

CLINICAL PRACTICE GUIDELINE

on the **Management of Patients  
with Rheumatoid  
Arthritis**



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This clinical practice guideline serves to support decision-making in healthcare. Adherence is not obligatory, and the guideline does not replace the clinical judgement of health professionals.

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Spanish Society of Rheumatology (SER)

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## Foreword

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

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

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

The GUIPCAR gathers together the evidence available up to 2024 and some studies published in 2025. Depending on advances in knowledge and the emergence of new evidence, it is envisaged that the guideline will be updated again in 4 years.

Authors and collaborators

**GUIPCAR working group for the development of  
the Clinical Practice Guideline on the  
Management of Patients with Rheumatoid Arthritis**

## Coordination

Clinical coordinator.

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

Methodological coordinators.

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

**Noé Brito García**, Biologist, Research Unit, SER, Madrid, Spain

## Experts who developed the recommendations

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

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

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

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

**Fernando León Vázquez**, General Practitioner, Centro de Salud Universitario San Juan de la  
Cruz. Pozuelo de Alarcón. Madrid. Member of the Rheumatological Diseases Working Group,  
Spanish Society of Family and Community Medicine (SEMFYC).

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

**M<sup>a</sup> Asunción Nieto Barbero**, Head of the Pulmonology Department,  
Hospital Universitario Clínico San Carlos. Madrid.

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

**Lucía Silva Fernández**, Rheumatologist,  
University Hospital Complex in Pontevedra. Pontevedra, Spain.

## Reviewers of the scientific evidence

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

**Raquel Dos Santos Sobrín**, Rheumatologist, Hospital Clínico Universitario de Santiago, Santiago  
de Compostela.

**María López Lasanta**, Rheumatologist,  
Hospital Universitario Vall d'Hebron, Barcelona.

**María Martín López**, Rheumatologist, Hospital Universitario 12 de Octubre, Madrid.

**Pablo Francisco Muñoz-Martínez**, Rheumatology Department, Hospital Universitario y  
Politécnico La Fe, Valencia.

**Ariadna Auladell-Rispau**, Freelance scientific consultant, Girona

**Hye Sang Park**, Rheumatologist, Hospital Universitari de la Santa Creu i Sant Pau, Barcelona.

**Lucía Silva Fernández**, Rheumatologist,  
University Hospital Complex in Pontevedra. Pontevedra, Spain.

**Virginia Villaverde García**, Rheumatologist, Hospital Universitario de Móstoles, Madrid.

## Patient representative in the working group

**Laly Alcaide Cornejo**, Patient with rheumatoid arthritis, National arthritis coordinator,  
ConArtritis (umbrella group for local patients' associations), Madrid, Spain.

## Literature and database search strategy

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

## Estimation of disease burden

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

## Collaborations

### Qualitative research with patients

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

### Updating of patient information

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

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

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

### External review

**Emilce Edith Schneeberger**, Specialist in internal medicine and rheumatologist, Head of the  
training and research department, Psychophysical Rehabilitation Institute (IREP), Argentina.

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

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Unit, for helping to maintain the editorial independence of this CPG.

## Collaborating organisations

Spanish Society of Rheumatology (SER)

Spanish Society of Cardiology (SEC)

Spanish Society of Family 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 CPG.

**Declaration of interests:**

All members of the GUIPCAR working group have declared potential conflicts of interest as documented in Appendix 5.

**Public scrutiny:**

This guideline was made available for public scrutiny. Information concerning this process is available in the Clinical Practice Guidelines section (under Research) on the SER website ([www.ser.es](http://www.ser.es)).

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The development of this CPG, under the auspices of SER, was funded by Alfasigma, Lilly, Nordic and Sanofi. The Foundation of the Spanish Society of Rheumatology (FER) is the sole body responsible for employing the staff of the SER Research Unit and coordinating all payments to panellists and reviewers, and from these pharmaceutical companies. The agreement signed between this foundation and the funders safeguards the editorial independence of the guideline development process and states that funders must have no direct or indirect influence on the selection of panellists, search for or interpretation of the evidence, or any part of the final draft of the guideline, the aforementioned companies committing to fund the guideline even if the evidence were to recommend against the use of any of their products. In this way, it was ensured that the design of the guideline development process and analysis and interpretation of the results were conducted completely independently of the industrial funders.

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## Guideline recommendations

### Classification/Diagnosis

<b>Clinical question:</b> In patients with recent-onset rheumatoid arthritis (RA), what is the clinical utility of the 2010 classification criteria compared to those published in 1987?	<b>Strength of the recommendation</b>
<b>Recommendation 1:</b> In patients with seropositive arthritis, use the 2010 ACR/EULAR classification criteria to support the clinical judgement of the rheumatologist.	<i>Strong, in favour<sup>v</sup></i>
<b>Recommendation 2:</b> In patients with seronegative arthritis, the use of these classification criteria is not recommended, and diagnosis should be based on the clinical judgement of the rheumatologist.	<i>Good clinical practice<sup>v</sup></i>

### Initial pharmacological treatment

<b>Clinical question:</b> In patients with RA, what is the efficacy of initial treatment with glucocorticoids at doses equivalent to more than 10 mg of prednisone, added to any DMARD?	<b>Strength of the recommendation</b>
<b>Recommendation 3:</b> In patients with RA, use glucocorticoids at doses equivalent to prednisone 10–30 mg/day as initial treatment in combination with one of several conventional DMARDs followed by gradual dose tapering.	<i>Strong, in favour<sup>v</sup></i>
<b>Clinical question:</b> In DMARD-naïve patients with RA, what is the effect of treatment with bDMARDs or tsDMARDs, compared to csDMARDs?	<b>Strength of the recommendation</b>
<b>Recommendation 4:</b> In DMARD-naïve patients with RA, use MTX as initial treatment, usually in combination with glucocorticoids.	<i>Strong, in favour<sup>u</sup></i>
<b>Recommendation 5:</b> Consider avoiding TNF inhibitors in combination with MTX, IL-6R inhibitors, ABA, or JAK inhibitors as first-line treatment because, although associated with significantly better clinically-relevant outcomes than MTX monotherapy, the magnitude of the difference was found to be small, a significant percentage of patients responded well to MTX alone, and MTX was not combined with glucocorticoids.	<i>Weak, against<sup>u</sup></i>

### Important clinical considerations

- Subgroups to consider:
  - Give preference to options other than JAK inhibitors in  $\geq 65$ -year-olds, current smokers (and former smokers who have a long history of smoking or have been heavy smokers), and people with an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible effective dose.

### Treatment of RA in patients resistant to csDMARDs

<b>Clinical question:</b> In patients with RA who have an inadequate response to MTX monotherapy, is it more effective to add a bDMARD or to use csDMARD combination therapy?	<b>Strength of the recommendation</b>
<b>Recommendation 6:</b> In patients with RA who have an inadequate response to MTX monotherapy, use either a combination of csDMARDs or a bDMARD, depending on the patient's characteristics.	<i>Strong, in favour<sup>v</sup></i>
<b>Clinical question:</b> In patients with RA who have an inadequate response to csDMARDs, is it more effective to add a bDMARD or a tsDMARD?	<b>Strength of the recommendation</b>
<b>Recommendation 7:</b> In patients with RA who have an inadequate response to csDMARDs, use combination therapy, with either a bDMARD or a tsDMARD, depending on the patient's characteristics and risk*  *considering risk factors for cardiovascular disease and cancer	<i>Strong, in favour<sup>v</sup></i>

### Treatment with a first bDMARD or tsDMARD

<b>Clinical question:</b> In patients with RA, what is the efficacy of the combination of any bDMARD with a csDMARD other than MTX?	<b>Strength of the recommendation</b>
<b>Recommendation 8:</b> In patients with RA eligible for biological therapy with contraindications or intolerance to MTX, consider using LEF in combination with a bDMARD.	<i>Weak, in favour<sup>v</sup></i>

<b>Clinical question:</b> In patients with RA, what dose of MTX in combination with a bDMARD is associated with the best clinical outcomes, highest drug concentrations and lowest antibody production?	<b>Strength of the recommendation</b>
<b>Recommendation 9:</b> In patients with RA receiving combination treatment with MTX and TNF inhibitors, use MTX at doses of at least 10 mg/week.	<i>Strong, in favour<sup>V</sup></i>
<b>Clinical question:</b> In patients with RA, are there differences in efficacy between the different bDMARDs used as first-line treatment?	<b>Strength of the recommendation</b>
<b>Recommendation 10:</b> In patients with RA, it is not currently possible to recommend a specific bDMARD for first-line therapy in combination with MTX.	<i>Weak, against<sup>V</sup></i>
<b>Recommendation 11:</b> For monotherapy, consider using an IL-6R inhibitor rather than a TNF inhibitor.	<i>Weak, in favour<sup>V</sup></i>
<b>Clinical question:</b> In patients with RA, what is the efficacy of tsDMARD monotherapy compared to csDMARD or bDMARD monotherapy?	<b>Strength of the recommendation</b>
<b>Recommendation 12:</b> In patients eligible for bDMARD or tsDMARD therapy in whom, for any reason, these drugs cannot be used in combination with csDMARDs, the GDG considers JAK inhibitor monotherapy a good alternative treatment, except in high-risk cases.	<i>Good clinical practice<sup>V</sup></i>

### Treatment after an inadequate response to a first bDMARD

<b>Clinical question:</b> In patients with RA who have an inadequate response to a first TNF inhibitor, what is the effect of a second TNF inhibitor, a non-TNF-inhibitor bDMARD or a tsDMARD?	<b>Strength of the recommendation</b>
<b>Recommendation 13:</b> In patients with RA who have had an inadequate response to a first TNF inhibitor, consider using a bDMARD with a different mechanism of action, a JAK inhibitor or a second TNF inhibitor.	<i>Weak, in favour<sup>U</sup></i>
<p><u>Important clinical considerations</u></p> <ul style="list-style-type: none"> <li>• Implementation-related factors: <ul style="list-style-type: none"> <li>- Factors such as age, disease characteristics, associated comorbidities, and reasons for discontinuing previous treatment may help guide the choice of the most appropriate treatment for each patient.</li> </ul> </li> </ul>	

- Subgroups to consider:
  - Give preference to options other than JAK inhibitors in  $\geq 65$ -year-olds, current smokers (and former smokers who have a long history of smoking or have been heavy smokers), and people with an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible effective dose.

### Remission/dose tapering

<b>Clinical question:</b> In patients with RA treated with a bDMARD who have achieved disease remission, what is the rate of relapse when the dose is tapered?	<b>Strength of the recommendation</b>
<b>Recommendation 14:</b> In patients with RA who have achieved remission or low disease activity with a bDMARD for at least 6 months, consider tapering the dose of the biologic, despite the risk of relapse.	<i>Weak, in favour<sup>v</sup></i>

### Interstitial lung disease

<b>Clinical question:</b> In patients with RA and interstitial lung disease (ILD), which drugs have been shown to be efficacious, effective, and safe for the treatment of the lung disease?	<b>Strength of the recommendation</b>
<b>Recommendation 15:</b> In patients with RA and ILD who require treatment intensification to control joint symptoms, use RTX, ABA, an IL-6R inhibitor, or a JAK inhibitor as they are considered the safest options for lung disease.	<i>Strong, in favour<sup>u</sup></i>
<b>Recommendation 16:</b> In patients with RA and stable ILD treated with a TNF inhibitor, there is no conclusive evidence to justify withdrawal if good control of joint symptoms has been achieved, since there is insufficient evidence to warrant a blanket contraindication of these drugs in this group.	<i>Good clinical practice<sup>u</sup></i>

Important clinical considerations

- Monitoring- and assessment-related factors:
  - It should be taken into account that the clinical course of RA-associated ILD is very variable. In 45% of patients, ILD is stable or progresses slowly, while the other 55% experience more or less rapid worsening of lung function.
  - Given that the majority of studies do not describe the pattern of changes in pulmonary function tests (PFTs) before starting biological therapy, and that monitoring PFT data are not reported for all patients, it is not possible to assume that all have active and progressive ILD. Consequently, the assessment of the efficacy of treatments in slowing ILD progression is associated with high levels of uncertainty and variability.
  - This constrains the ability to draw robust and reliable conclusions regarding their efficacy in ILD, and hence, recommendations are primarily based on their safety in ILD.
- Subgroups to consider:
  - Give preference to options other than JAK inhibitors in  $\geq 65$ -year-olds, current smokers (and former smokers who have a long history of smoking or have been heavy smokers), and people with an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible effective dose.

**Recommendation 17:** In the subgroup of patients with RA and progressive fibrosing ILD, use NTB while maintaining background RA treatment.

*Strong, in favour<sup>U</sup>*

**Recommendation 17.1:** In patients with intolerance to NTB, consider using PFN.

*Weak, in favour<sup>U</sup>*

Important clinical considerations

- Monitoring- and assessment-related factors
  - While 55% of patients with ILD experience more or less rapid worsening of lung function, it has been estimated that 40% meet the criteria for the diagnosis of progressive fibrosing ILD in the first 5 years after disease onset.
  - In accordance with the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society and Latin American Thoracic Society guideline, progressive pulmonary fibrosis is defined by fulfilling at least 2 of the following 3 criteria: (1) increase in fibrosis on computed tomography, (2) worsening of respiratory symptoms, and/or (3) a  $\geq 5\%$  decline in predicted forced vital capacity

(FVC) or a  $\geq 10\%$  decline in diffusing capacity of the lungs for carbon monoxide (DLCO) over 1 year of follow-up.

- Unlike NTB, PFN is not currently approved by the Spanish Agency of Medicines and Medical Devices (AEMPS) for this condition.

### Cardiovascular comorbidity

<b>Clinical question:</b> In patients with RA, what is the risk of cardiovascular events and thromboembolic disease associated with bDMARDs and tsDMARDs?	<b>Strength of the recommendation</b>
<b>Recommendation 18:</b> In patients with RA who do not have related cardiovascular or thromboembolic risk factors, use either bDMARDs or tsDMARDs.	<i>Strong, in favour<sup>U</sup></i>
<b>Recommendation 19:</b> In patients with RA aged $\geq 65$ years and those with cardiovascular or thromboembolic risk factors, consider avoiding tsDMARDs unless no other treatment options are available. If these drugs are required, the lowest possible effective dose should be used and cardiovascular risk factors closely monitored.	<i>Weak, against<sup>U</sup></i>
<p><u>Important clinical considerations</u></p> <ul style="list-style-type: none"> <li>• Pretreatment assessment- and monitoring-related factors           <ul style="list-style-type: none"> <li>- Before and after starting bDMARD or tsDMARD therapy, potentially modifiable cardiovascular and thromboembolic risk factors should be assessed.</li> </ul> </li> </ul>	

## Serious infections

<b>Clinical question:</b> In patients with RA treated with bDMARDs who have had a serious infection, is it safe to restart the biological therapy?	<b>Strength of the recommendation</b>
<b>Recommendation 20:</b> Before initiating bDMARD or tsDMARD therapy in patients with RA, a comprehensive assessment of the risk of infection should be performed, considering factors such as age, concomitant treatments, comorbidities and vaccination status, to accurately identify potential risk factors for serious infection.	<i>Good clinical practice<sup>v</sup></i>
<b>Recommendation 21:</b> In patients with RA and no risk factors for infection, consider using bDMARDs or tsDMARDs as safe options.	<i>Weak, in favour<sup>v</sup></i>
<b>Recommendation 22:</b> In patients with RA aged $\geq 65$ years with concomitant lung disease or a history of smoking, JAK inhibitors should only be used if no suitable alternative treatments are available.	<i>Good clinical practice<sup>v</sup></i>
<p><u>Important clinical considerations</u></p> <ul style="list-style-type: none"> <li>Implementation-related factors: <ul style="list-style-type: none"> <li>Based on the results of the ORAL Surveillance study on tofacitinib (TOF) and data on the other three JAK inhibitors available in the EU, the European Medicines Agency (EMA) and AEMPS have issued recommendations to minimise the risk of major adverse events associated with this class of drugs in the treatment of various chronic diseases. These adverse effects include cardiovascular events, thrombosis, malignancies, and infections.</li> </ul> </li> </ul>	

