin Arthritis Rheum. 2011;41(2):256-64.
393. Hadjinicolaou AV, Nisar MK, Bhagat S, Parfrey H, Chilvers ER, Ostor AJ. Non-infectious pulmonary complications of newer biological agents for rheumatic diseases--a systematic literature review. Rheumatology (Oxford). 2011;50(12):2297-305.
394. Dixon WG, Hyrich KL, Watson KD, Lunt M, Symmons DP. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2010;69(6):1086-91.

395. Yousem SA, Dacic S. Pulmonary lymphohistiocytic reactions temporally related to etanercept therapy. Mod Pathol. 2005;18(5):651-5.
396. Gifre L, Ruiz-Esquide V, Xaubet A, Gomez-Puerta JA, Hernandez MV, Sanmarti R. Lung sarcoidosis induced by TNF antagonists in rheumatoid arthritis: a case presentation and a literature review. Arch Bronconeumol. 2011;47(4):208-12.
397. Herrinton LJ, Harrold LR, Liu L, Raebel MA, Taharka A, Winthrop KL, *et al.* Association between anti-TNF-alpha therapy and interstitial lung disease. Pharmacoepidemiol Drug Saf. 2013;22(4):394-402.
398. Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor alpha agents, a retrospective cohort study. Arthritis Res Ther. 2015;17:319.
399. Garcia-Vicuña R OA, Carmona L, Ibañez M, Castrejón I, Laffón A. Inflammatory interstitial lung disease in rheumatoid arthritis patients treated with biologic treatment. Incidence and mortality rates compared with patients non receiving biologics [Abstract]. Ann Rheum Dis. 2005; 64 (Suppl (III):470.
400. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, *et al.* Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol. 2014;41(1):15-23.
401. Matteson EL, Bongartz T, Ryu JH, Crowson CS, Hartman TE and Dellaripa PF. Open-Label, Pilot Study of the Safety and Clinical Effects of Rituximab in Patients with Rheumatoid Arthritis-Associated Interstitial Pneumonia, Open Journal of Rheumatology and Autoimmune Diseases, Vol. 2 No. 3, 2012, pp. 53-58.
402. Narváez J RM, Alegre JJ, Albert Espí G, Gómez Vaquero C, Borrell H, *et al.* Rituximab efficacy in the treatment of diffuse interstitial lung disease associated with rheumatoid arthritis [abstract]. Arthritis Rheum 2015;67 (Suppl S10):1569.
403. Becerra E, Cambridge G, Leandro M. Safety and efficacy of rituximab in patients with rheumatoid arthritis and lung involvement [Abstract]. Ann Rheum Dis 2013;72(Suppl. 3):450.
404. Dass S AF, Vital E, Bingham S, Buch M, Beirne P, *et al.* Safety of rituximab in patients with rheumatoid arthritis and concomitant lung disease. Ann Rheum Dis 2011;70(Suppl. 3):71.
405. Dogu B, Atilla N, Cetin GY, Yilmaz N, Oksuz H. A case of acute respiratory failure in a rheumatoid arthritis patient after the administration of abatacept. Eur J Rheumatol. 2016;3(3):134-5.
406. Wada T, Akiyama Y, Yokota K, Sato K, Funakubo Y, Mimura T. [A case of rheumatoid arthritis complicated with deteriorated interstitial pneumonia after the administration of abatacept]. Nihon Rinsho Meneki Gakkai Kaishi. 2012;35(5):433-8.
407. Weinblatt ME, Moreland LW, Westhovens R, Cohen RB, Kelly SM, Khan N, *et al.* Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. The Journal of Rheumatology [Internet]. 2013; 40(6):[787-97 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/715/CN-01123715/frame.html.
408. Nakashita T, Ando K, Takahashi K, Motojima S. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. Respir Investig. 2016;54(5):376-9.

409. Fernández Díaz C LJ, Castañeda S, Ojeda-Garcia C, Olivé A, Carreira PE, *et al.* Abatacept in rheumatoid arthritis with interstitial lung disease: a multicenter study of 55 patients [abstract]. Arthritis Rheumatol 2016;68 (Suppl S10): 2583.
410. Mori S, Koga Y, Sugimoto M. Organizing pneumonia in rheumatoid arthritis patients: A case-based review. Clin Med Insights Circ Respir Pulm Med. 2015;9(Suppl 1):69-80.
411. Kawasumi H, Gono T, Tanaka E, Kaneko H, Kawaguchi Y, Yamanaka H. Clinical characteristics and cytokine profiles of organizing pneumonia in patients with rheumatoid arthritis treated with or without biologics. J Rheumatol. 2016;43(4):738-44.
412. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, *et al.* Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 2006;354(25):2655-66.
413. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, *et al.* Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4(9):708-19.
414. Fischer A, Brown KK, Du Bois RM, Frankel SK, Cosgrove GP, Fernandez-Perez ER, *et al.* Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. J Rheumatol. 2013;40(5):640-6.