## Cancer

<b>Clinical question:</b> In patients with RA, what is the risk of new or recurrent cancer (melanoma or nonmelanoma skin cancer, solid tumours or haematological cancer) associated with bDMARD or tsDMARD therapy?	<b>Strength of the recommendation</b>
<b>Recommendation 23:</b> In patients with RA, the drugs with the best safety profiles in relation to cancer risk are TNF inhibitors, IL-6R inhibitors and RTX. Do not use tsDMARDs unless no alternative treatments are available.	<i>Strong, against<sup>u</sup></i>

<p><b>Recommendation 24:</b> In patients with RA and a history of solid tumours who require bDMARD or tsDMARD therapy, TNF inhibitors, IL-6R inhibitors and RTX should be preferred</p>	<p><i>Good clinical practice<sup>U</sup></i></p>
<p><b>Recommendation 25:</b> In patients with RA and a history of haematological cancer or lymphoma who require bDMARD or tsDMARD therapy, RTX should be preferred.</p>	<p><i>Good clinical practice<sup>U</sup></i></p>
<p><u>Important clinical considerations</u></p> <ul style="list-style-type: none"> <li>• Subgroups to consider: <ul style="list-style-type: none"> <li>- Give preference to options other than JAK inhibitors in <math>\geq 65</math>-year-olds, current smokers (and former smokers who have a long history of smoking or have been heavy smokers), and people with an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible effective dose.</li> <li>- Drug class: Although there are some differences between the various TNF inhibitors and JAK inhibitors, the GDG has decided that recommendations should be made by drug class, as it is not currently possible to demonstrate that small differences in the mechanism of action between drugs in the same class lead to significant differences in safety profile. Nonetheless, it should be recalled that TOF is the only drug for which an increase in cancer risk has been demonstrated.</li> </ul> </li> </ul>	

## Treatment adherence

<p><b>Clinical question:</b> In patients with RA, which individual-, disease- and treatment-related factors are associated with poor treatment adherence/persistence?</p>	<p><b>Strength of the recommendation</b></p>
<p><b>Recommendation 26:</b> In patients with RA, treatment adherence should be monitored, especially in women, as well as individuals with advanced age or multimorbidity.</p>	<p><i>Good clinical practice<sup>V</sup></i></p>
<p><b>Recommendation 27:</b> To improve treatment adherence, patient education programmes should be run and relationships of trust fostered between patients and doctors.</p>	<p><i>Good clinical practice<sup>V</sup></i></p>

## The role of nursing

<b>Clinical question:</b> In patients with RA, what is the efficacy of nurse-led educational intervention programmes?	<b>Strength of the recommendation</b>
<b>Recommendation 28:</b> Specific individual or group-based educational programmes delivered by nursing staff should be part of the routine follow-up for patients with RA.	<i>Good clinical practice<sup>V</sup></i>
<b>Recommendation 29:</b> Continuity should be ensured in the delivery of specific nurse-led education programmes.	<i>Good clinical practice<sup>V</sup></i>

## General advice on patient management

The management of RA should take into account individual patient characteristics.	<i>Good clinical practice<sup>V</sup></i>
Treatment should be started as early as possible; hence, prompt diagnosis is essential. It is also crucial to avoid delays in changing treatment when a patient does not respond well to a given therapy or experiences a flare-up.	<i>Good clinical practice<sup>V</sup></i>
Before starting a treatment, patients should be adequately informed about the pharmacological properties of the medication, treatment duration, and expected benefits, as well as potential adverse effects, taking their preferences into account.	<i>Good clinical practice<sup>V</sup></i>
Before prescribing bDMARDs or tsDMARDs, the following should be considered: age, previous treatment, patient preferences, tolerance, the risk of adverse events, the possibility of pregnancy, and the cost-effectiveness ratio.	<i>Good clinical practice<sup>V</sup></i>
In the treatment of RA, it is essential to take into account the assessment and management of related comorbidities.	<i>Good clinical practice<sup>V</sup></i>
Patients and/or their families should be instructed in joint self-care and in self-management of bDMARD and tsDMARD therapy.	<i>Good clinical practice<sup>V</sup></i>

<sup>V</sup> Recommendations from GUIPCAR 2019 that are considered to be still valid

<sup>N</sup> Recommendations related to questions that are new in the 2025 GUIPCAR guideline

<sup>U</sup> Recommendations from GUIPCAR 2019 that have been updated



## 1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory systemic autoimmune disease that mainly affects the joints. The damage is first noted in the synovial membrane, and then spreads to neighbouring structures, compromising the cartilage, ligaments, joint capsules and bone. On the other hand, systemic inflammatory changes can lead to involvement of the heart, lungs, kidneys, skin and eyes, among other organs, as well as the hematopoietic and/or neuro-psychiatric systems. If patients are not adequately treated, the disease usually results in joint destruction and functional impairment and increases the risk of death<sup>1</sup>.

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, sexual, environmental, infectious and genetic susceptibility factors that may increase the likelihood of developing RA<sup>2</sup>.

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 a clinical practice guideline (CPG), with the participation of a multidisciplinary team of health professionals involved in their care. A CPG can be defined as a document that gathers a set of recommendations based on a systematic review (SR) of the evidence and assessment of the risks and benefits of alternative care options, seeking to optimise the provision of healthcare<sup>3</sup>.

The recommendations of the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) have been the most widely used internationally<sup>4,5</sup>. In Spain, the benchmark guideline (GUIPCAR) was first developed by the SER in 2001 and has been updated three times, in 2007, 2011 and 2019<sup>6,7</sup>. Major advances in recent years, especially in the field of treatment, warrant a new update of the guideline content. In this context, we have developed the GUIPCAR 2025, a CPG for the management of patients with RA, which seeks to guide users on the optimal use of available treatments for this disease, as well as assess their effectiveness.

## 1.1 2025 Update

Since the publication of GUIPAR 2019, the development and approval of new treatment options for RA have prompted SER to update the guideline. There is a need to include new biological therapies for the disease, such as Janus kinase (JAK) inhibitors, the strategies for recent-onset RA, studies that provide new evidence concerning the use and safety of glucocorticoids (GCs) in older people, and new treatments approved for interstitial lung disease in patients with RA. It is also necessary to review emerging concerns about the role of JAK inhibitors in clinical practice, given potential associations with the occurrence of major cardiovascular events and cancer.

Lastly, it is essential to take into account recent data that warrant modifications in recommendations on treatment tapering in RA.

The new guideline, GUIPAR 2025, is the result of the work of a considerable number of health professionals from across Spain involved in the management of patients with RA. The guideline is organised into chapters that provide an answer to the questions posed at the start of each one. Then, the recommendations are presented, followed by a summary of the evidence.

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.

## 2. Scope and objectives

### 2.1. Scope

This guideline focuses on the care of adult patients with RA. It seeks to provide users with guidance concerning an ideal approach to using the various therapeutic interventions available for this disease, as well as general principles of diagnosis and monitoring.

Patients with juvenile idiopathic arthritis are beyond the scope of the guideline.

It addresses factors associated with treatment of the disease, including alternative treatment options, and covers general matters concerning diagnosis, prognostic factors, monitoring and collaboration with other specialities (pulmonologists, cardiologists and general practitioners [GPs]).

### 2.2. Objectives of the guideline

#### **Main objective:**

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

#### **Specific objectives:**

- To enhance the clinical skills of health professionals involved in the care of adults with RA to improve the quality of 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 potential pharmacological and non-pharmacological treatments
- To summarise the scientific evidence to increase the knowledge of all health professionals involved in the care process, seeking to improve patient quality of life
- To improve the clinical approach to RA with recommendations focused on the early initiation of treatment to minimise 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 informational materials for patients with RA and their families and caregivers to help them better understand the process and the factors that have an impact on the course of the disease.

### **2.3. Target users of the guideline**

Seeking to achieve comprehensive patient care, this guideline is 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, trauma, rehabilitation, family medicine, and nursing, as well as other specialists participating in the care of these patients. It is also aimed at patients and family members seen by these health professionals. For patients and families, this is a tool that can help them learn about the potential strategies for RA treatment and what this treatment may achieve, to minimise the use of treatment regimens that are not backed by scientific evidence or strong expert consensus.

### 3. Method of development

To update this CPG for the management of patients with RA, we followed a series of steps, as described below. The methods used have been based on the methodology handbook for updating CPGs in the Spanish Health System<sup>8</sup>.

#### **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 CPG 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 by contacting the relevant scientific societies. As members of the expert panel, these people were responsible for drafting the recommendations in the CPG.
- Reviewers of the scientific evidence: several rheumatologists, members of the SER working group and external experts were responsible for systematically reviewing the available scientific evidence.
- Patients: apart from clinical professionals, one patient 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 guideline and deadlines.

#### **Review of the existing GUIPCAR and decisions on the update**

This guideline is a partial update of GUIPCAR 2019. The process for reviewing this previous version and deciding which aspects needed updating involved various steps:

1. Before updating the guideline, a survey was conducted concerning the topics included in previous versions.

2. A ranked list was drawn up of clinical questions that potentially needed updating based on the results of the aforementioned survey and on clinical factors, and consensus was reached on the new content to be included in the guideline.

3. A review and formal ranking process was conducted, involving face-to-face and online discussions, and in the end, five of the clinical questions in the previous guideline were updated.

### **Definition of the scope and objectives**

The time since publication of the previous GUIPCAR and the new evidence that has emerged during that period warranted updating the guideline. This new GUIPCAR is a partial update and replaces the previous version. Its scope and objectives were defined by consensus based on the clinical experience and knowledge of the participating health professionals.

### **Drafting of the clinical questions**

The GDG analysed and reviewed the clinical questions from the previous guideline to determine which should be prioritised for review and to make decisions on their updating. After establishing the criteria to be applied to identify questions that could be maintained with no changes in the associated recommendations, those that needed to be modified, and those to be included in the guideline for the first time, the GDG decided on the following categories of questions:

- New clinical questions, identified and agreed on by members of the GDG and redrafted using the Patient, Intervention, Comparison and Outcome (PICO) framework; three such questions were identified.
- Questions addressed in GUIPCAR 2019 that needed updating, given that the GDG were aware of new evidence that might influence the drafting of the associated recommendations; two such questions were identified.
- Questions that could still be considered valid based on the hypothesis that the associated recommendations would not differ from those in the previous version; 15 such questions were identified.

### **Literature search, evaluation and evidence synthesis**

A literature search was conducted in the following databases: Medline (through PubMed), Embase (Elsevier), and Cochrane Library (Wiley Online Library). These databases were selected because they are among the key sources of biomedical information to which we had access.

In the case of questions for which recommendations remained valid, the literature search was updated using the same strategy as for GUIPCAR 2019, but seeking to retrieve studies published after the drafting of that version, that is, as of the start of 2019. For the newly developed questions, no restrictions were placed on publication date, and searches were performed up to June 2024. Initially, all the search strategies were designed to retrieve only primary studies from the aforementioned databases; however, when this approach yielded few or irrelevant results, it was supplemented by a manual search performed using reference lists of key documents selected for the review. References proposed by researchers and reviewers were also included. In this way, we identified studies published in 2025, which is later than the scope of the initial literature search. Studies published in Spanish, English or French were considered.

The references retrieved were managed using EndNote X7.

### **Study inclusion criteria**

Studies were included if they had the characteristics described below:

*Study population:* adults diagnosed with RA

*Intervention:* conventional synthetic, biological or targeted synthetic disease-modifying antirheumatic drugs (csDMARDs, bDMARDs or tsDMARDs, respectively), treatment failure, management involving pulmonologists or cardiologists; and risk factors for cardiovascular events or cancer.

*Outcome variables:* efficacy in reducing disease activity and structural damage, measured with the usual clinical parameters; functional capacity; quality of life (patient-reported outcome measures); progression of radiographic damage or pulmonary function test results; respiratory infections; cardiovascular events; survival; major adverse events; and occurrence or recurrence of cancer.

*Study design:* meta-analyses and SRs of randomised controlled trials (RCTs), double-blind phase III and IV RCTs, retrospective or prospective observational and descriptive studies (cohort and case-control studies) and registries.

## Exclusion criteria

The following were excluded: studies in children, adolescents and pregnant women; studies for which the PICO framework is not suitable, due to 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.

## Analysis and synthesis of the scientific evidence

Studies likely to be relevant were selected based on the aforementioned selection criteria. The quality of the evidence was assessed using the methods developed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)<sup>9</sup> working group. For determining the quality of evidence or certainty in evidence, as well as the design and methodological quality of individual studies, the GRADE system considers other factors that influence the confidence in the estimates reported. Specifically, the following were analysed: the consistency of results between studies, the directness or indirectness of the evidence (including indirect comparisons of the interventions of interest and/or differences in the population, the intervention, the comparator and/or the results of interest with regard to the objectives of this document), the precision of the estimates and potential publication bias. As shown in Table 1, taking these factors into account, the quality of the evidence for each critical or important outcome was classified and defined as high ⊕⊕⊕⊕ (very unlikely that new studies would change the estimate), moderate ⊕⊕⊕⊖ (likely that new studies would change the confidence in the estimate), low ⊕⊕⊖⊖ (very likely that new studies would have an effect on the confidence in the estimate and might change it) or very low ⊕⊖⊖⊖ (any estimated outcome is highly uncertain). The outcomes considered in each question and their importance can be consulted in Appendix 4.

**Table 1. GRADE approach to rating the quality of evidence<sup>9</sup>**

Quality	Study design	Factors that can reduce the quality of the evidence*	Factors that can increase the quality of the evidence**
High ⊕⊕⊕⊕	RCT	<ul style="list-style-type: none"> <li>• Limitations in study quality (design): Large (-1) Very large (-2)</li> </ul>	Association: <ul style="list-style-type: none"> <li>• Scientific evidence of a strong association (RR&gt;2 or &lt;0.5 based on observational studies with no plausible confounders) (+1)</li> </ul>
Moderate ⊕⊕⊕⊖	--	<ul style="list-style-type: none"> <li>• Inconsistency: Large (-1) Very large (-2)</li> <li>• Indirectness of evidence: Large (-1) Very large (-2)</li> </ul>	<ul style="list-style-type: none"> <li>• Scientific evidence of a very strong association (RR&gt;5 or &lt;0.2 based on studies with a low risk of bias) (+2)</li> <li>• Dose-response gradient (+1)</li> </ul>
Low		<ul style="list-style-type: none"> <li>• Indirectness of evidence: Large (-1) Very large (-2)</li> </ul>	

⊕⊕⊕⊕	Observational studies	<ul style="list-style-type: none"> <li>• Imprecision: Large (-1) Very Large (-2)</li> </ul>	<ul style="list-style-type: none"> <li>• All plausible confounding would reduce the demonstrated effect (+1)</li> </ul>
Very low ⊕⊕⊕⊕	Studies with other designs	<ul style="list-style-type: none"> <li>• High risk of publication bias: (-1)</li> </ul>	

\* In the case of RCTs, the rating of the quality of the scientific evidence may decrease  
 \*\* In the case of observational studies, the rating of the quality of the evidence may increase  
 RCT: randomised controlled trial; RR: relative risk.

To standardise the visual presentation of the quality of the evidence, in the case of questions from previous GUIPCAR CPGs for which the recommendations were considered to be still valid or were updated through a restricted literature search or search for secondary evidence, the Oxford Centre for Evidence-based Medicine levels of evidence have been transformed to the GRADE system<sup>10-12</sup>.

### Formulation of recommendations

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

- 1) The quality or certainty of the scientific evidence identified
- 2) Patient values and preferences
- 3) The balance between the desirable and undesirable effects of the interventions
- 4) Considerations such as equity, acceptability and feasibility of implementing the interventions
- 5) Other factors.

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

**Table 2. Implication of the strength of recommendations in the GRADE approach<sup>9</sup>**

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

On the other hand, on some occasions, the GDG identified important practical issues it wanted to highlight, but for which there was unlikely to be any supporting evidence. In general, these issues concern aspects of treatment considered good clinical practice and which are not commonly questioned. Such issues have been evaluated as recommendations for good clinical practice.

The recommendations associated with the questions from earlier GUIPCAR CPGs which were still considered valid have also been transformed from the Oxford Centre for Evidence-based Medicine system for grading recommendations to the GRADE system<sup>10-12</sup>.

### **Information for patients**

After the updating of the guideline incorporating new evidence on the treatment of RA, we addressed the task of updating the information for patients.

### **External review and publication of the final document**

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

After this, the guideline was externally reviewed by professionals selected for their knowledge of this condition and guideline development methods.

## **Public scrutiny**

The draft of the complete version of this CPG entered a process of public scrutiny by the members of the SER and stakeholders (pharmaceutical industry, other scientific societies and patients' associations). It was made available on the website of the SER for 15 days, together with a questionnaire to collect comments, seeking to gather data on people's opinions and scientific assessment of the guideline's methods and/or recommendations. Detailed information concerning this process is provided in an appendix on the SER website: [www.ser.es](http://www.ser.es), 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), and the Spanish Society of Family and Community Medicine (SemFYC) and a national coordinator of associations for patients with arthritis and their families in Spain (ConArtritis).

## **How to use this guideline**

This CPG is organised into chapters. Each chapter referring to treatment states a PICO question followed by a brief introduction to the question, lists the associated recommendations and summarises the amount of evidence, its consistency, applicability, and relevance in our setting.

## 4. Epidemiological data and clinical manifestations

### 4.1. Epidemiology and size of the problem

As described in the EPISER<sup>13, 14</sup> study, there is considerable variability in prevalence between geographical areas. Globally, the annual incidence was found to range from 25 to 50 per 100,000 people and prevalence from 0.5% to 1%<sup>15</sup>. In Europe, reported prevalence rates vary, with values of 0.65% in Germany<sup>16</sup> and Sweden<sup>17</sup>, 0.19% in France<sup>18</sup> and 0.41% in Italy<sup>19</sup>. As well as showing geographical variability, disease frequency also differs by age, sex, and socioeconomic status and depending on the methods and case definitions used to estimate prevalence<sup>20</sup>.

In Spain, the EPISER<sup>13, 14</sup> study estimated a prevalence of RA of 0.82% (95% CI: 0.59 to 1.15) overall, 0.76% (95% CI: 0.44 to 1.31) in men and 0.88% (95% CI: 0.58 to 1.35) in women. Further, it calculated that between 220,000 and 430,000 people over 20 years old had RA in 2016. The mean age of the cases of RA identified was  $60.48 \pm 14.85$  years, and the male-to-female ratio was 38.5%:61.5%.

### 4.2. Clinical manifestations

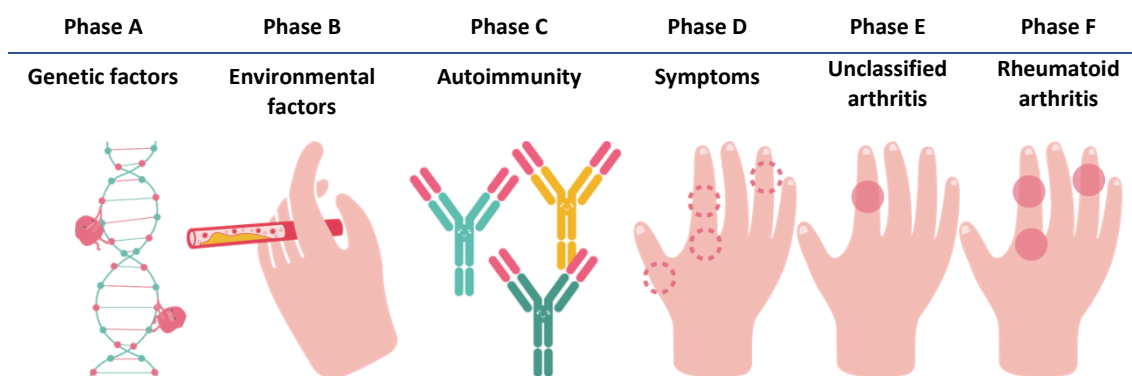
A detailed description of the clinical manifestations of RA is beyond the scope of this guideline. In brief, the key signs and symptoms of RA are pain and swelling in the joints involved, particularly the hands, with a symmetrical pattern. Additionally, it presents with general symptoms such as fatigue, malaise, morning stiffness, weakness, functional limitation and depression. These symptoms, potentially in combination with involvement of extra-articular sites –such as the skin, cardiovascular system, bones, nervous system, eyes, and lungs, among others– reduce both quality of life and life expectancy<sup>1, 21</sup>.

## 5. Pathogenesis. The development of RA

Currently, it is accepted that there are several phases in the development of RA (Figure 1), which the EULAR study group for risk factors for RA attempted to define and classify in 2012<sup>22</sup>. The published report defines the following phases in the development of the disease:

- 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: arthritis is detected, but described as unclassified or undifferentiated, as there is insufficient evidence to confirm the diagnosis of RA
- Phase F: RA

**Figure 1. Phases in the development of RA**



Source: 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 finally 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<sup>23</sup>. 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 missing in ACPA-negative patients. The genetic factor most strongly 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. This association is particularly strong among ACPA-

positive individuals. Certain 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<sup>24</sup>. Several other environmental factors have also been associated with the development of RA including periodontal disease, occupational silica exposure, consumption of salt and alcohol (the latter having a protective effect, and hormonal levels<sup>25</sup>.

The presence of both rheumatoid factor (RF) and ACPA has been detected several years before the development of RA. The risk of developing RA is higher with positive ACPA than positive RF and higher the longer the time horizon<sup>26,27</sup>.

A further step in the development of the disease is the onset of signs and symptoms with no clinically detectable inflammation. Various studies 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-traumatic 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<sup>28</sup>. 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<sup>29</sup>.

Continuing along the progression of the pathological process, there are 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<sup>30</sup>.

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<sup>31</sup>. Understanding the phases of pathogenesis of the disease should facilitate early treatment, which has been shown to be one of the most important factors in the long term<sup>32</sup> in the context of the concept of a window of opportunity<sup>33</sup>. Advancing our knowledge of the phases during 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 how we identify individuals who are going to develop RA, how we decide which patients to treat and what type of treatment is appropriate. 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 ACR criteria or radiological damage. Nonetheless, given that none of these factors is sufficient on its own, using a combination of predictors is likely to be the best approach to predicting disease persistence.

Overall, 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 the expansion of the therapeutic arsenal in recent years, have led to a revolution in our conception of the disease and its prognosis.

## 6. Clinical research questions (PICO)

### **Classification/Diagnosis**

In patients with recent-onset RA, what is the clinical utility of the 2010 classification criteria compared to those published in 1987?<sup>V</sup>

### **Initial pharmacological treatment**

In patients with RA, what is the efficacy of initial treatment with glucocorticoids at doses equivalent to more than 10 mg of prednisone, added to any DMARD?<sup>V</sup>

In patients with RA, what is the efficacy of initial treatment with triple csDMARD therapy?<sup>V</sup>

In DMARD-naïve patients with RA, what is the effect of treatment with bDMARDs or tsDMARDs, compared to csDMARDs?<sup>N</sup>

### **Treatment of patients who are refractory to conventional DMARDs**

In patients with RA who have an inadequate response to methotrexate (MTX) monotherapy, is it more effective to add a bDMARD or to use csDMARD combination therapy?<sup>V</sup>

In patients with RA who have an inadequate response to csDMARDs, is it more effective to add a bDMARD or a tsDMARD?<sup>V</sup>

### **Treatment with a first biological or targeted DMARD**

In patients with RA, what is the efficacy of the combination of any bDMARD with a csDMARD other than MTX?<sup>V</sup>

In patients with RA, what dose of MTX in combination with a bDMARD is associated with the best clinical outcomes, highest drug concentrations and lowest antibody production?<sup>V</sup>

In patients with RA, are there differences in efficacy between the different bDMARDs used as first-line treatment?<sup>V</sup>

In patients with RA, what is the efficacy of tsDMARD monotherapy compared to csDMARD or bDMARD monotherapy?<sup>V</sup>

### **Treatment after an inadequate response to a first bDMARD**

In patients with RA who have an inadequate response to a first TNF inhibitor, what is the effect of a second TNF inhibitor, a non-TNF-inhibitor bDMARD or a tsDMARD?<sup>U</sup>

### **Remission/dose tapering**

In patients with RA treated with a bDMARD who have achieved disease remission, what is the rate of relapse when the dose is tapered?<sup>V</sup>

### **Interstitial lung disease**

In patients with RA and interstitial lung disease (ILD), which drugs have been shown to be efficacious/effective/safe for the treatment of the lung disease?<sup>U</sup>

### **Cardiovascular comorbidity**

In patients with RA, what is the risk of cardiovascular events and thromboembolic disease associated with bDMARDs and tsDMARDs?<sup>N</sup>

### **Serious infections**

In patients with RA treated with bDMARDs who have had a serious infection, is it safe to restart the biological therapy?<sup>V</sup>

### **Cancer**

In patients with RA, what is the risk of new or recurrent cancer (melanoma or nonmelanoma skin cancer, solid tumours or haematological cancer) associated with bDMARD or tsDMARD therapy?<sup>N</sup>

### **Treatment adherence**

In patients with RA, which individual-, disease- and treatment-related factors are associated with poor treatment adherence/persistence?<sup>V</sup>

### **The role of nursing**

In patients with RA, what is the efficacy of nurse-led educational interventions?<sup>V</sup>

<sup>V</sup> Questions from GUIPCAR 2019 that are considered to be still valid

<sup>N</sup> New questions

<sup>U</sup> Questions from GUIPCAR 2019 that have been updated

## 7. Classification/Diagnosis

### 7.1. New criteria (2010 ACR/EULAR)

**Clinical question 1** (valid)

In patients with recent-onset RA, what is the clinical utility of the 2010 classification criteria compared to those published in 1987?

### Recommendations

**Recommendation 1:** In patients with seropositive arthritis, use the 2010 ACR/EULAR classification criteria to support the clinical judgement of the rheumatologist ([Strong recommendation, in favour](#))<sup>v</sup>.

**Recommendation 2:** In patients with seronegative arthritis, the use of these classification criteria is not recommended, and diagnosis should be based on the clinical judgement of the rheumatologist ([Good clinical practice](#))<sup>v</sup>.

<sup>v</sup>[Recommendation related to a question in the previous GUIPCAR guideline considered still valid](#)

The GDG considers that these two recommendations from the 2019 GUIPCAR remain valid since the 2010 ACR/EULAR criteria have replaced the previous ones and are used in both clinical practice and clinical trials with no modifications.

### 7.2. Sources of delays in patient care

Delaying the start of treatment with the first DMARD after the onset of RA is associated with a poorer prognosis. It is now widely accepted that the optimal management of RA requires early diagnosis and initiation of DMARD therapy, ideally within the first 12 weeks after the onset of symptoms<sup>34-39</sup>. Unfortunately, the reality of rheumatology care in Spain is that patients wait an average of more than 6 months to receive their first DMARD after symptom onset, although it is not easy to accurately determine the date of the onset of symptoms of the clinical condition eventually diagnosed as RA<sup>40</sup>. According to the emAR study, the lag between symptom onset and starting DMARDs has progressively shortened in recent decades, but remains considerably longer than would be ideal<sup>41</sup>.

Although treatment delays are widespread, and can be attributed to many underlying social and cultural factors<sup>42</sup>, a key issue in both diagnostic and therapeutic delays is patients' perception that they do not have a serious condition and specifically that joint pain is a minor symptom for which they do not need to seek medical care<sup>43</sup>. Potential points of delay include the time patients take to recognise that they have a health problem, and seek an appointment with their GP, and the time it takes for this physician to refer patients to a rheumatologist, as well as waiting lists in rheumatology departments and for diagnostic tests, and delays in appointments for receiving results and starting treatment.

There are important delays in patient care not only around the time of diagnosis but also when treatment is being adjusted to induce a state of remission or, at least, of low inflammatory activity. The treatment-to-target approach is now generally accepted<sup>38, 43, 44</sup> and this type of strategy requires patients' condition to be reviewed every 1 to 3 months during the induction of remission.

Each of these factors needs to be addressed by specific measures, some of which depend on the organisation of health systems, while others clearly involve health education for the general population. Regarding measures to be implemented, experts agree on the following:

#### **Delays until seeking an appointment in primary care**

Campaigns to raise awareness among the general population about the initial symptoms of RA. These could be delivered through schools and colleges, targeting young people, or through the media, targeting the general population.

#### **Delays until referral to a rheumatologist**

Closer collaboration between GPs and rheumatology departments, through continuing medical education initiatives (performance of metatarsophalangeal and metacarpophalangeal squeeze tests, and hand and foot X-rays, requests for ACPA and RF tests).

#### **Waiting lists for specialists**

Proper allocation of human resources and systems facilitating communication and pathways for priority referral between primary care and rheumatology. Teleconsultations for patients, remote interprofessional consultations<sup>45</sup>, and/or rheumatologist clinics at local health centres may also prove useful.

### **Delays until appointments for receiving test results and starting treatment**

Establishment of protocols in early arthritis clinics and agreements with imaging departments and laboratories for prioritising tests when RA is suspected.

### **Difficulties in monitoring treatment response every 1 to 3 months**

Proper allocation of human resources and direct management of prioritised follow-up appointment scheduling by rheumatology departments themselves. In this regard, the intervals between appointments could be adjusted in accordance with the healthcare quality standards of the SER and the Rheumatology Society of the Madrid Region (SORCOM)<sup>46-48</sup>.

## 7.3. Primary care: general practitioners' role in detection and referral of patients with RA

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

In line with the numerous studies that recommend a well-planned, systematic approach to achieve accurate, rapid suspicion and early diagnosis of RA, the role of GPs is key to minimising delays in the treatment of RA. The earlier a suitable therapy is started, the greater the likelihood of controlling the inflammatory process and reducing structural damage; that is, the higher the chance of taking action during the window of opportunity for treatment. Early arthritis diagnosis is one of the keystones of disease control; therefore, when cases of suspected recent-onset arthritis are seen in primary care, experts advise acting fast and following a standardised protocol<sup>32, 33, 40, 42, 49-52</sup>.

### **Clinical assessment of a patient with suspected arthritis**

In accordance with current guidelines for the early diagnosis of RA, the initial assessment of a patient with recent-onset arthritis in primary care should be based on a detailed clinical history and a thorough physical examination, as well as a series of relevant ancillary tests<sup>50, 52, 53</sup>.

The *medical history* should cover both personal and family history, including history of smoking, socioeconomic data, and the history of the disease and changes therein, as well as past and current treatments.

In the *physical examination*, in addition to a routine examination by organ and system, it is particularly important to carry out a detailed assessment of the musculoskeletal system and

promptly detect any inflammatory patterns in the event of either oligoarticular or polyarticular involvement, and whether there is also systemic involvement<sup>29, 54-57</sup>.

Regarding *ancillary tests*, various reviews and sets of recommendation suggest carrying out blood tests that include a complete blood count, measurement of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and RF levels, ACPA status (whenever laboratories offer this), biochemical parameters, and liver and kidney function, as well as routine urinalysis<sup>50, 53, 55, 58</sup>. Regarding the initial assessment of structural damage, X-rays should be taken of hands and feet. Other imaging such as ultrasound and magnetic resonance imaging (MRI) should be used in selected cases in which there is a high level of suspicion but arthritis is not clinically evident<sup>50, 59-64</sup>.

In patients with signs and symptoms suggesting early arthritis, various studies have demonstrated that assessing RF levels and ACPA status and performing a complete blood count and imaging tests help in the diagnosis of suspected cases<sup>50, 53, 55</sup>.