415. Schupp JC, Kohler T, Muller-Quernheim J. Usefulness of Cyclophosphamide Pulse Therapy in Interstitial Lung Diseases. Respiration. 2016;91(4):296-301.
416. Tokano Y, Ogasawara H, Ando S, Fujii T, Kaneko H, Tamura N, *et al.* Cyclosporin A therapy for interstitial pneumonitis associated with rheumatic disease. Mod Rheumatol. 2002;12(4):305-10.
417. Barnes H, Holland AE, Westall GP, Goh NS, Glaspole IN. Cyclophosphamide for connective tissue disease-associated interstitial lung disease. Cochrane Database Syst Rev. 2018;1:Cd010908.
418. Md Yusof MY, Kabia A, Darby M, Lettieri G, Beirne P, Vital EM, *et al.* Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single centre. Rheumatology (Oxford). 2017;56(8):1348-57.
419. Fernandez-Diaz C, Loricera J, Castaneda S, Lopez-Mejias R, Ojeda-Garcia C, Olive A, *et al.* Abatacept in patients with rheumatoid arthritis and interstitial lung disease: A national multicenter study of 63 patients. Semin Arthritis Rheum. 2018.
420. Chartrand S, Swigris JJ, Peykova L, Fischer A. Rituximab use in patients with rheumatoid arthritis-associated interstitial lung disease and other connective tissue disease-associated interstitial lung disease: a single center experience [Abstract 1419]. ACR 2014.
421. Fernández Díaz C, Martin-Lopez M, Carrasco-Cubero M, Reina-Sanz D, Rubio-Muñoz P, Urruticoechea-Arana A, *et al.* Rituximab in rheumatoid arthritis with interstitial lung disease: a multicenter study. [Abstract FRI0226]. EULAR 2017.
422. Accortt NA, Bonafede MM, Collier DH, Iles J, Curtis JR. Risk of subsequent infection among patients receiving tumor necrosis factor inhibitors and other disease-modifying antirheumatic drugs. Arthritis Rheumatol. 2016;68(1):67-76.
423. Yun H, Xie F, Delzell E, Chen L, Levitan EB, Lewis JD, *et al.* Risk of hospitalised infection in rheumatoid arthritis patients receiving biologics following a previous infection while on treatment with anti-TNF therapy. Ann Rheum Dis. 2015;74(6):1065-71.
424. Ramiro S, Gaujoux-Viala C, Nam JL, Smolen JS, Buch M, Gossec L, *et al.* Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 up-

date of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2014;73(3):529-35.

425. Raaschou P, Frisell T, Askling J. TNF inhibitor therapy and risk of breast cancer recurrence in patients with rheumatoid arthritis: a nationwide cohort study. Ann Rheum Dis. 2015;74(12):2137-43.
426. Phillips C, Zeringue AL, McDonald JR, Eisen SA, Ranganathan P. Tumor Necrosis Factor Inhibition and Head and Neck Cancer Recurrence and Death in Rheumatoid Arthritis. PLoS One. 2015;10(11):e0143286.
427. Silva-Fernandez L, Lunt M, Kearsley-Fleet L, Watson KD, Dixon WG, Symmons DP, *et al.* The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis. Rheumatology (Oxford). 2016;55(11):2033-9.
428. Dixon WG, Watson KD, Lunt M, Mercer LK, Hyrich KL, Symmons DP. Influence of anti-tumor necrosis factor therapy on cancer incidence in patients with rheumatoid arthritis who have had a prior malignancy: results from the British Society for Rheumatology Biologics Register. Arthritis Care Res (Hoboken). 2010;62(6):755-63.
429. Strangfeld A, Hierse F, Rau R, Burmester GR, Krummel-Lorenz B, Demary W, *et al.* Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res Ther. 2010;12(1):R5.
430. Shacter E, Weitzman SA. Chronic inflammation and cancer. Oncology (Williston Park). 2002;16(2):217-26, 29; discussion 30-2.
431. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther. 2015;17:212.
432. Rink L, Kirchner H. Recent progress in the tumor necrosis factor-alpha field. Int Arch Allergy Immunol. 1996;111(3):199-209.
433. Bongartz T, Warren FC, Mines D, Matteson EL, Abrams KR, Sutton AJ. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis. 2009;68(7):1177-83.
434. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis. 2009;68(7):1136-45.
435. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, *et al.* Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis. 2005;64(10):1421-6.
436. Mercer LK, Green AC, Galloway JB, Davies R, Lunt M, Dixon WG, *et al.* The influence of anti-TNF therapy upon incidence of keratinocyte skin cancer in patients with rheumatoid arthritis: longitudinal results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2012;71(6):869-74.
437. Raaschou P, Simard JF, Holmqvist M, Askling J. Rheumatoid arthritis, anti-tumour necrosis factor therapy, and risk of malignant melanoma: nationwide population based prospective cohort study from Sweden. Bmj. 2013;346:f1939.