### **Initial treatment and referral to a rheumatologist of patients with suspected early arthritis**

#### *Initial treatment: analgesics, NSAIDs and glucocorticoids*

Various studies have concluded that if early arthritis is suspected, and initial treatment in primary care is required, this should focus on controlling symptoms with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). Symptomatic treatment should be started in parallel with referral to a rheumatologist, to avoid delays in analysing the aetiology of the case and achieve a definitive diagnosis as quickly as possible<sup>32, 33, 51</sup>. At this stage, oral glucocorticoids should be avoided or used at low doses for a limited period. If early arthritis is suspected, glucocorticoid therapy should only be prescribed by a rheumatologist and always in combination with a DMARD and based on its effect<sup>6</sup>.

#### *Referral to the rheumatologist*

Prompt referral of cases of early arthritis from GPs to rheumatologists helps avoid delays in diagnosis and treatment, making it possible to take advantage of the so-called “window of opportunity”<sup>32, 42, 49, 51</sup>. Table 3 summarises the rheumatology referral criteria of the SERAP project, developed by the SER in collaboration with GPs and the referral criteria for RA established by Emery et al.<sup>65</sup>. 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 in the case of suspected septic arthritis, which should be referred immediately, without waiting to confirm symptoms.

**Table 3. Criteria for referral from primary care to rheumatology**

Arthritis referral criteria from the SERAP project At least a 4-week history of the following:
<ol style="list-style-type: none"><li>1. Swelling of two or more joints</li><li>2. Pain on palpation of the metacarpophalangeal joints and/or carpal bones (positive squeeze test)</li><li>3. Morning stiffness lasting more than 30 minutes</li></ol>
<b>Specific criteria for referral for RA were established by Emery et al.</b>
<ol style="list-style-type: none"><li>1. Swelling of three or more joints</li><li>2. Metacarpophalangeal or metatarsophalangeal joint involvement (positive squeeze test)</li><li>3. Morning stiffness of <math>\geq 30</math> minutes</li></ol>

### **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 SR of Hua et al.<sup>50</sup>. One of the objectives of the review was to assess which tools, if used by GPs in patients with suspected early arthritis, might help them differentiate between inflammatory arthritis and other clinical conditions. Only two studies<sup>66, 67</sup> described simple questionnaires with items concerning 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 tested in small samples and have not been validated. The SR concluded that there was insufficient evidence to provide clear recommendations on this issue. Nonetheless, this same SR<sup>50, 68, 69</sup> 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 assessing RF levels and especially ACPA status, as well as identifying radiological changes, may help achieve an early diagnosis and improve the prognosis of patients with early arthritis.

#### *Proposals for improving the referral process*

To ensure that patients with suspected arthritis start treatment as early as possible, thereby delaying the impact of the disease and minimising the damage due to its progression, in turn, improving patient quality of life and prognosis, experts agree that it would be useful to:

- a) Develop and reach a consensus with GPs on protocols to help identify patients with early arthritis
- b) Establish referral pathways, in accordance with the aforementioned protocols in each region or healthcare area in Spain, that result in real reductions in the current delay in referral and improvements in the management of cases of suspected early arthritis, with a commitment to conduct regular reviews of their efficacy, the extent to which they are used and their suitability or need for improvement.

The ability of primary care clinicians to diagnose RA is strengthened by a direct and smooth relationship with rheumatology departments, and with early arthritis units (where they exist), or with an assigned rheumatologist, especially if all parties collaborate on creating the aforementioned referral protocols with well-defined criteria.

#### *Communication and coordination*

Finally, experts also consider that there is a set of strategies that can facilitate and improve communication and interaction between primary care and rheumatology, including:

- Promoting and strengthening the role of the assigned rheumatologist, already established in some Spanish 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, 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
- Improve the quality of interprofessional consultation reports concerning patients referred to rheumatology departments, in terms of the inclusion of appropriate information both in the referral by the GP and in the response by the rheumatologist. Providing all available information 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 models for networking, that is, for the “management of shared care”, which allow an appropriate level of communication and the

development of relationships, thereby facilitating the exchange of information, as well as interaction and participation in the decision-making process.

## 8. Treatment

### 8.1. 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 for a level of improvement known to be achievable, motivated by a perception that existing drugs were limited in number and effectiveness. This mindset has significantly changed both in terms of the development of a new treatment strategy and the availability of new, more effective drugs. These advances have led to the formulation of new recommendations for improving the therapeutic approach to RA<sup>36,37</sup>, the main 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 set more ambitious goals, 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<sup>70-72</sup>. This is related to the concept of a “window of opportunity”, defined as the period of time during which the disease is much more susceptible to treatment. In fact, very early treatment is associated with a higher probability of achieving disease remission, even treatment-free remission; moreover, it has been found, though with less certainty, that the approximate end of this window of opportunity is 15 to 20 weeks after the onset of symptoms<sup>51</sup>. Extending this idea, it has been recommended that early treatment with DMARDs be started even in patients with undifferentiated arthritis when progression to RA is strongly suspected<sup>53</sup>. In line with this, the classification criteria for RA have been changed, making them more applicable to patients with earlier RA<sup>31</sup>.

The key elements in a T2T strategy are the reaching of a treatment target, preferably sustained remission or, if not, a state of low disease activity, as measured using a validated tool for disease monitoring, and regular check-ups until this target is reached<sup>44</sup>. The importance of achieving remission is reflected in the fact that patients in clinical remission show no structural or functional progression<sup>73, 74</sup>. 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, Simplified 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<sup>75</sup>.

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 not be necessary for defining remission, given the good correlation between clinical and imaging remission<sup>76, 77</sup>. Indeed, recent studies have found that strategies based on imaging were not superior to considering the clinical remission of RA<sup>78, 79</sup>. This in no way rules out the use of ultrasound or MRI in certain situations in the management of patients with RA.

### **New 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 key targets in the disease pathogenesis. Most recently, small molecules have been developed for intracellular targets (targeted therapies) that widen treatment options, while also increasing the complexity of strategies for managing RA. These novel drugs are analysed in another section of this guideline.

### **Final considerations**

We should not overlook the importance of a set of general principles for managing RA. Treatment should be based on joint decision-making between patients and rheumatologists, in which adequate explanations of the disease, treatment options and treatment targets play an essential role<sup>36, 37</sup>. Given the complexity of RA and the numerous treatments available, rheumatologists are the specialists who should be responsible for managing the disease<sup>80, 81</sup>, though patient care should be delivered by a multidisciplinary team, involving nurses and other specialists. Lastly, recommendations on the importance of 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.

## 8.2. Drugs used in RA

### **Non-steroidal anti-inflammatory drugs**

NSAIDs are a group of chemically heterogeneous compounds which interfere with the production of eicosanoids and have moderate analgesic and anti-inflammatory effects. There are currently more than 20 different NSAIDs available for human use in numerous pharmaceutical formulations.

Most NSAIDs used clinically inhibit, to different extents, the isoforms of the cyclooxygenase enzyme (COX): COX-1 and COX-2. There is no evidence that combinations of NSAIDs are more effective than any one of them alone, and no sufficiently large randomised clinical trial 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<sup>82</sup>; 2) renal, involving the retention of sodium and water, which is responsible for the development of peripheral oedema, and also for triggering or worsening heart failure or hypertension; or 3) cardiovascular, increasing the incidence of cardiovascular events<sup>83</sup>, 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 4). Five general recommendations can be made regarding their use. 1) The decision to use a classical NSAID or COX-2 inhibitor should mainly depend on the patient's 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 gastroprotection with PPIs. 2) Although both classical NSAIDs and COX-2 inhibitors are associated with a higher cardiovascular risk, these adverse effects are generally 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 response to NSAIDs is somewhat idiosyncratic, and hence, they should be prescribed taking into account patients' prior experience with these drugs, in terms of effectiveness and tolerability. 5) Except for acetylsalicylic acid (ASA) at antiplatelet doses, no more than one NSAID should be used at a time in a given patient.

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

**Table 4. Usual doses of NSAIDs**

DRUG	TOTAL DOSE (mg/24 h)	DOSING INTERVAL (h)
Acetylsalicylic acid	3,000 – 6,000	6-8
Ibuprofen	1,200 – 2,400	8
Flurbiprofen	200 – 300	12
Prolonged-release flurbiprofen	200	24
Mefenamic acid	750 – 1,500	8
Meclofenamate Sodium	200 – 400	8
Diflunisal	500 – 1,000	12
Naproxen	500 – 1,000	12
Ketoprofen	200	8-12
Prolonged-release ketoprofen	200	24
Aceclofenac	200	12
Diclofenac	150 – 200	8-12
Prolonged-release diclofenac	100	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 widely used in RA (Table 5). In countries neighbouring Spain, patients with active RA often receive glucocorticoids concomitantly with conventional DMARDs, with use rates ranging from 38%<sup>84</sup> to 55%<sup>85</sup>, while in the AREXCELLENCE study<sup>86</sup> 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 symptoms by inhibiting inflammation. Nonetheless, research over the last decade has demonstrated that glucocorticoid treatment delays both the start and the progression of radiological joint damage, and hence, they are now considered a standard component of conventional DMARD therapy.

The favourable safety profile associated with these drugs at low doses (< 7.5 mg/day of prednisone or equivalent)<sup>87-89</sup>, and the variety of agents, routes of administration and regimens available, together with their low cost, make glucocorticoids in combination with conventional DMARDs a highly 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-dose glucocorticoids based on the opinions of experts and patients. These recommendations concluded that, in routine clinical practice, there is no need for special monitoring of such patients, except for screening for osteoporosis and pretreatment assessment of fasting blood glucose levels, risk factors for glaucoma and potential ankle oedema<sup>90</sup>.

To date, there is no evidence of significant differences in efficacy or adverse effects between 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 (first shifting from divided to single daily dosing, then gradually reducing it) until complete withdrawal of the medication if the clinical response is adequate.

**Table 5. Classification of glucocorticoids by duration of action**

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

Intra-articular 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 are injected.

## **Disease-modifying antirheumatic drugs**

DMARDs are a heterogeneous group of agents with different mechanisms of action and toxicity used in patients with RA to reduce inflammation and generally prevent potential negative outcomes of the disease (Table 6). 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 a full understanding of the mechanisms of action. The development and approval of biological and synthetic drugs for specific targets have expanded the family of DMARDs to include agents that selectively or specifically block extra- or intracellular therapeutic targets.

DMARDs are currently divided into two groups:

- Conventional synthetic DMARDs (csDMARDs): 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.

Although by definition all DMARDs modify rheumatic disease processes, there is a fundamental difference in the mechanism of action between these 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 plays a role in disease activity. In contrast, the synthetic chemical compounds are low-molecular-weight molecules that work by interfering with intracellular processes.

With the arrival of new synthetic DMARDs that recognise specific targets, the classification has been modified to:

- a. csDMARDs: antirheumatic drugs designed in the traditional way, such as MTX, leflunomide (LEF) and sulfasalazine (SSZ)
- b. 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.
- c. targeted synthetic DMARDs (tsDMARDs): oral synthetic drugs such as tofacitinib (TOF), baricitinib (BAR), upadacitinib (UPA) and filgotinib (FIL), developed to interact in a specific way with well-defined molecules.

## 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 that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product<sup>91</sup>. Regulation of these agents differs between countries and regions across the world<sup>92</sup>.

Over 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 undergone rigorous clinical tests and analysis in head-to-head comparisons with the reference product<sup>93</sup>. Currently, in Spain, biosimilars are being marketed or under development for various biological agents, including rituximab (RTX) and tocilizumab (TCZ), as well as several different tumour necrosis factor (TNF) inhibitors –infliximab (IFX), etanercept (ETN) and adalimumab (ADA)– for use in rheumatic diseases. A recent SR included the results of 19 observational and clinical trials comparing TNF- $\alpha$  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<sup>94</sup>. This review found that the efficacy and safety of these agents were indistinguishable from those of the original products they copied. 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. Further, 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<sup>94</sup>.

Most biologics are used long term. This has led to intense discussion about the safety of switching from a reference product to a biosimilar, with immunogenicity being the main concern. Evidence from clinical trials such as PLANETAS<sup>95</sup> and PLANETRA<sup>96</sup> and routine practice studies such as NOR-Switch<sup>97</sup> suggests that switching between comparable versions of the same active ingredient, as approved by EU legislation, would not be expected to increase 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<sup>98</sup>, a finding that needs to be confirmed in future research.

Currently, in Spain, biosimilars are available for IFX, TEN, ADA, RTX and TCZ, with as many as five different brands of the same biologic on the market in some cases, e.g., ADA.

## Small molecules or tsDMARDs

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 bound intracellularly to hormone receptors on the cell membrane, although some JAKs are also found in soluble form 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), a range of interleukins ([IL]; IL-2, IL-4, IL-7, IL-6, IL-10, IL-12, and IL-23), granulocyte-macrophage colony-stimulating factor (GM-CSF) and endocrine factors such as erythropoietin, thrombopoietin, growth hormone, oncostatin M, leukaemia inhibitory factor, ciliary neurotrophic factor, and prolactin<sup>99</sup>.

JAK inhibitors block the activity of JAK family enzymes by interfering with the JAK signal transducer and activator of transcription (STAT) signalling pathway. There are four types of JAKs (JAK1, JAK2, JAK3 and Tyk2), and they work in pairs, each with distinct biological effects. The inhibitors of these four types of JAKs 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 proinflammatory signalling activated by cytokines. Hence, the inhibition of JAK1 is expected to have a beneficial effect on a range of inflammatory conditions, as well as other diseases triggered by JAK-mediated signalling pathways.
- *JAK2* is involved in a series of differentiation pathways in haematopoiesis, by modulating mainly proteins such as erythropoietin, thrombopoietin and GM-CSF. JAK2 activity 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 (e.g., V617F) or JAK2 fusions, leading to overactivation of the JAK2-STAT pathways<sup>100, 101</sup>; for this reason, JAK2 is considered 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 has been considered a key target for immunosuppression. JAK3 inhibitors have been successfully developed for use in clinical practice, first to mitigate rejection in organ transplantation<sup>102</sup>, and more recently, to treat immunoinflammatory diseases.

- Tyrosine kinase 2 (*TYK2*) is a potential target for immunoinflammatory diseases, having been validated by various genetic studies in humans and knockout mice<sup>103</sup>.

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<sup>104, 105</sup> (see Table 7).

**Table 7: Biological processes and diseases mediated by receptors associated with JAKs**

Receptor	JAK	Related biology	Impact of the disease
Type I IFN ( $\alpha$ , $\beta$ )	JAK1 TYK2	Antiviral response Immunoregulation	Systemic erythematous lupus/connective tissue disease Granuloma development (sarcoidosis)
Type II IFN ( $\gamma$ )	JAK1 JAK2	Antiviral response Immunoregulation T cell-mediated macrophage activation	Systemic erythematous lupus/connective tissue disease Granuloma development (sarcoidosis)
GP130 (IL-6, IL-11, iliary neurotrophic factor, CT-1, GM- CSF, leukaemia inhibitory factor, oncostatin M)	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 (erythropoietin, thrombopoietin, prolactin, growth hormone)	JAK2	Erythropoiesis Thrombopoiesis Breastfeeding Sexual function Metabolism	Polycythaemia Thrombocythaemia Hyperprolactinaemia Acromegaly

The in vitro cytokine receptor inhibition profiles of various JAK inhibitors, namely, TOF, BAR, UPA and FIL, and their metabolites, are similar when considering doses clinically effective in RA. Only small numerical differences are observed in the percentage of cytokine receptor inhibition, suggesting limited differences between these inhibitors in terms of JAK pharmacology, each of them showing a different level of selectivity for the inhibition of the JAK1 heterodimer, the type of inhibition provided by all these drugs<sup>106</sup>.

### **Tofacitinib**

TOF inhibits JAK1 and JAK3<sup>107</sup>. It is indicated for oral use in combination with MTX for the treatment of active moderate-to-severe RA in adult patients with an inadequate 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, while there is also an 11 g prolonged-release formulation for once-daily administration.

### **Baricitinib**

BAR is a selective inhibitor of JAK1 and JAK2<sup>107</sup>. It is indicated for oral use for the treatment of active moderate-to-severe RA in adult patients with an inadequate 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 generally 4 mg, once daily. In adults with an elevated risk of cardiovascular events or cancer, the recommended dose is 2 mg, once daily, though this can be increased gradually up to 4 mg a day if a lower dose fails to achieve good disease control. In patients in sustained remission, a 2 mg dose has also been used.

### **Upadacitinib**

UPA is a selective inhibitor of JAK1<sup>107</sup>. It is indicated for the oral treatment of moderate-to-severe active RA in adults with an inadequate 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 15 mg once daily.

### **Filgotinib**

Similarly, FIL is a selective inhibitor of JAK1<sup>107</sup>, indicated for the oral treatment of moderate-to-severe active RA in adults with an inadequate response or intolerance to one or more DMARDs, and 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 200 mg once daily. In adults with an elevated risk of cardiovascular events or cancer, the recommended dose is 100 mg, once daily, though this can be increased gradually each day if a lower dose fails to achieve good disease control.

**Table 6. Disease-modifying drugs: doses and trade names**

DRUG	TREATMENT REGIMEN	TRADE NAMES
<b>ABATACEPT (ABA)<sup>a</sup></b>	<ul style="list-style-type: none"> <li>• Adjust the dose to body weight:               <ul style="list-style-type: none"> <li>- &lt; 60 kg: 500 mg</li> <li>- 60 to 100 kg: 750 mg</li> <li>- &gt; 100 kg: 1,000 mg</li> </ul> </li> <li>• Intravenous infusion for 30 minutes. Subsequently, two additional doses 2 and 4 weeks after the first infusion, then one dose every 4 weeks</li> <li>• Administer the subcutaneous formulation at a dose of 125 mg weekly</li> <li>• It can be used alone or combined with another DMARD</li> </ul>	<p>ORENCIA®</p> <ul style="list-style-type: none"> <li>• Vial containing 250 mg of lyophilised powder for reconstitution</li> <li>• 125 mg in a volume of 1 ml in a prefilled syringe for weekly administration</li> <li>• Prefilled pen containing 125 mg in a volume of 1 ml for weekly administration</li> </ul>
<b>ADALIMUMAB (ADA)<sup>a</sup></b>	<ul style="list-style-type: none"> <li>• 40 mg/14 days, subcutaneously</li> <li>• Shorten the dosing interval to 7-10 days (instead of the recommended 14 days) as required in selected patients</li> <li>• Adding MTX may improve treatment response in selected patients</li> <li>• It can also be used alone or combined with another DMARD</li> </ul>	<p>HUMIRA®</p> <ul style="list-style-type: none"> <li>• Prefilled syringe containing 40 mg</li> <li>• Prefilled pen containing 40 mg</li> </ul> <p>AMGEVITA®            YUFLYMA®            HUKYNDRA®            HYRIMOZ®            HULIO®            IDACIO®            IMRALDI®</p>
<b>ANAKINRA (ANA)<sup>a</sup></b>	<ul style="list-style-type: none"> <li>• 100 mg/day, subcutaneously</li> </ul>	<p>KINERET®</p> <ul style="list-style-type: none"> <li>• Prefilled syringe containing 100 mg</li> </ul>

<b>AZATHIOPRINE (AZA)<sup>bd</sup></b>	<ul style="list-style-type: none"> <li>• 1.5–2.5 mg/kg/day, orally</li> <li>• 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</li> </ul>	<b>IMUREL®</b> <ul style="list-style-type: none"> <li>• 50-mg film-coated tablet</li> <li>• Vial containing 50 mg of lyophilised powder</li> </ul>
<b>BARICITINIB (BAR)<sup>c</sup></b>	<ul style="list-style-type: none"> <li>• 4 mg once daily</li> <li>• 2 mg once daily is appropriate for patients with an elevated risk of venous thromboembolism, major adverse cardiovascular events or cancer, for patients <math>\geq 65</math> years old and for those with a history of chronic or recurrent infections</li> <li>• Consider increasing the dose to 4 mg once daily if adequate disease control is not achieved using 2 mg once daily</li> <li>• Consider a dose of 2 mg once daily in patients who have achieved sustained low disease activity on 4 mg once daily and are suitable candidates for gradual dose tapering</li> </ul>	<b>OLUMIANT®</b> <ul style="list-style-type: none"> <li>• 2- and 4-mg tablets</li> </ul>
<b>CERTOLIZUMAB PEGOL (CZP)<sup>a</sup></b>	<ul style="list-style-type: none"> <li>• 400 mg at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every other week</li> <li>• During treatment with Cimzia®, MTX should be continued when appropriate</li> </ul>	<b>CIMZIA®</b> <ul style="list-style-type: none"> <li>• Prefilled syringe containing 200 mg</li> <li>• Prefilled pen containing 200 mg</li> </ul>
<b>CYCLOPHOSPHAMIDE (CP)<sup>bd</sup></b>	<ul style="list-style-type: none"> <li>• 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</li> <li>• 3 to 6 mg/kg of body weight per day (equivalent to 120 to 240 mg/m<sup>2</sup> of body surface), as an intravenous infusion</li> </ul>	<b>GENOXAL®</b> <ul style="list-style-type: none"> <li>• 50-mg tablet</li> <li>• 1000-mg IV vial</li> <li>• 200-mg IV vial</li> </ul>
<b>CHLOROQUINE (CQ)<sup>bd</sup></b>	<ul style="list-style-type: none"> <li>• 250 mg/day, orally</li> <li>• Do not exceed 4 mg/kg/day</li> </ul>	<b>RESOCHIN®</b> <ul style="list-style-type: none"> <li>• 250-mg tablet</li> </ul>

<b>CICLOSPORIN<sup>bd</sup></b>	<ul style="list-style-type: none"> <li>• 2.5-5.0 mg/kg/day, orally</li> <li>• It can be increased by 0.5 mg/kg/day every other week up to 5 mg/kg/day</li> </ul>	<b>SANDIMMUN NEORAL®</b> <ul style="list-style-type: none"> <li>• 25-, 50-, and 100-mg tablets</li> <li>• 100 mg/ml oral solution</li> </ul>
<b>ETANERCEPT (ETN)<sup>a</sup></b>	<ul style="list-style-type: none"> <li>• 50 mg, once a week</li> <li>• In children, 25 mg a week</li> <li>• In combination or alone</li> </ul>	<b>ENBREL®</b> <b>BENEPALI®</b> <b>ERELZY®</b> <ul style="list-style-type: none"> <li>• Prefilled syringe and pen containing 50 mg</li> </ul>
<b>FILGOTINIB (FIL)<sup>c</sup></b>	<ul style="list-style-type: none"> <li>• 100 or 200 mg once daily, orally</li> <li>• Alone or in combination with MTX</li> <li>• 200 mg once daily is the dose recommended in adults with an elevated risk of venous thromboembolism, major adverse cardiovascular events or cancer</li> <li>• 100 mg once daily is the dose recommended in patients with moderate-to-severe renal failure (creatinine clearance between 15 and 60 ml/min)</li> <li>• Do not use in patients with severe liver failure</li> </ul>	<b>JYSELECA®</b>
<b>GOLIMUMAB (GOL)<sup>a</sup></b>	<ul style="list-style-type: none"> <li>• 50 mg, once a month, on the same day each month</li> <li>• It should be used together with MTX</li> </ul>	<b>SIMPONI®</b> <ul style="list-style-type: none"> <li>• Prefilled syringe containing 50 mg</li> <li>• Prefilled pen containing 50 mg</li> </ul>
<b>HYDROXYCHLOROQUINE (HCQ)<sup>b</sup></b>	<ul style="list-style-type: none"> <li>• 200 mg/day, orally</li> <li>• Do not exceed 6.5 mg/kg/day</li> </ul>	<b>DOLQUINE®</b> <ul style="list-style-type: none"> <li>• 200-mg tablet</li> </ul>
<b>INFLIXIMAB (IFX)<sup>a</sup></b>	<ul style="list-style-type: none"> <li>• 3 mg/kg under intravenous infusion for 2 hours</li> <li>• Subsequently, additional infusions of 3 mg/kg doses, 2 and 6 weeks after the first one, and then one every 8 weeks, increasing the dose to 5 mg/kg if not effective or if there is relapse. Shorten the infusion</li> </ul>	<b>REMICADE®</b> <b>INFLECTRA®</b> <b>REMSIMA®</b> <b>FLIXABI®</b> <ul style="list-style-type: none"> <li>• Vial containing 100 mg of lyophilised powder</li> </ul>

	<p>interval to 4-6 weeks (instead of the 8 weeks recommended for maintenance) as required in selected patients</p> <ul style="list-style-type: none"> <li>• It should be used in combination with MTX or another immunomodulator (such as LEF or AZA)</li> </ul>	
<b>LEFLUNOMIDE (LEF)<sup>b</sup></b>	<ul style="list-style-type: none"> <li>• 20 mg/day, orally</li> </ul>	<p>ARAVA<sup>®</sup></p> <ul style="list-style-type: none"> <li>• 10- and 20-mg tablets</li> </ul>
<b>METHOTREXATE (MTX)<sup>b</sup></b>	<ul style="list-style-type: none"> <li>• 15 mg/week, orally or subcutaneously for 4-6 weeks and then, if not effective, increase to 20-25 mg/week</li> <li>• Folic or folinic acid (5-15 mg/week) must be given 24 hours after MTX</li> </ul>	<p>METHOTREXATE ALMIRALL<sup>®</sup></p> <ul style="list-style-type: none"> <li>• Injectable solution, 50 mg/2 ml vial</li> </ul> <p>METHOTREXATE LEDERLE<sup>®</sup></p> <ul style="list-style-type: none"> <li>• 2.5-mg tablet</li> <li>• Injectable solution 25 mg/ml</li> </ul> <p>METOJECT<sup>®</sup></p> <ul style="list-style-type: none"> <li>• Prefilled syringes (7.5; 10; 12.5; 15; 17.5; 20; 22.5; 25; 27.5 and 30 mg)</li> </ul> <p>QUINUX<sup>®</sup></p> <ul style="list-style-type: none"> <li>• Prefilled syringes (7.5; 10; 15; 20; 25 mg)</li> </ul> <p>NORDIMET<sup>®</sup></p> <ul style="list-style-type: none"> <li>• Prefilled pens (7.5; 10; 12.5; 15; 17.5; 20; 22.5; 25 mg)</li> </ul> <p>IMETH<sup>®</sup></p>

		<ul style="list-style-type: none"> <li>• Prefilled pens (7.5; 10; 12.5, 15; 17.5; 20; 22.5, 25 mg)</li> </ul> <p>BERTANEL®</p> <ul style="list-style-type: none"> <li>• Prefilled pens (7.5; 10; 15, 20, 25, 30 mg)</li> </ul> <p>GLOFER®</p> <ul style="list-style-type: none"> <li>• Prefilled pens (7,5; 10; 15; 20; 25 mg)</li> </ul>
<b>RITUXIMAB (RTX)<sup>a</sup></b>	<ul style="list-style-type: none"> <li>• Two 1,000-mg IV infusions, 2 weeks apart, in combination with MTX</li> <li>• Methylprednisolone 100 mg IV (or equivalent) should be given before the infusion to reduce the incidence and severity of adverse reactions</li> </ul>	<p>MABTHERA®</p> <ul style="list-style-type: none"> <li>• 100- and 500-mg vials</li> </ul> <p>TRUXIMA®</p> <ul style="list-style-type: none"> <li>• 100- and 500-mg vials</li> </ul>
<b>SARILUMAB (SAR)<sup>a</sup></b>	<ul style="list-style-type: none"> <li>• 200 mg once every other week, subcutaneously</li> <li>• If neutropaenia, thrombocytopaenia and/or elevated liver enzymes appear, the dose should be reduced to 150 mg every other week</li> </ul>	<p>KEVZARA®</p> <ul style="list-style-type: none"> <li>• Prefilled syringes and pens (150 mg and 200 mg)</li> </ul>
<b>SULFASALAZINE (SSZ)<sup>b</sup></b>	<ul style="list-style-type: none"> <li>• 2-3 g/day, orally</li> </ul>	<p>SALAZOPYRINA®</p> <ul style="list-style-type: none"> <li>• 500-mg tablet</li> </ul>
<b>TOCILIZUMAB (TCZ)<sup>a</sup></b>	<ul style="list-style-type: none"> <li>• 8 mg/kg body weight IV once every 4 weeks</li> <li>• In individuals weighing over 100 kg, the dose should not exceed 800 mg</li> <li>• If neutropaenia, thrombocytopaenia and/or elevated liver enzymes appear, the dose should be reduced to 4mg/kg</li> </ul>	<p>ROACTEMRA®</p> <ul style="list-style-type: none"> <li>• 80-, 200- and 400-ml vials</li> <li>• Prefilled syringe 162 mg/sc/week.</li> </ul> <p>TYENNE®</p>
<b>TOFACITINIB (TOF)<sup>c</sup></b>	<ul style="list-style-type: none"> <li>• 5 mg twice daily, orally or 11 mg once daily, orally</li> </ul>	<p>XELJANZ®</p>

	<ul style="list-style-type: none"> <li>• Alone or in combination with MTX</li> <li>• Treatment should not be started in patients with an absolute lymphocyte count less than 750 cells/mm<sup>3</sup></li> <li>• Do not use in patients with severe liver failure</li> <li>• In patients with severe kidney failure, use 5 mg daily</li> </ul>	<ul style="list-style-type: none"> <li>• 5-mg tablet</li> <li>• 11-mg tablet</li> </ul>
<b>UPADACITINIB (UPA)<sup>c</sup></b>	<ul style="list-style-type: none"> <li>• 15 mg once daily, orally</li> <li>• Alone or in combination with MTX</li> <li>• Use with care in patients with severe kidney failure</li> <li>• Do not use in patients with severe liver failure</li> </ul>	RINVOQ <sup>®</sup>

a: bDMARD; b: csDMARD; c: tsDMARD; d: suitable for occasional use.

## 8.3. Pharmacological treatment

### 8.3.1. Initial pharmacological treatment

#### **Clinical question 2** (valid)

In patients with RA, what is the efficacy of initial treatment with glucocorticoids at doses equivalent to more than 10 mg of prednisone, added to any DMARD?

### **Recommendations**

**Recommendation 3:** In patients with RA, use glucocorticoids at doses equivalent to prednisone 10–30 mg/day as initial treatment in combination with one of several conventional DMARDs followed by gradual dose tapering (Strong recommendation, in favour)<sup>v</sup>.

<sup>v</sup> Recommendation related to a question in the previous GUIPCAR guideline considered still valid.

The 2022 update of the EULAR recommendations regarding the treatment of RA states, contrary to the ACR recommendations, that first-line treatment should include MTX, and if there are no contraindications, in combination with glucocorticoids. The update specifies that glucocorticoid treatment should be short term, and if patients respond well, it should be withdrawn after around 3 months<sup>5</sup>.

### **Recommendations considered not valid**

Regarding the following question from GUIPCAR 2019, 'In patients with RA, what is the efficacy of initial treatment with triple conventional DMARD therapy?', the GDG decided that the related recommendation is no longer valid. Hence, it has been removed from the updated guideline.

#### **Clinical question** (new)

In DMARD-naïve patients with RA, what is the effect of treatment with bDMARDs or tsDMARDs, compared to csDMARDs?

## **Context/Background**

The pharmacological approach to RA includes initiating a DMARD-based strategy. Currently, DMARDs are divided into three main groups: csDMARDs (MTX, LEF, HCQ, or SSZ); bDMARDs, such as anti-tumour necrosis factor agents, i.e., TNF inhibitors (ADA, CZP, ETN, IFX, GOL), abatacept (ABA, anti-cluster of differentiation 80 [CD80] inhibitor), IL-6 receptor (IL-6R) inhibitors (sarilumab [SAR], TCZ), and RTX (anti-CD20); and tsDMARDs, to date, JAK inhibitors (BAR, FIL, TOF and UPA).

Current guidelines from scientific societies such as EULAR, ACR and SER recommend using MTX with rapid dose escalation as first-line treatment in RA, and following a treat-to-target strategy, using composite response indices and promptly adjusting therapy if the treatment goal is not achieved (ideally remission in cases of DMARD-naïve RA).