438. Askling J, Baecklund E, Granath F, Geborek P, Fored M, Backlin C, *et al.* Anti-tumour necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register. Ann Rheum Dis. 2009;68(5):648-53.
439. Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, Pollono EN, Cueto JP, Gonzales-Crespo MR, *et al.* Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. Jama. 2012;308(9):898-908.
440. de La Forest Divonne M, Gottenberg JE, Salliot C. Safety of biologic DMARDs in RA patients in real life: A systematic literature review and meta-analyses of biologic registers. Joint Bone Spine. 2017;84(2):133-40.
441. Mercer LK, Low AS, Galloway JB, Watson KD, Lunt M, Symmons DP, *et al.* Anti-TNF therapy in women with rheumatoid arthritis with a history of carcinoma in situ of the cervix. Ann Rheum Dis. 2013;72(1):143-4.
442. Kourbeti IS, Ziakas PD, Mylonakis E. Biologic therapies in rheumatoid arthritis and the risk of opportunistic infections: a meta-analysis. Clin Infect Dis. 2014;58(12):1649-57.
443. Carmona L, Gomez-Reino J, Gonzalez-Gonzalez R. [Spanish registry of adverse events of biological therapies in rheumatic diseases (BIOBADASER): report as of january 14, 2005]. Reumatol Clin. 2005;1(2):95-111.
444. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, *et al.* American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum. 2008;59(6):762-84.
445. Ostuni P, Botsios C, Punzi L, Sfriso P, Todesco S. Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. Ann Rheum Dis. 2003;62(7):686-7.
446. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. Rheumatology (Oxford). 2006;45(10):1294-7.
447. Vassilopoulos D, Apostolopoulou A, Hadziyannis E, Papatheodoridis GV, Manolakopoulos S, Koskinas J, *et al.* Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. Ann Rheum Dis. 2010;69(7):1352-5.
448. Anelli MG, Torres DD, Manno C, Scioscia C, Iannone F, Covelli M, *et al.* Improvement of renal function and disappearance of hepatitis B virus DNA in a patient with rheumatoid arthritis and renal amyloidosis following treatment with infliximab. Arthritis Rheum. 2005;52(8):2519-20.
449. Zein NN. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. J Hepatol. 2005;42(3):315-22.
450. Ferri C, Ferraccioli G, Ferrari D, Galeazzi M, Lapadula G, Montecucco C, *et al.* Safety of anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection. J Rheumatol. 2008;35(10):1944-9.
451. Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V, Montero D, Pascual-Gomez E, Mola EM, *et al.* Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum. 2005;52(6):1766-72.

452. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum. 2006;54(9):2807-16.
453. 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]. Reumatol Clin. 2011;7(5):284-98.
454. Cepeda EJ, Williams FM, Ishimori ML, Weisman MH, Reveille JD. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. Ann Rheum Dis. 2008;67(5):710-2.
455. Kaur PP, Chan VC, Berney SN. Successful etanercept use in an HIV-positive patient with rheumatoid arthritis. J Clin Rheumatol. 2007;13(2):79-80.
456. Scott DL. Prognostic factors in early rheumatoid arthritis. Rheumatology (Oxford). 2000;39 Suppl 1:24-9.
457. Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, Hazes JM. Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. Arthritis Rheum. 1999;42(9):1854-60.
458. Sharp JT, Strand V, Leung H, Hurley F, Loew-Friedrich I. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis: results from three randomized controlled trials of leflunomide in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. Arthritis Rheum. 2000;43(3):495-505.
459. Perry LM, Winthrop KL, Curtis JR. Vaccinations for rheumatoid arthritis. Curr Rheumatol Rep. 2014;16(8):431.
460. Ostensen M, Villiger PM. The remission of rheumatoid arthritis during pregnancy. Semin Immunopathol. 2007;29(2):185-91.
461. de Man YA, Dolhain RJ, van de Geijn FE, Willemsen SP, Hazes JM. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. Arthritis Rheum. 2008;59(9):1241-8.
462. Hazes JM, Coulie PG, Geenen V, Vermeire S, Carbonnel F, Louis E, *et al.* Rheumatoid arthritis and pregnancy: evolution of disease activity and pathophysiological considerations for drug use. Rheumatology (Oxford). 2011;50(11):1955-68.
463. Forger F, Vallbracht I, Helmke K, Villiger PM, Ostensen M. Pregnancy mediated improvement of rheumatoid arthritis. Swiss Med Wkly. 2012;142:w13644.
464. Lin HC, Chen SF, Lin HC, Chen YH. Increased risk of adverse pregnancy outcomes in women with rheumatoid arthritis: a nationwide population-based study. Ann Rheum Dis. 2010;69(4):715-7.
465. Norgaard M, Larsson H, Pedersen L, Granath F, Askling J, Kieler H, *et al.* Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. J Intern Med. 2010;268(4):329-37.
466. Barnabe C, Faris PD, Quan H. Canadian pregnancy outcomes in rheumatoid arthritis and systemic lupus erythematosus. Int J Rheumatol. 2011;2011:345727.