The growing availability of bDMARDs and JAK inhibitors raises the possibility of using these targeted DMARDs (biologics or JAK inhibitors) as first-line treatment in RA, before MTX. In RA, there is a window of opportunity to achieve effective disease control. The earlier remission is achieved after disease onset, the greater the likelihood of preventing radiographic structural damage and an irreversible impact on function and quality of life, indicating the importance of choosing an appropriate first DMARD.

## **Recommendations**

**Recommendation 4:** In DMARD-naïve patients with RA, use MTX as initial treatment, usually in combination with glucocorticoids (**Strong recommendation, in favour**)<sup>U</sup>.

**Recommendation 5:** Consider avoiding TNF inhibitors in combination with MTX, IL-6R inhibitors, ABA, or JAK inhibitors as first-line treatment because, although associated with significantly better clinically-relevant outcomes than MTX monotherapy, the magnitude of the difference

was found to be small, a significant percentage of patients responded well to MTX alone, and MTX was not combined with glucocorticoids ([Weak recommendation, against](#))<sup>U</sup>.

<sup>U</sup> Recommendation related to a question in the previous GUIPCAR guideline that has been updated.

### Important clinical considerations

- Subgroups to consider:
  - Give preference to options other than JAK inhibitors in  $\geq 65$ -year-olds, current smokers (or former smokers who have a long history of smoking or have been heavy smokers), and people with an elevated risk of cancer or other risk factors for cardiovascular or thromboembolic disease. If JAK inhibitors are required in such patients, use the lowest possible effective dose.

## Rationale

Several high-quality clinical trials have highlighted that for first-line treatment in DMARD-naïve patients with RA both bDMARDs and tsDMARDs are superior to MTX monotherapy in terms of clinically relevant outcomes. Nonetheless, the magnitude of the difference is small.

When MTX is combined with glucocorticoids, the advantages of using bDMARDs or tsDMARDs disappear during the first months of treatment.

MTX has an excellent safety and efficacy profile, and it remains unproven whether initiating targeted DMARDs (biologic or synthetic) significantly improves functional prognosis and quality of life, in a treat-to-target approach, with timely changes in therapy if preset goals of remission or at least low disease activity are not achieved.

## Detailed rationale

### **bDMARDs**

#### TNF inhibitor monotherapy vs conventional therapy (MTX)

The review identified four RCTs<sup>108-111</sup> assessing the efficacy of TNF inhibitor monotherapy compared to MTX for treating patients with RA.

The first RCT<sup>109</sup> compared the efficacy and safety of ETN with that of MTX in 632 patients with early RA, assessing reduction in disease activity and prevention of joint damage. Among the participants, the mean age was 50 years, the mean time since RA diagnosis was  $\leq 3$  years, and 75% were women. Follow-up was for 1 year.

The second RCT<sup>110</sup> assessed the efficacy and safety of ADA compared to MTX in 799 MTX-naïve patients with early RA. Across the groups, the mean age was 52 years, the mean duration of active disease was  $\leq 3$  years, and 74% were women. Follow-up was for 2 years.

The third RCT<sup>111</sup> assessed the efficacy and safety of GOL with or without MTX in 637 MTX-naïve patients with active RA. The patients' mean age was 50 years, and 82% were women. Follow-up was for 24 weeks.

The fourth RCT<sup>108</sup> evaluated clinical, radiographic, and functional outcomes after treatment with MTX or ETN monotherapy in 550 patients who were MTX-naïve or had previously shown intolerance or an inadequate response to MTX.

The quality of the evidence was rated as low to very low due to the high risk of bias and due to the imprecision associated with wide 95% confidence intervals (CIs), and/or the study estimates including both higher and lower risk scenarios.

The GDG considers that the only outcome with statistically significant findings is the slowing of radiographic damage progression. Nonetheless, the impact of this difference on functional outcome and quality of life in the medium and long term is questionable, due to differences between MTX and TNF inhibitors, as well as the regular use of MTX with low-dose glucocorticoids as bridging therapy, and therefore, this result is not relevant in relation to the question posed.

After weighing the benefits and risks, the GDG considers that the low quality of the evidence and the methodological limitations of the studies make the results concerning the effectiveness of TNF inhibitor monotherapy for disease control and remission uncertain, and no definitive conclusions can be drawn about its additional benefit compared to MTX alone. The same applies to the evidence on quality of life and adverse events, which is insufficient to draw strong conclusions, as it was considered that further research might change the effect size.

#### TNF inhibitors plus csDMARDs vs. conventional therapy (MTX)

The review identified 12 RCTs evaluating the efficacy of TNF inhibitors combined with MTX compared to MTX monotherapy for the treatment of patients RA<sup>73, 110-118, 383-384</sup>. Three of these studies have already been cited above<sup>73, 110, 111</sup>.

One RCT compared a first-line treatment combining MTX and ADA to MTX monotherapy in 65 patients with early active RA<sup>112</sup>. The mean age was 48 years, follow-up was 1 year, and 81% were female.

A second RCT evaluated the efficacy of a therapy combining MTX and IFX compared to MTX monotherapy in 1,049 patients with early RA with a disease duration of less than 3 years<sup>113</sup>. The mean age was 50 years, 71% were women, and follow-up was 1 year.

A third RCT evaluated the efficacy and safety of ADA plus MTX compared to MTX monotherapy in achieving low disease activity (DAS28 < 3.2) and clinical, radiographic and functional outcomes in 1,032 patients with early RA<sup>73</sup>. The mean age was 50.5 years, 74% were women, and follow-up was 6 months.

Similarly, another RCT evaluated the effect of early treatment with ADA plus MTX compared to MTX monotherapy in 148 patients with early RA<sup>114</sup>. The mean age was 47 years, 59% were women, and follow-up was 1.1 years.

Another of the RCTs assessed the long-term effect of induction therapy with ADA plus MTX over 24 weeks, followed by MTX monotherapy up to week 48, compared to MTX monotherapy in 172 csDMARD-naïve patients with early RA. The patients' mean age was 50 years, 69% were women, and follow-up was for 1 year<sup>383</sup>.

The impact of early treatment with IFX plus MTX compared to MTX alone was also assessed in 20 patients with RA and poor prognostic factors, using MRI to assess synovitis and structural damage<sup>115</sup>. Patients' mean age was 52 years, 65% were women, and follow-up was 2 years.

Another RCT evaluated whether treatment combining ADA with a strategy based on MTX plus intra-articular triamcinolone injections in early RA increased the rate of remission, compared to MTX plus intra-articular triamcinolone injections and placebo, based on 180 patients<sup>116</sup>. The mean age was 54.2 years, 69% were women, and follow-up was 1 year.

One RCT evaluated the efficacy and safety of a treatment with CZP combined with dose-optimised MTX compared to dose-optimised MTX monotherapy in 879 patients with early active RA and poor prognostic factors<sup>117</sup>. The mean age was 50.6 years, 76.8% were women, and follow-up was 1 year.

Similarly, another RCT evaluated the efficacy and safety of a treatment combining CZP and MTX compared to MTX monotherapy in 316 MTX-naïve patients with early RA and with poor prognostic factors. The patients' mean age was 54 years, 78% were women, and follow-up was 1 year<sup>384</sup>.

Lastly, it was evaluated whether induction therapy with IFX plus MTX was able to achieve drug-free remission in 90 patients with very early inflammatory arthritis ( $\leq 12$  weeks of duration)<sup>118</sup>. Of these patients, 68.4% were women, and follow-up was 2 years.

The quality of the evidence was rated as moderate due to the risk of imprecision bias associated with wide 95% CIs, and the estimates of the studies assessed including both higher and lower risk scenarios.

After weighing the benefits and risks, the evidence identified supports the idea that combination therapy with TNF inhibitors and MTX probably improves disease control, compared to MTX monotherapy. The treatments had similar rates of adverse events. Though the certainty and quality of the evidence should be taken into account, this combination therapy may also reduce radiographic progression and improve quality of life.

Nonetheless, the GDG considers that the advantages of starting combination therapy with a TNF inhibitor plus MTX over MTX monotherapy observed under RCT conditions do not necessarily translate into benefits in real-world clinical practice using a treat-to-target strategy. Therefore, widespread implementation of initial therapy with MTX plus a TNF inhibitor, rather than MTX monotherapy with timely dose escalation, would lead to overtreatment of patients who could achieve remission with appropriately adjusted MTX monotherapy.

#### IL-6R inhibitors alone or combined with csDMARDs vs. conventional therapy (MTX)

The review identified two RCTs (FUNCTION<sup>119, 120</sup> and U-ACT-EARLY<sup>121</sup>), included in two SRs<sup>122, 123</sup>, assessing the efficacy of IL-6R inhibitors alone or combined with MTX, compared to MTX monotherapy, for the treatment of DMARD-naïve patients with RA.

The first RCT<sup>119, 120</sup> assessed the effect of TCZ alone or in combination with MTX compared to MTX monotherapy in 1162 MTX-naïve patients with early RA. The mean age was 50 years, 78% were women, and follow-up was 1 year.

The other RCT<sup>121</sup> included 317 csDMARD-naïve patients newly diagnosed with RA. The study was designed to evaluate stepwise treatment strategies. In the first stage (24 weeks), participants were randomly allocated to TCZ as monotherapy, TCZ combined with MTX, or MTX

monotherapy. The patients' mean age was 54 years, 67% were women, and follow-up was 2 years.

The quality of the evidence was rated as moderate or high depending on the outcome considered, given the risk of bias either from inconsistencies, since the CIs of the studies included different scenarios, or from imprecision, since some of the studies reported fewer than 300 events per arm and did not meet the optimal information size.

After weighing the expected desirable and undesirable effects, the evidence available indicates that TCZ alone or combined with MTX reduces disease activity and increases the percentage of patients who achieve remission compared to MTX alone, based on several different measurements (high and moderate quality of evidence respectively for 20% improvement in ACR criteria [ACR20], and for ACR50, ACR70, DAS28 and good EULAR response). Nonetheless, IL-6R inhibitor monotherapy may not provide better control of structural damage than MTX, and when combined with MTX, the differences in the impact on radiographic progression are minimal. Regarding quality of life, a moderate improvement is observed in functional capacity (Health Assessment Questionnaire [HAQ]).

Overall, the GDG considers that the advantages of starting IL-6R inhibitors alone or in combination with MTX over MTX monotherapy observed under RCT conditions do not necessarily translate into benefits in real-world clinical practice with a treat-to-target strategy. Therefore, widespread implementation of initial therapy with an IL-6R inhibitor, instead of MTX monotherapy with timely dose escalation, would lead to overtreatment of patients who could achieve remission with appropriately adjusted MTX monotherapy.

#### Abatacept combined with csDMARD vs. csDMARD monotherapy

The review identified two relevant RCTs<sup>124, 125</sup>, one of which was included in an SR<sup>126</sup>, assessing the effect of treatment with ABA plus MTX, compared to MTX monotherapy.

The first RCT<sup>124</sup> included 509 patients (76.6% women) with a mean age of 50.1 years and a 1-year follow-up.

The second RCT<sup>125</sup> included 752 patients (77% women) with a mean age of 49 years and a 2-year follow-up.

The quality of the evidence was rated as high for most outcomes; although it was downgraded for some due to imprecision associated with wide 95% CIs that reflect uncertainty in the estimates.

After weighing the expected desirable and undesirable effects, the available evidence indicates that treatment combining ABA and MTX significantly improves clinical response (ACR20, ACR50 and ACR70), increases the percentage of patients who achieve disease remission (DAS28-CRP, SDAI) and slows radiographic progression, compared to csDMARD monotherapy.

In addition to improving quality of life as measured by the HAQ-Disability Index (DI) and the Short Form (SF)-36 Health Survey, combination therapy with ABA and MTX was not associated with a significant increase in the rate of serious adverse events, compared to csDMARD monotherapy.

Nonetheless, the GDG considers that the advantages of initiating a therapy combining ABA plus MTX over MTX monotherapy under RCT conditions do not necessarily translate into benefits in real-world clinical practice with a treat-to-target strategy. Therefore, widespread implementation of an initial regimen with ABA combined with MTX, instead of MTX monotherapy with timely dose escalation, would lead to overtreatment of patients who could achieve remission with appropriately adjusted MTX monotherapy.

### **JAK inhibitors vs a csDMARD (MTX)**

The review identified 11 RCTs<sup>127-138</sup>, 7 of which were included in SRs<sup>122, 139-141</sup>, evaluating the safety and effectiveness of JAK inhibitors compared to MTX.

Five studies evaluated the efficacy and safety of TOF compared to MTX. The first was based on 109 patients (82.6% women), with a mean age of 48.8 years and a follow-up of 1 year<sup>127</sup>; and the second on 588 patients (73% women), with a mean age of 51.3 years and a follow-up of 1 year<sup>128</sup>. The third study was based on 958 patients followed up for 2 years; across the groups, the mean age ranged from 49.3 to 50.3 years, and 76.7% to 82.4% were women<sup>129</sup>. The fourth study included 956 patients, with a mean age of 50.3 years and a follow-up of 2 years<sup>130</sup>. The

fifth study included 100 patients followed up for 3 months; across the groups, the mean age ranged from 42 to 45 years, and 78.4% to 79.6% of patients were women<sup>134</sup>.

Three studies evaluated the efficacy of UPA compared to MTX based on clinical trial data. The earliest study included 947 patients (76% women), with a mean age of 53 years and a follow-up of 1 year<sup>131</sup>, whereas the second and third both included 945 patients (76% women), with a mean age of 53 years and a 3-month follow-up<sup>137,138</sup>.

In addition, studies have assessed the efficacy of FIL compared to MTX, based on 1252 patients (77% women) with a mean age of 53 years and a follow-up of 1 year<sup>132</sup>; and BAR compared to MTX, based on 584 patients followed up for 1 year (across the groups, between 70% and 76% of patients were women, and the mean age ranged from 50.5 to 50.9 years)<sup>133</sup>.

Two studies evaluated the efficacy and safety of BAR with or without MTX, compared to MTX monotherapy, based on clinical trial data. Both analysed 584 patients (76% women) with a mean age of 49.3 years and a follow-up of 1 year<sup>135,136</sup>.

The quality of the evidence was rated as high for some outcomes; however, in other cases, it was downgraded to moderate or low, either due to imprecision, associated with small event numbers and subsequent wide CIs and therefore the possibility of no effect, indicating uncertainty in the estimate, or due to inconsistency from substantial heterogeneity.

After weighing the expected desirable and undesirable effects, the available evidence shows that JAK inhibitors alone or combined with MTX lead to improvements in ACR20, ACR50 and ACR70 responses and increase the likelihood of disease remission as measured by DAS28 and CDAI, compared to MTX alone, though the effects may be modest for some patients, particularly in certain measures of remission. Notably, an advantage of JAK inhibitors over MTX is also evident with composite response indices, such as the CDAI score (which excludes measures of acute-phase reactants), since JAK inhibitors also block IL-6 signal transduction from the cell membrane to the nucleus. Moreover, the evidence suggests that JAK inhibitor monotherapy may not slow radiographic progression or reduce serious adverse events more than MTX.

The GDG therefore considers that the evidence is uncertain regarding the additional benefit of a therapy combining JAK inhibitors and MTX for key outcomes (e.g., radiographic progression and quality of life), meaning that no conclusions can be drawn.

The advantage of starting a treatment comprising JAK inhibitors alone or in combination with MTX over MTX monotherapy under RCT conditions does not necessarily translate to clinical benefits in real-world clinical practice with a treat-to-target strategy. Therefore, widespread implementation of an initial regimen with a JAK inhibitor, instead of MTX monotherapy with timely dose escalation, would lead to overtreatment of patients who could achieve remission with appropriately adjusted MTX monotherapy.

### 8.3.2. Treatment after an inadequate response to csDMARDs

#### Clinical question 5 (valid)

In patients with RA who have an inadequate response to MTX monotherapy, is it more effective to add a bDMARD or to use csDMARD combination therapy?

#### Recommendations

**Recommendation 6:** In patients with RA who have an inadequate response to MTX monotherapy, use either a combination of csDMARDs or a bDMARD, depending on the patient's characteristics (Strong recommendation, in favour)<sup>v</sup>.