467. Wallenius M, Skomsvoll JF, Irgens LM, Salvesen KA, Nordvag BY, Koldingsnes W, *et al.* Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth. Arthritis Rheum. 2011;63(6):1534-42.

468. Mitchell K, Kaul M, Clowse ME. The management of rheumatic diseases in pregnancy. Scand J Rheumatol. 2010;39(2):99-108.
469. Ostensen M, Forger F. How safe are anti-rheumatic drugs during pregnancy? Curr Opin Pharmacol. 2013;13(3):470-5.
470. Hyrich KL, Verstappen SM. Biologic therapies and pregnancy: the story so far. Rheumatology (Oxford). 2014;53(8):1377-85.
471. Izmirly PM, Saxena A, Kim MY, Wang D, Sahl SK, Llanos C, *et al.* Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. Circulation. 2011;124(18):1927-35.
472. Bermas BL. Non-steroidal anti inflammatory drugs, glucocorticoids and disease modifying anti-rheumatic drugs for the management of rheumatoid arthritis before and during pregnancy. Curr Opin Rheumatol. 2014;26(3):334-40.
473. Berthelsen BG, Fjeldsoe-Nielsen H, Nielsen CT, Hellmuth E. Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding. Rheumatology (Oxford). 2010;49(11):2225-7.
474. Ferrante M, Vermeire S, Rutgeerts PJ. Drug safety evaluation of certolizumab pegol. Expert Opin Drug Saf. 2014;13(2):255-66.
475. Mahadevan U, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, *et al.* Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2013;11(3):286-92; quiz e24.
476. Ojeda-Uribe M, Afif N, Dahan E, Sparsa L, Haby C, Sibilia J, *et al.* Exposure to abatacept or rituximab in the first trimester of pregnancy in three women with autoimmune diseases. Clin Rheumatol. 2013;32(5):695-700.
477. Clowse ME, Wolf DC, Forger F, Cush JJ, Golembesky A, Shaughnessy L, *et al.* Pregnancy Outcomes in Subjects Exposed to Certolizumab Pegol. J Rheumatol. 2015;42(12):2270-8.
478. Zelinkova Z, van der Ent C, Bruin KF, van Baalen O, Vermeulen HG, Smalbraak HJ, *et al.* Effects of discontinuing anti-tumor necrosis factor therapy during pregnancy on the course of inflammatory bowel disease and neonatal exposure. Clin Gastroenterol Hepatol. 2013;11(3):318-21.
479. Nielsen OH, Jess T. IBD: Can TNF inhibitors be administered during the third trimester? Nat Rev Gastroenterol Hepatol. 2013;10(3):130-1.
480. Hughes C, Nissim A. Progress and clinical potential of antibody-targeted therapy for arthritic damage. Expert Rev Proteomics. 2016;13(6):539-43.
481. Mahadevan U, Cucchiara S, Hyams JS, Steinwurz F, Nuti F, Travis SP, *et al.* The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. Am J Gastroenterol. 2011;106(2):214-23; quiz 24.
482. Martinez Lopez JA, Garcia Vivar ML, Caliz R, Freire M, Galindo M, Hernandez MV, *et al.* Recommendations for the evaluation and management of patients with rheumatic autoimmune and inflammatory diseases during the reproductive age, pregnancy, postpartum and breastfeeding. Reumatol Clin. 2017;13(5):264-81.
483. Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling. Available from: https://www.ema.europa.eu/documents/scientific-guideline/guideline-risk-assessment-medicinal-products-human-reproduction-lactation-data-labelling_en.pdf.

484. Burke LE, Dunbar-Jacob JM, Hill MN. Compliance with cardiovascular disease prevention strategies: a review of the research. Ann Behav Med. 1997;19(3):239-63.
485. Sabaté E. Adherence to long-term therapies: Evidence for action [Internet]. Geneva: World Health Organization; 2004. [accessed 25 July 2017]. Available from: https://www.who.int/chp/knowledge/publications/adherence_full_report.pdf.
486. Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. Arch Intern Med. 2000;160(21):3278-85.
487. Fautrel B, Balsa A, Van Riel P, Casillas M, Capron JP, Cueille C, *et al.* Influence of route of administration/drug formulation and other factors on adherence to treatment in rheumatoid arthritis (pain related) and dyslipidemia (non-pain related). Curr Med Res Opin. 2017;33(7):1231-46.
488. Lopez-Gonzalez R, Leon L, Loza E, Redondo M, Garcia de Yebenes MJ, Carmona L. Adherence to biologic therapies and associated factors in rheumatoid arthritis, spondyloarthritis and psoriatic arthritis: a systematic literature review. Clin Exp Rheumatol. 2015;33(4):559-69.
489. Riemsma RP, Taal E, Kirwan JR, Rasker JJ. Systematic review of rheumatoid arthritis patient education. Arthritis Rheum. 2004;51(6):1045-59.
490. Gronning 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 Educ Couns. 2012;88(1):113-20.
491. 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. Ann Rheum Dis. 2012;71(1):13-9.
492. Zangi HA, Ndosi M, Adams J, Andersen L, Bode C, Bostrom C, *et al.* EULAR recommendations for patient education for people with inflammatory arthritis. 2015;74(6):954-62.
493. Hooker RS. The extension of rheumatology services with physician assistants and nurse practitioners. Best Pract Res Clin Rheumatol. 2008;22(3):523-33.
494. Rauch A, Kirchberger I, Boldt C, Cieza A, Stucki G. Does the Comprehensive International Classification of Functioning, Disability and Health (ICF) Core Set for rheumatoid arthritis capture nursing practice? A Delphi survey. Int J Nurs Stud. 2009;46(10):1320-34.
495. Simons G, Mallen CD, Kumar K, Stack RJ, Raza K. A qualitative investigation of the barriers to help-seeking among members of the public presented with symptoms of new-onset rheumatoid arthritis. J Rheumatol. 2015;42(4):585-92.
496. Brand C, Claydon-Platt K, McColl G, Bucknall T. Meeting the needs of people diagnosed with rheumatoid arthritis: an analysis of patient-reported experience. Journal of Nursing & Healthcare of Chronic Illnesses. 2010;2(1):75-83 9p.
497. Sheppard J, Kumar K, Buckley CD, Shaw KL, Raza K. 'I just thought it was normal aches and pains': a qualitative study of decision-making processes in patients with early rheumatoid arthritis. Rheumatology (Oxford). 2008;47(10):1577-82.
498. 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. Reumatol Clin. 2013;9(6):334-9.
499. Kumar K, Raza K, Gill P, Greenfield S. The impact of using musculoskeletal ultrasound imaging and other influencing factors on medication adherence in patients with rheumatoid arthritis: A qualitative study. Patient Preference and Adherence. 2016;10:1091-100.

500. Molbaek K, Horslev-Petersen K, Primdahl J. Diagnostic Delay in Rheumatoid Arthritis: A Qualitative Study of Symptom Interpretation Before the First Visit to the Doctor. Musculoskeletal Care. 2016;14(1):26-36.
501. Simons G, Belcher J, Morton C, Kumar K, Falahee M, Mallen CD, *et al.* Symptom recognition and perceived urgency of help-seeking for rheumatoid arthritis and other diseases in the general public: A mixed method approach. Arthritis Care Res (Hoboken). 2017;69(5):633-41.
502. Simons G, Lumley S, Falahee M, Kumar K, Mallen CD, Stack RJ, *et al.* The pathway to consultation for rheumatoid arthritis: Exploring anticipated actions between the onset of symptoms and face-to-face encounter with a healthcare professional. BMC Musculoskeletal Disorders. 2017;18(1).
503. Kostova Z, Caiata-Zufferey M, Schulz PJ. The process of acceptance among rheumatoid arthritis patients in Switzerland: a qualitative study. Pain Res Manag. 2014;19(2):61-8.
504. Falahee M, Simons G, Buckley CD, Hansson M, Stack RJ, Raza K. Patients' perceptions of their relatives' risk of developing rheumatoid arthritis and of the potential for risk communication, prediction, and modulation. Arthritis Care & Research. 2017;69(10):1558-65.
505. Stack RJ, Stoffer M, Englbrecht M, Mosor E, Falahee M, Simons G, *et al.* Perceptions of risk and predictive testing held by the first-degree relatives of patients with rheumatoid arthritis in England, Austria and Germany: A qualitative study. BMJ Open. 2016;6(6).
506. Bala SV, Samuelson K, Hagell P, Svensson B, Fridlund B, Hesselgard K. The experience of care at nurse-led rheumatology clinics. Musculoskeletal Care. 2012;10(4):202-11.
507. Bath J, Hooper J, Giles M, Steel D, Reed E, Woodland J. Patient perceptions of rheumatoid arthritis. Nurs Stand. 1999;14(3):35-8.
508. Carr A, Hewlett S, Hughes R, Mitchell H, Ryan S, Carr M, *et al.* Rheumatology outcomes: the patient's perspective. J Rheumatol. 2003;30(4):880-3.
509. Häggström E, Nilsson A. The meaning of living with rheumatoid arthritis -- a single case study based on one woman's eight-year diary. Nordic Nursing Research / Tidsskrift for Sygeplejeforskning. 2009;25(3):9-15 7p.
510. Poh LW, Chan W-CS, Mak A, Lee CCS, Cheung P, He H-G. Research in brief - A qualitative study on the experiences of adult patients with rheumatoid arthritis in Singapore. Singapore Nursing Journal. 2014;41(3):39-40 2p.
511. Pouchot J, Le Parc JM, Queffelec L, Sichere P, Flinois A. Perceptions in 7700 patients with rheumatoid arthritis compared to their families and physicians. Joint Bone Spine. 2007;74(6):622-6.