<sup>v</sup>Recommendation related to a question in the previous GUIPCAR guideline considered still valid

Patients with RA who have an inadequate response to MTX monotherapy can be treated with either csDMARDs or a bDMARD, preferably in combination with MTX, depending on whether a given patient has poor prognostic factors, such as high disease activity, erosions, or high RF/ACPA titres.

#### Clinical question 6 (valid)

In patients with RA who have an inadequate response to csDMARDs, is it more effective to add a bDMARD or a tsDMARD?

#### Recommendations

**Recommendation 7:** In patients with RA who have an inadequate response to csDMARDs, use combination therapy with either a bDMARD or a tsDMARD, depending on the patient's characteristics and risk\* (Strong recommendation, in favour)<sup>v</sup>.

\*considering risk factors for cardiovascular disease and cancer

<sup>v</sup>Recommendation related to a question in the previous GUIPCAR guideline considered still valid

Patients with RA who have an inadequate response to csDMARDs can be treated with either bDMARDs or tsDMARDs. Though comparisons between JAK inhibitors and bDMARDs in this population have shown higher efficacy for some JAK inhibitors, the ACR only currently allows the use of these drugs in patients who have failed to respond to a bDMARD; and while EULAR

does not give preference to one over the other, the presence of risk factors for cardiovascular disease and/or cancer must be taken into account.

### 8.3.3. Treatment with the first bDMARD or tsDMARD

**Clinical question 7** (valid)

In patients with RA, what is the efficacy of the combination of any bDMARD with a csDMARD other than MTX?

### Recommendations

**Recommendation 8:** In patients with RA eligible for biological therapy with contraindications or intolerance to MTX, consider using LEF in combination with a bDMARD (*Weak recommendation, in favour*)<sup>∨</sup>.

<sup>∨</sup> Recommendation related to a question in the previous GUIPCAR guideline considered still valid

The GDG has decided that this recommendation is still valid, given that it has not been contradicted by any research published since the previous guideline.

**Clinical question 8** (valid)

In patients with RA, what dose of MTX in combination with a bDMARD is associated with the best clinical outcomes, highest drug concentrations and lowest antibody production?

## Recommendations

**Recommendation 9:** In patients with RA receiving combination treatment with MTX and TNF inhibitors, use MTX at doses of at least 10 mg/week ([Strong recommendation, in favour](#))<sup>v</sup>.

<sup>v</sup>Recommendation related to a question in the previous GUIPCAR guideline considered still valid.

The GDG has decided that this recommendation is still valid given that it has not been contradicted by any research published since the previous guideline.

**Clinical question 9** (valid)

In patients with RA, are there differences in efficacy between the different bDMARDs used as first-line treatment?

## Recommendations

**Recommendation 10:** In patients with RA, it is not currently possible to recommend a specific bDMARD for first-line therapy in combination with MTX ([Weak recommendation, against](#))<sup>v</sup>.

**Recommendation 11:** For monotherapy, consider using an IL-6R inhibitor rather than a TNF inhibitor ([Weak recommendation, in favour](#))<sup>v</sup>.

<sup>v</sup>Recommendation related to a question in the previous GUIPCAR guideline considered still valid.

The GDG considers that TNF inhibitor monotherapy is clearly inferior to TNF inhibitors in combination with MTX, and in general, all bDMARDs have greater efficacy when combined with MTX, but no particular one has shown superiority in this context.

### Clinical question 10

In patients with RA, what is the efficacy of tsDMARD monotherapy compared to csDMARD or bDMARD monotherapy?

## Recommendations

**Recommendation 12:** In patients eligible for bDMARD or tsDMARD therapy in whom, for any reason, these drugs cannot be used in combination with csDMARDs, the GDG considers JAK inhibitor monotherapy a good alternative treatment, except in high-risk cases\* ([Good clinical practice](#))<sup>v</sup>.

<sup>v</sup>Recommendation related to a question in the previous GUIPCAR guideline considered still valid.

In patients in whom csDMARDs cannot be used, the recommendation is to use IL-6R inhibitor or tsDMARD monotherapy.

\*Based on the results of the ORAL Surveillance study on tofacitinib (TOF)<sup>142</sup> and data on the other three JAK inhibitors available in the EU, the EMA<sup>143</sup> and AEMPS<sup>144</sup> have issued recommendations to minimise the risk of major adverse events associated with this class of drugs in the treatment of various chronic diseases. These adverse effects include cardiovascular events, thrombosis, malignancies and infections.

### 8.3.4. Treatment after an inadequate response to a first bDMARD

#### Clinical question 11 (updated)

In patients with RA who have an inadequate response to a first TNF inhibitor, what is the effect of a second TNF inhibitor, a non-TNF-inhibitor bDMARD or a tsDMARD?

#### Context/Background

Although there is a growing number of targeted drugs, both biological and synthetic, with different mechanisms of action for treating patients with RA, TNF inhibitors remain the most widely used as first-line advanced therapy. This treatment often needs to be changed, however, due to lack of efficacy or loss of efficacy over time, as well as for other reasons such as intolerance or adverse events. Therefore, it is essential to gather evidence on treatments to be administered in patients who fail to respond to TNF inhibitors as first-line targeted therapy.

#### Recommendations

**Recommendation 13:** In patients with RA who have had an inadequate response to a first TNF inhibitor, consider using a bDMARD with a different mechanism of action, a JAK inhibitor or a second TNF inhibitor (*Weak recommendation, in favour*)<sup>U</sup>.

<sup>U</sup> Recommendation related to a question in the previous GUIPCAR guideline that has been updated.

#### Important clinical considerations

- Implementation-related factors:
  - Factors such as age, disease characteristics, associated comorbidities and reasons for discontinuing previous treatment may help guide the choice of the most appropriate treatment for each patient.
- Subgroups to consider:
  - Give preference to options other than JAK inhibitors in ≥65-year-olds, current smokers (and former smokers who have a long history of smoking or have been heavy smokers), and those who have an elevated risk of cancer or other risk factors for cardiovascular and thromboembolic disease. If JAK inhibitors are required in such patients, use the lowest possible effective dose.

## Rationale

Although numerous published studies have sought to answer this clinical question, only four have been considered of sufficiently high quality, from an evidence-based medicine perspective, to be included in the SR conducted to serve as a basis for this recommendation.

Of these studies, two are clinical trials<sup>145, 146</sup>. The first was terminated early because the planned sample size was not reached, while the second had an open-label design and interpretation of its outcomes requires also considering the potential effect of TCZ on activity indices. The other two studies are observational cohort studies<sup>147, 148</sup>.

All these studies compare a second TNF inhibitor with a biologic that has a different mechanism of action, specifically ABA, RTX or TCZ. Although the results of these studies can be considered homogeneous, their limitations in both evidence quality and methodological rigour weaken the strength of the recommendation.

## Detailed rationale

### **Efficacy in controlling disease activity**

The review identified two clinical trials and one prospective cohort study assessing the effect on disease activity of a second TNF inhibitor compared to other biologics in patients with RA after discontinuation of a first TNF inhibitor for lack of effectiveness.

The first, the SWITCH<sup>145</sup> study, is a multicentre open-label non-inferiority clinical trial that investigated changes in DAS28 after 24 weeks of treatment. It included 122 patients (83.6% women) with RA in whom treatment with a first TNF inhibitor had been withdrawn for ineffectiveness. Patients were randomly allocated to receive a second TNF inhibitor (n = 41), ABA (n = 41) or RTX (n = 40). They had a mean age of 56.7 years, mean disease duration of 6.7 years and mean DAS28-ESR of 6.1 at inclusion. Overall, 82% of patients were RF or ACPA positive. The study was terminated early without achieving the planned sample size (477 patients). The researchers sought to extend the study up to week 96, but over 20% of the original sample was lost to follow-up, and hence, only the results up to week 24 could be analysed.

The second, the ROC study<sup>146</sup>, a multicentre, open-label, superiority clinical trial comparing the proportion of patients with RA who achieved a good or moderate EULAR response after 24 weeks of treatment with a second TNF inhibitor, ABA, RTX or TCZ after an inadequate response to a first TNF inhibitor. It included 292 patients, 146 receiving second TNF inhibitors and 146

receiving a non-TNF-inhibitor drug. Overall, 83% were women, while 83% were positive for RF and 82% for ACPA. The patients had a mean age of 57.1 years, mean disease duration of 10 years and mean baseline DAS28-ESR of 5.1.

The third was a prospective cohort study<sup>147</sup> assessing the proportion of patients with RA achieving a good or moderate EULAR response at 6, 12 and 24 months with a second TNF inhibitor, ABA, TCZ or RTX after discontinuation of a first TNF inhibitor, although in this case not exclusively due to lack of effectiveness. It included 127 patients (84% women) with a median age of 55 to 57 years, a mean disease duration at inclusion of 11 to 12 years and baseline DAS28-ESR of 5.1 to 5.3 across the groups. Rates of RF and ACPA positivity ranged from 43 to 59% and 41 to 66% respectively.

The overall quality of the evidence was rated as moderate or low depending on the outcome considered, due to imprecision associated with 95% CIs crossing either the line of no effect or the threshold of clinical significance. In addition, the quality of the evidence is limited by certain methodological issues, including early termination in the case of one of the clinical trials, the open-label nature of the research and the potential effect of TCZ on disease activity indices in the other, and the fact that the other two sources are cohort studies.

- Regarding a good or moderate EULAR response, this was achieved in a lower proportion of patients when using a second TNF inhibitor than a non-TNF-inhibitor biologic, according to the 6-month results from the meta-analysis of data from two clinical trials<sup>145, 146</sup> and one observational study<sup>147</sup>, the 12-month results from one clinical trial<sup>146</sup>, and the 12- and 24-month results from one observational study<sup>147</sup>.

- Regarding low disease activity, results were similar, i.e., in favour of a non-TNF inhibitor, both at 6 and 12 months according to the ROC study.

- Regarding remission, the proportion of patients in whom this is achieved at 6 and 12 months seems to be smaller using a second TNF inhibitor, based on the meta-analysis of data from two clinical trials.

### **Efficacy in slowing radiographic progression**

No studies were found assessing differences in efficacy in relation to structural damage.

### **Efficacy as assessed by patient-reported outcome measures**

The SWITCH<sup>145</sup> study found no differences in mean values of or changes in European Quality of Life-5 Dimensions (EQ-5D) questionnaire scores between patients treated with a second TNF inhibitor and those treated with a non-TNF-inhibitor biologic.

Regarding functional capacity as measured by the HAQ, the ROC<sup>146</sup> study did not show significant differences between the group treated with a TNF inhibitor and another group treated with a non-TNF-inhibitor biologic.

### **Safety**

Two clinical trials and two observational studies assessed the occurrence of adverse events in patients with RA treated with a second TNF inhibitor or other biologics after discontinuation of a first TNF inhibitor for lack of effectiveness. These correspond to the three studies described in the section on efficacy in controlling disease activity (above), and additionally, an observational study based on the British Society for Rheumatology Rheumatoid Arthritis Register (BSRBR-RA, previously called the British Society for Rheumatology Biologics Register, BSRBR)<sup>148</sup>, assessing the risk of serious infections among patients treated for 1 year with a second TNF inhibitor or with RTX after failure of a first TNF inhibitor. It included 4,815 patients; across the groups, 77 to 80% of patients were women, and 63 to 67% were RF positive, while the mean age ranged from 55.9 to 58.3 years and mean disease duration from 11 to 12 years.

One of the observational studies<sup>147</sup> indicates a lower risk of adverse events using a TNF inhibitor. On the other hand, regarding adverse events leading to treatment discontinuation, the results are unfavourable to the use of a second TNF inhibitor according to the same observational study<sup>147</sup> and the findings of one of the RCTs<sup>145</sup>.

The other observational study<sup>148</sup> and the results of the two meta-analyses of trial data<sup>145, 146</sup> did not detect any differences in the rate of serious infections.

The results from these meta-analyses favour the use of TNF inhibitors in relation to the risk of death and cardiovascular events.

The overall quality of the evidence was rated as low or moderate for the various outcomes due to imprecision associated with 95% CIs crossing either the line of no effect or the threshold of clinical significance. In addition, the quality of the evidence is limited by certain methodological issues, including early termination in the case of one of the clinical trials, the open-label nature

of the research and the potential effect of TCZ on disease activity indices in the other, and the fact that the other two sources are cohort studies.

### **Other considerations**

Besides the four studies identified above, other research has further explored the question underlying the recommendation. One observational study<sup>149</sup> included 209 patients who, after failing to respond to a first TNF inhibitor, received a second TNF inhibitor (n=69), a non-TNF-inhibitor bDMARD (TCZ, ABA or RTX; n=106) or a JAK inhibitor (TOF or BAR; n=34). A significantly higher percentage of patients achieved remission or low disease activity in the group treated with a non-TNF-inhibitor biologic than in those treated with a second TNF inhibitor (p=0.009) or a JAK inhibitor (p=0.003). The loss to follow-up of 55 patients (26.3%) due to treatment changes led to the exclusion of the study from the SR.

Secondly, a multicentre observational real-world study<sup>150</sup> of 643 patients compared the effectiveness of a second TNF inhibitor (n=390) with that of TCZ (n=147) and RTX (n=106) after discontinuation of a first TNF inhibitor. Significant differences in response were found in favour of TCZ based on DAS28 < 3.2 at 6, 12 and 24 months. No differences were found considering CDAI ≤ 10, SDAI ≤ 11 or HAQ scores. Significant differences in patient baseline characteristics, as well as the loss of 297 patients (46.2%) due to treatment changes, led to the exclusion of the study from the SR.

A multicentre prospective cohort study<sup>151</sup> of 103 patients assessed the effectiveness and safety of a second TNF inhibitor (n=49) with those of RTX (n=54) after discontinuation of a first TNF inhibitor. This study did not find significant differences between a second TNF inhibitor or RTX in HAQ scores or the proportion of patients achieving a good or moderate EULAR response or experiencing an adverse event within 6 months after starting treatment. It was excluded from the SR due to the loss of 10 patients given a second TNF inhibitor and 11 patients given RTX, together with methodological weaknesses and the small sample size.

Another multicentre observational study based on registry data<sup>152</sup> comparing the persistence and efficacy of a second TNF inhibitor to those of a targeted non-TNF-inhibitor biologic (ABA, ANA, RTX, TCZ or TOF) in 613 patients (281 and 332, respectively, in each group) after discontinuation of a first TNF inhibitor. The study provides data on CDAI, DAS28-ESR, DAS28-CRP and Routine Assessment of Patient Index Data 3 scores finding no significant differences at 1 year, though it did show reductions in CDAI, DAS28-ESR and DAS28-CRP in favour of the non-TNF inhibitors. It was excluded from the SR due to missing data on 21.6% of patients at 1 year.

A study based on the Swedish registry<sup>153</sup>, providing data on patients treated with RTX, TCZ and ABA after failure of a TNF inhibitor, reported a good EULAR response in a significantly higher percentage of patients on RTX or TCZ but not ABA compared to that with a second TNF inhibitor (24.8%, 34.1%, and 13.1% of patients, respectively, versus 11.6%).

A cohort study of 10,442 patients with RA who had failed to respond to a TNF inhibitor<sup>154</sup> analysed treatment persistence, which can be considered a surrogate for efficacy. It reported a longer persistence of therapy in patients treated with a non-TNF or JAK inhibitor as second advanced therapy (median treatment duration of 605 days with a non-TNF or JAK inhibitor versus 489 days with a TNF inhibitor;  $p < 0.001$ ).

Lastly, the EXXELERATE<sup>155</sup> clinical trial, though not exactly addressing the question underlying this recommendation, compared the efficacy of two TNF inhibitors (CZP and ADA) after failure of the other. It found that 12 weeks after the treatment change, 58% of patients who switched to CZP and 62% of those who switched to ADA achieved low disease activity or a decrease in DAS28-ESR of at least 1.2, confirming the effectiveness of a second TNF inhibitor after failure of a first one.

In general, despite their limitations, the results of these studies are consistent with the findings of research included in the SR conducted to address this question.