512. Walter M, Spijker A, Pasma A, Hazes J, Luime J, Walter MJM, *et al.* Focus group interviews reveal reasons for differences in the perception of disease activity in rheumatoid arthritis. Quality of Life Research. 2017;26(2):291-8.
513. Connolly D, Fitzpatrick C, O'Toole L, Doran M, O'Shea F. Impact of fatigue in rheumatic diseases in the work environment: A qualitative study. International Journal of Environmental Research and Public Health. 2015;12(11):13807-22.
514. Davis MC, Okun MA, Kruszewski D, Zautra AJ, Tennen H. Sex differences in the relations of positive and negative daily events and fatigue in adults with rheumatoid arthritis. J Pain. 2010;11(12):1338-47.
515. Mortada M, Abdul-Sattar A, Gossec L. Fatigue in Egyptian patients with rheumatic diseases: a qualitative study. Health Qual Life Outcomes. 2015;13:134.

516. Nikolaus S, Bode C, Taal E, van de Laar MA. Four different patterns of fatigue in rheumatoid arthritis patients: Results of a Q-sort study. Rheumatology (Oxford). 2010;49(11):2191-9.
517. Parrish BP, Zautra AJ, Davis MC. The role of positive and negative interpersonal events on daily fatigue in women with fibromyalgia, rheumatoid arthritis, and osteoarthritis. Health Psychology. 2008;27(6):694-702 9p.
518. Repping-Wuts H, Uitterhoeve R, van Riel P, van Achterberg T. Fatigue as experienced by patients with rheumatoid arthritis (RA): a qualitative study. Int J Nurs Stud. 2008;45(7):995-1002.
519. Gutweniger S, Kopp M, Mur E, Gunther V. Body image of women with rheumatoid arthritis. Clin Exp Rheumatol. 1999;17(4):413-7.
520. Halls S, Dures E, Kirwan J, Pollock J, Baker G, Edmunds A, *et al.* Stiffness is more than just duration and severity: a qualitative exploration in people with rheumatoid arthritis. Rheumatology (Oxford). 2015;54(4):615-22.
521. Orbai AM, Smith KC, Bartlett SJ, De Leon E, Bingham CO, 3rd. "Stiffness has different meanings, I think, to everyone": examining stiffness from the perspective of people living with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2014;66(11):1662-72.
522. Fraenkel L, Seng EK, Cunningham M, Mattocks K. Understanding how patients (vs physicians) approach the decision to escalate treatment: a proposed conceptual model. Rheumatology (Oxford). 2015;54(2):278-85.
523. Kalkan A, Roback K, Hallert E, Carlsson P. Factors influencing rheumatologists' prescription of biological treatment in rheumatoid arthritis: an interview study. Implement Sci. 2014;9:153.
524. 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. Disabil Rehabil. 2015;37(10):854-63.
525. Meyfroidt S, van Hulst L, De Cock D, Van der Elst K, Joly J, Westhovens R, *et al.* Factors influencing the prescription of intensive combination treatment strategies for early rheumatoid arthritis. Scand J Rheumatol. 2014;43(4):265-72.
526. Sanders L, Donovan-Hall M, Borthwick A, Bowen CJ. Experiences of mobility for people living with rheumatoid arthritis who are receiving biologic drug therapy: implications for podiatry services. J Foot Ankle Res. 2017;10:14.
527. van der Elst K, Meyfroidt S, De Cock D, De Groef A, Binnard E, Moons P, *et al.* Unraveling Patient-Preferred Health and Treatment Outcomes in Early Rheumatoid Arthritis: A Longitudinal Qualitative Study. Arthritis Care Res (Hoboken). 2016;68(9):1278-87.
528. Kumar K, Gordon C, Barry R, Shaw K, Horne R, Raza K. 'It's like taking poison to kill poison but I have to get better': a qualitative study of beliefs about medicines in Rheumatoid arthritis and Systemic lupus erythematosus patients of South Asian origin. Lupus. 2011;20(8):837-44.
529. Lempp H, Hofmann D, Hatch SL, Scott DL. Patients' views about treatment with combination therapy for rheumatoid arthritis: a comparative qualitative study. BMC Musculoskelet Disord. 2012;13:200.
530. Lindblad AK, Hartzema AG, Jansson L, Feltelius N. Patients' views of priority setting for new medicines. A qualitative study of patients with rheumatoid arthritis. Scand J Rheumatol. 2002;31(6):324-9.

531. Linden C, Bjorklund A. Living with rheumatoid arthritis and experiencing everyday life with TNF-alpha blockers. Scand J Occup Ther. 2010;17(4):326-34.
532. Mathews AL, Coleska A, Burns PB, Chung KC. Evolution of patient decision-making regarding medical treatment of rheumatoid arthritis. Arthritis Care and Research. 2016;68(3):318-24.
533. Hayden C, Neame R, Tarrant C. Patients' adherence-related beliefs about methotrexate: A qualitative study of the role of written patient information. BMJ Open. 2015;5(5).
534. Kobue B, Moch S, Watermeyer J. "It's so hard taking pills when you don't know what they're for": a qualitative study of patients' medicine taking behaviours and conceptualisation of medicines in the context of rheumatoid arthritis. BMC Health Serv Res. 2017;17(1):303.
535. Markusse IM, Akdemir G, Huizinga TW, Allaart CF. Drug-free holiday in patients with rheumatoid arthritis: a qualitative study to explore patients' opinion. Clin Rheumatol. 2014;33(8):1155-9.
536. van Tuyl LHD, Hewlett S, Sadlonova M, Davis B, Flurey C, Hoogland W, *et al.* The patient perspective on remission in rheumatoid arthritis: 'You've got limits, but you're back to being you again'. Annals of the Rheumatic Diseases. 2014.
537. Ahlmen M, Nordenskiold U, Archenholtz B, Thyberg I, Ronnqvist R, Linden L, *et al.* Rheumatology outcomes: the patient's perspective. A multicentre focus group interview study of Swedish rheumatoid arthritis patients. Rheumatology (Oxford). 2005;44(1):105-10.
538. Pasma A, van 't Spijker A, Luime JJ, Walter MJ, Busschbach JJ, Hazes JM. Facilitators and barriers to adherence in the initiation phase of Disease-modifying Antirheumatic Drug (DMARD) use in patients with arthritis who recently started their first DMARD treatment. J Rheumatol. 2015;42(3):379-85.
539. Sanderson T, Calnan M, Morris M, Richards P, Hewlett S. The impact of patient-perceived restricted access to anti-TNF therapy for rheumatoid arthritis: a qualitative study. Musculoskeletal Care. 2009;7(3):194-209.
540. Voshaar M, Vriezekolk J, van Dulmen S, van den Bemt B, van de Laar M. Barriers and facilitators to disease-modifying antirheumatic drug use in patients with inflammatory rheumatic diseases: a qualitative theory-based study. BMC Musculoskelet Disord. 2016;17(1):442.
541. Brandstetter S, Hertig S, Loss J, Ehrenstein B, Apfelbacher C. 'The lesser of two evils...' - views of persons with rheumatoid arthritis on medication adherence: a qualitative study. Psychol Health. 2016;31(6):675-92.
542. Treharne GJ, Lyons AC, Kitas GD. Medication adherence in rheumatoid arthritis: Effects of psychosocial factors. Psychology, Health and Medicine. 2004;9(3):337-49.
543. Iaquinta ML, Larrabee JH. Phenomenological lived experience of patients with rheumatoid arthritis. Journal of Nursing Care Quality. 2004;19(3):280-9 10p.
544. Josefsson KA, Gard G. Women's experiences of sexual health when living with rheumatoid arthritis--an explorative qualitative study. BMC Musculoskelet Disord. 2010;11:240.
545. Plach SK, Stevens PE, Moss VA. Corporeality: women's experiences of a body with rheumatoid arthritis. Clin Nurs Res. 2004;13(2):137-55.
546. Malm K, Bremander A, Arvidsson B, Andersson ML, Bergman S, Larsson I. The influence of lifestyle habits on quality of life in patients with established rheumatoid arthri-

tis-A constant balancing between ideality and reality. Int J Qual Stud Health Well-being. 2016;11:30534.

547. Goodacre LJ, Candy FJ. 'If I didn't have RA I wouldn't give them house room': the relationship between RA, footwear and clothing choices. Rheumatology (Oxford). 2011;50(3):513-7.
548. Williams AE, Graham AS. 'My feet: visible, but ignored . . .' A qualitative study of foot care for people with rheumatoid arthritis. Clin Rehabil. 2012;26(10):952-9.
549. Williams AE, Nester CJ, Ravey MI. Rheumatoid arthritis patients' experiences of wearing therapeutic footwear - a qualitative investigation. BMC Musculoskelet Disord. 2007;8:104.
550. Wilson O, Kirwan J, Dures E, Quest E, Hewlett S. The experience of foot problems and decisions to access foot care in patients with rheumatoid arthritis: a qualitative study. J Foot Ankle Res. 2017;10:4.
551. Fair BS. Contrasts in patients' and providers' explanations of rheumatoid arthritis. J Nurs Scholarsh. 2003;35(4):339-44.
552. Conner TS, Tennen H, Zautra AJ, Affleck G, Armeli S, Fifield J. Coping with rheumatoid arthritis pain in daily life: within-person analyses reveal hidden vulnerability for the formerly depressed. Pain. 2006;126(1-3):198-209.
553. Sharpe L, Sensky T, Allard S. The course of depression in recent onset rheumatoid arthritis: the predictive role of disability, illness perceptions, pain and coping. Journal of psychosomatic research [Internet]. 2001; 51(6):[713-9 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/505/CN-00376505/frame.html.
554. Akkuş Y, Nakas D, Kalyoncu U. Factors affecting the sexual satisfaction of patients with rheumatoid arthritis and ankylosing spondylitis. Sexuality and Disability. 2010;28(4):223-32.
555. Kwissa-Gajewska Z, Olesińska M, Tomkiewicz A. Optimism, pain coping strategies and pain intensity among women with rheumatoid arthritis. Reumatologia. 2014;52(3):166-71.
556. Baxter S, Smith C, Treharne G, Stebbings S, Hale L. What are the perceived barriers, facilitators and attitudes to exercise for women with rheumatoid arthritis? A qualitative study. Disability & Rehabilitation. 2016;38(8):773-80 8p.
557. Law RJ, Breslin A, Oliver EJ, Mawn L, Markland DA, Maddison P, *et al.* Perceptions of the effects of exercise on joint health in rheumatoid arthritis patients. Rheumatology (Oxford). 2010;49(12):2444-51.
558. Loeppenthin K, Esbensen B, Ostergaard M, Jennum P, Thomsen T, Midtgaard J. Physical activity maintenance in patients with rheumatoid arthritis: a qualitative study. Clin Rehabil. 2014;28(3):289-99.
559. Thomsen T, Beyer N, Aadahl M, Hetland ML, Loppenthin K, Midtgaard J, *et al.* Sedentary behaviour in patients with rheumatoid arthritis: A qualitative study. Int J Qual Stud Health Well-being. 2015;10:28578.
560. Withall J, Haase AM, Walsh NE, Young A, Cramp F. Physical activity engagement in early rheumatoid arthritis: A qualitative study to inform intervention development. Physiotherapy (United Kingdom). 2015.
561. Holtzman S, Delongis A. One day at a time: The impact of daily satisfaction with spouse responses on pain, negative affect and catastrophizing among individuals with rheumatoid arthritis. Pain. 2007;131(1-2):202-13.

562. Nyman A, Lund ML. Influences of the social environment on engagement in occupations: the experience of persons with rheumatoid arthritis. Scand J Occup Ther. 2007;14(1):63-72.
563. Mancuso CA, Paget SA, Charlson ME. Adaptations made by rheumatoid arthritis patients to continue working: a pilot study of workplace challenges and successful adaptations. Arthritis Care Res. 2000;13(2):89-99.
564. Detaille SI, Haafkens JA, van Dijk FJ. What employees with rheumatoid arthritis, diabetes mellitus and hearing loss need to cope at work. Scand J Work Environ Health. 2003;29(2):134-42.
565. Lacaille D, White MA, Backman CL, Gignac MA. Problems faced at work due to inflammatory arthritis: new insights gained from understanding patients' perspective. Arthritis Rheum. 2007;57(7):1269-79.
566. Dures E, Hewlett S, Ambler N, Jenkins R, Clarke J, Gooberman-Hill R. A qualitative study of patients' perspectives on collaboration to support self-management in routine rheumatology consultations. BMC Musculoskeletal Disorders. 2016;17(1).
567. 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 Educ Couns. 2004;52(2):169-74.
568. Ackerman IN, Jordan JE, Van Doornum S, Ricardo M, Briggs AM. Understanding the information needs of women with rheumatoid arthritis concerning pregnancy, post-natal care and early parenting: A mixed-methods study. BMC Musculoskeletal Disorders. 2015;16(1).
569. Dwarswaard J, Bakker EJ, van Staa A, Boeije HR. Self-management support from the perspective of patients with a chronic condition: a thematic synthesis of qualitative studies. Health Expect. 2016;19(2):194-208.
570. Hardware B, Johnson D, Hale C, Ndosi M, Adebajo A. Patients and nursing staff views of using the education needs assessment tool in rheumatology clinics: a qualitative study. J Clin Nurs. 2015;24(7-8):1048-58.
571. Ryan S, Lillie K, Thwaites C, Adams J. 'What I want clinicians to know'-- experiences of people with arthritis. British Journal of Nursing. 2013;22(14):808-12 5p.
572. van Eijk-Hustings Y, Ammerlaan J, Voorneveld-Nieuwenhuis H, Maat B, Veldhuizen C, Repping-Wuts H. Patients' needs and expectations with regard to rheumatology nursing care: results of multicentre focus group interviews. Ann Rheum Dis. 2013;72(6):831-5.
573. Salt E, Frazier SK. Adherence to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a narrative review of the literature. Orthop Nurs. 2010;29(4):260–275. doi:10.1097/NOR.0b013e3181e5c2c9.
574. Joplin S, van der Zwan R, Joshua F, Wong PK. Medication adherence in patients with rheumatoid arthritis: the effect of patient education, health literacy, and musculoskeletal ultrasound. Biomed Res Int. 2015;2015:150658. doi:10.1155/2015/150658.
575. Pasma A, van't Spijker A, Hazes JM, Busschbach JJ, Luime JJ. Factors associated with adherence to pharmaceutical treatment for rheumatoid arthritis patients: a systematic review. Semin Arthritis Rheum. 2013;43(1):18-28.