After weighing the benefits and risks, the low quality of the evidence and the methodological limitations of the studies mean that it is not possible to establish whether there are differences in efficacy and safety between a second TNF inhibitor and a non-TNF-inhibitor biologic or a JAK inhibitor, in patients in whom previous TNF inhibitor therapy is discontinued for inadequate response. For this reason, the GDG refrains from stipulating the order in which a second TNF inhibitor, a non-TNF-inhibitor biologic and a JAK inhibitor should be used after discontinuation of a first TNF inhibitor for an inadequate response.

In the case of JAK inhibitors, take into account the warning issued by the AEMPS<sup>144</sup> following the results of the ORAL Surveillance study<sup>142</sup> that these drugs should only be used when no alternative treatments are available and at the lowest dose possible in the case of over-65-year-olds, current smokers or former smokers with a long history of smoking, and people with other cardiovascular or thromboembolic risk factors or at high risk of developing cancer.

### **Equity, acceptability and feasibility of the implementation**

In our setting, there are likely to be inequities in access to bDMARDs mentioned in this document as a function of geographical location and regional differences in administrative processes. These inequities are attributable to differences in drug administration routes, some biologics potentially requiring specific facilities for IV administration, and to the existence of protocols that give preference to certain drugs over others.

There is judged to be no risk of inequity based on economic status, given the characteristics of the healthcare system in our setting, or on race or ethnic origin.

Given the good efficacy of all the drugs and their low adverse effect profiles, as well as the experience accumulated over recent years in the use of advanced therapies in patients with RA, their use in routine clinical practice is likely to be accepted by all parties involved (healthcare authorities, specialists, and patients).

The drugs included in the recommendation have been commonly used in our setting for years, and this facilitates their use in routine practice.

### **Outcome assessment by patients**

Variability in how patients rate the main outcomes is considered unlikely.

### **Resource use**

No specific search has been conducted for data on drug costs, as this topic is usually deemed to be beyond the scope of CPGs. Therefore, the GDG believes that it has insufficient information to make any recommendations regarding resource use.

## 9. Treatment of RA in special situations

### 9.1. RA as a complex disease

RA is a systemic disease and is considered complex due to the variability in the symptoms and the numerous related conditions. It is also difficult to differentiate the extra-articular manifestations of RA from the comorbidities associated with the disease, since sustained inflammation is the mechanism underlying many of these conditions<sup>156</sup>.

In many cases, the level of control of the inflammatory disease determines the level of control of the comorbidity. It is important to adjust treatment according to extra-articular manifestations and associated comorbidities since these can also increase morbidity and mortality in patients with RA. The various RA-associated conditions should be monitored by the patient's rheumatologist in collaboration with the GP and other specialists<sup>156, 157</sup>.

#### ***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<sup>157</sup>. Although severe extra-articular manifestations (e.g., interstitial lung disease, pericarditis, and pleurisy) may occasionally precede articular signs and symptoms, they more commonly appear in patients with long-standing RA<sup>158</sup>.

#### **Rheumatoid nodules**

The most common extra-articular manifestations are subcutaneous rheumatoid nodules, which are found in 7% of patients at diagnosis and up to 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 disease duration, and it is more common in older patients. It tends to be benign, with mild or imperceptible symptoms (dry eyes and mouth) that are related to disease activity. Patients with secondary Sjögren's syndrome generally have 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<sup>159, 160</sup>.

#### **Blood dyscrasias**

- *Anaemia*: the majority of patients with RA have mild normocytic normochromic anaemia, which correlates with disease activity. It may also be multifactorial (associated with iron, vitamin B12 or folic acid deficiency)<sup>161</sup>.
- *Thrombocytosis*: this is often found and is related to the inflammatory activity<sup>162</sup>.
- *Felty's syndrome* (<1%): this is characterised by the triad of RA, neutropaenia and splenomegaly. There are no controlled clinical trials of any specific treatments<sup>163</sup>.

### **Lung diseases**

These are among 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 be asymptomatic or symptoms may be masked by a low level of physical activity due to the underlying disease<sup>164</sup>.

- *Pleural disorders*: most commonly pleural effusion, but also may include thickening, empyema, nodules, and pneumothorax
- *Interstitial lung disease*: see Section 9.3 of the guideline
- *Bronchiectasis* (2-3.1%): RA-associated bronchiectasis is associated with more infectious complications, poorer course and prognosis, and higher mortality than other types of bronchiectasis. According to experts, antibiotic prophylaxis should be considered for 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 uncommon and tend to occur in patients with high disease activity or long-standing disease<sup>165</sup>.

- *Pericarditis*: the most common manifestation (found in up to 40% of autopsies, though only 2% of cases are symptomatic)
- *Myocarditis*: rare
- *Valvular heart disease*: the most common type is mitral valve insufficiency, followed by aortic regurgitation, and most patients are usually asymptomatic
- *Coronary heart disease*: patients with RA have a higher risk of ischaemic events, and hence, it is considered an independent cardiovascular risk factor (see Section 9.4 of the guideline)
- *Congestive heart failure*: usually with diastolic impairment but preserved systolic function

### **Ocular manifestations**

As well as dry eye (xerophthalmia), some patients have scleritis, episcleritis or both, although they are uncommon. These manifestations are associated with long-standing disease and related to the level of inflammatory activity<sup>166</sup>. Close collaboration between rheumatologists and ophthalmologists is essential<sup>167</sup>.

### **Renal dysfunction**

It is directly associated with age, female sex, disease duration and RF and/or ACPA positivity. There is also an association with cardiovascular risk factors (in particular, hypertension)<sup>168, 169</sup>.

### **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 long-standing 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<sup>170</sup>:

- 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 long-standing 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 patients present with proteinuria and/or renal impairment, although other organs, such as the thyroid gland, heart and gastrointestinal tract, may also be involved<sup>171</sup>.

### **Comorbidities in RA**

Patients with RA have an elevated risk of developing comorbidities<sup>44</sup>. The development of comorbidities in these patients is a key factor in the selection of their treatment, since the presence of particular conditions may be a contraindication to starting certain therapies, while new-onset comorbidities may be a reason for changing current treatments<sup>172</sup>. They can also affect physical functioning and quality of life, and even the course of the disease by modifying disease activity<sup>44, 157</sup>. For these reasons, rheumatologists must always identify potential comorbidities and current risk factors in patients with RA, especially those that may be preventable or affect the development of the disease or treatment<sup>156</sup>.

Patients with advanced age and long-standing RA and/or active disease have more comorbidities. This may be related to having received less intensive treatment due to their age or contraindications due to concurrent conditions or concomitant therapies. For all these reasons, particular attention should be paid to these patients, and they should be given intensive treatment, always taking into account their comorbidities<sup>44, 156, 173, 174</sup>. Experts in the field underline the importance of always properly documenting any long-term treatments for comorbidities<sup>174, 175</sup>. Women have a different pattern of comorbidities, characterised by a higher prevalence of depression and osteoporosis<sup>174</sup>. The comorbidities associated with a higher mortality rate are: cardiovascular and pulmonary diseases, cancer and depression<sup>176</sup>.

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<sup>177</sup>.

Table 8 summarises the consensus reached by experts on actions to take if we suspect comorbidities associated with RA.

**Table 8. Actions to take if we suspect or diagnose comorbidities associated with RA<sup>156, 178, 179</sup>**

Comorbidity	Recommendation
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Lung disease	If suspected, refer to a pulmonologist
Cardiovascular diseases	If they occur, refer to an appropriate specialist (cardiologist, neurologist, internist, etc.) Annual cardiovascular risk assessments
Gastrointestinal diseases	If suspected, refer to a gastroenterologist
Infections (HBV, HCV, TB, serious infections)	Vaccinations Dental hygiene
Cancer	Screening (for breast, cervical, colon, skin and/or prostate cancer), in accordance with current published guidelines and depending on risk factors Annual lymph node examinations
Psychiatric disorders (depression)	No specific screening
Osteoporosis	Densitometry using dual-energy x-ray absorptiometry (at least once a year in postmenopausal women) and monitoring of risk factors If fractures occur, treat
Fibromyalgia	Management in accordance with current guidelines
Osteoarthritis	Management in accordance with current guidelines
Carpal tunnel syndrome	Depending on the degree of involvement, consider conservative treatment or surgery

## 9.2. Patients in remission/dose reduction

### **Clinical question 12** (valid)

In patients with RA treated with a bDMARD who have achieved disease remission, what is the rate of relapse when the dose is tapered?

## Recommendations

**Recommendation 14:** In patients with RA who have achieved remission or low disease activity with a bDMARD for at least 6 months, consider tapering the dose of the biologic, despite the risk of relapse (Weak recommendation, in favour)<sup>Y</sup>.

<sup>Y</sup>Recommendation related to a question in the previous GUIPCAR guideline considered still valid.

The GDG considers that tapering of RA treatment when patients are in sustained remission is now commonplace with all DMARDs. Gradual tapering of bDMARDs is still recommended rather than abrupt discontinuation, and bDMARDs are preferred over csDMARDs due to fewer adverse effects and lower costs.

### 9.3. Interstitial lung disease

#### **Clinical question 13** (updated)

In patients with RA and interstitial lung disease (ILD), which drugs have been shown to be efficacious/effective/safe for the treatment of the lung disease?

Given the epidemiological importance of RA and the clinical impact of ILD in patients with RA, the SER Research Unit and the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) have recently published a guideline for the diagnosis and treatment of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) to support both rheumatologists and pulmonologists in the management of this complication. That guideline seeks to address common questions related to the incidence and prevalence of this extra-articular manifestation, and the treatments that may be the most effective and safe, as well as the potential role of new antifibrotic drugs. It is important that rheumatologists know how to assess pulmonary involvement, and that pulmonologists know when to suspect the presence of RA in patients with ILD of unknown cause. Consult the corresponding publications for the specific recommendations<sup>180, 181</sup>.

## Context/Background

ILD is one of the most common and severe extra-articular manifestations of RA, and it is the second leading cause of related premature death. The management of RA-ILD poses a clinical challenge, given that these patients tend to be excluded from RCTs, and very few placebo-

controlled studies have been conducted specifically assessing the efficacy of the treatments available.

In 2022, seeking to support decision-making in clinical practice, the SER and SEPAR published the first recommendations for the management of RA-ILD, based on the scientific evidence available up to October 2020<sup>180, 181</sup>. A total of 18 recommendations were made, 12 of which focus on the treatment of this complication.

During the updating of GUIPCAR 2019, these recommendations were also updated based on a review of the evidence up to June 2024.

### Recommendations

**Recommendation 15:** In patients with RA and ILD who require treatment intensification to control joint symptoms, use RTX, ABA, an IL-6R inhibitor, or a JAK inhibitor as they are considered the safest options for lung disease (*Strong recommendation, in favour*)<sup>U</sup>.

**Recommendation 16:** In patients with RA and stable ILD treated with a TNF inhibitor, there is no conclusive evidence to justify withdrawal if good control of joint symptoms has been achieved, since there is insufficient evidence to warrant a blanket contraindication of these drugs in this group (*Good clinical practice*)<sup>U</sup>.

<sup>U</sup> Recommendation related to a question in the previous GUIPCAR guideline that has been updated.

### Important clinical considerations

- *Monitoring- and assessment-related factors*
  - It should be taken into account that the clinical course of RA-ILD is very variable. In 45% of patients, ILD is stable or progresses slowly, while the other 55% experience more or less rapid worsening of lung function.
  - Given that the majority of studies do not describe the pattern of changes in pulmonary function tests (PFTs) before starting biological therapy, and that monitoring PFT data are not reported for all patients, it is not possible to assume that all have active and progressive ILD. Consequently, the assessment of the efficacy of treatments in slowing ILD progression is associated with high levels of uncertainty and variability.
  - This constrains the ability to draw robust and reliable conclusions regarding their efficacy in ILD, and hence, recommendations are primarily based on their safety in ILD.
- *Subgroups to consider:*

- Give preference to options other than JAK inhibitors in  $\geq 65$ -year-olds, current smokers (and former smokers who have a long history of smoking or have been heavy smokers), and people with an elevated risk of cancer or other risk factors for cardiovascular and thromboembolic disease. If JAK inhibitors are required in such patients, use the lowest possible effective dose.

**Recommendation 17:** In the subgroup of patients with RA and progressive fibrosing ILD, use NTB while maintaining background RA treatment (Strong recommendation, in favour)<sup>U</sup>.

**Recommendation 17.1:** In patients with intolerance to NTB, consider using PFN (Weak recommendation, in favour)<sup>U</sup>.

<sup>U</sup> Recommendation related to a question in the previous GUIPCAR guideline that has been updated.

#### Important clinical considerations

- *Monitoring- and assessment-related factors*
  - While 55% of patients with ILD experience more or less rapid worsening of lung function, it has been estimated that 40% meet the criteria for the diagnosis of progressive fibrosing ILD in the first 5 years after disease onset.
  - In accordance with the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society and Latin American Thoracic Society guideline, progressive pulmonary fibrosis is defined by fulfilling at least 2 of the following 3 criteria: (1) increase in fibrosis on computed tomography, (2) worsening of respiratory symptoms, and/or (3) a  $\geq 5\%$  decline in FVC or a  $\geq 10\%$  decline in DLCO over 1 year of follow-up.
  - Unlike NTB, PFN is not currently approved by AEMPS for this condition

#### Rationale

Although prognosis has improved significantly in recent years, patients with RA-ILD still have a 3- to 10-fold higher adjusted risk of mortality than patients with RA who do not have this complication, regardless of the follow-up period and the presence of comorbidities. The mean survival after ILD diagnosis ranges from 2.6 to 8.1 years, highlighting the need to identify and expand the treatment options available for its management.

The aforementioned guideline established a ranking of biologics for use in patients with RA-ILD, preferring ABA and RTX, given the larger body of evidence for these drugs. More recently, a growing number of studies have evaluated the efficacy and safety of IL-6R and JAK inhibitors in

these patients, providing a comparable level of evidence. Therefore, following a literature review, the GDG considers that some of these recommendations should be revised or refined.

## Detailed rationale

### **bDMARDs**

#### IL-6R inhibitors

The review identified one observational study assessing the safety of TCZ. This was a multicentre retrospective study that included 28 patients with RA-ILD treated with TCZ for a mean of 30 months. The lung function parameters (FVC and DLCO) remained stable in 56% of patients, improved in 20% and worsened in 24% of cases, while lung computed tomography showed radiological stability in 89% of patients<sup>182</sup>.

Other considerations: A Japanese study involving 55 patients with RA-ILD was identified. In this, TCZ was also not associated with an acceleration of disease progression, and a significant reduction in KL-6 levels was observed at 6 months<sup>183</sup>.

Additionally, a retrospective study of the Japanese KEIO-RA cohort assessed the impact of treatment with SAR in 21 patients with RA-ILD over 24 months. Chest CT findings were stable in 85.7% of patients, KL-6 levels did not change or improve in the majority of patients, and no serious adverse events were recorded<sup>184</sup>.

#### Abatacept

The review identified two observational studies assessing the use of ABA in RA-ILD<sup>185, 186</sup>, and both support the evidence gathered for the previous recommendations<sup>180, 181</sup>.

The first study compared the effectiveness of ABA in 190 patients with RA-ILD as a function of the radiological pattern: usual interstitial pneumonia (UIP) (n=106) or non-specific interstitial pneumonia (NSIP) (n=84)<sup>185</sup>. After 24 months of treatment, FVC and DLCO remained stable in both groups, with stabilisation or improvement of chest CT findings, and improvement of dyspnoea in more than 70% of cases. The results indicate that ABA is similarly effective in both radiological patterns and suggest that early use slows progression.

In the second, a prospective multicentre study, the safety and efficacy of ABA were evaluated in 57 patients with RA-ILD treated between 2015 and 2021<sup>186</sup>. After a median follow-up of 27.3

months, the disease was stable or improved in 71.9% of patients and worsened in 22.8% (the other patients [5.3%] died). No significant reductions in FVC and DLCO were observed. Only 10.5% of patients developed serious adverse effects, supporting the good safety profile of ABA.

Other considerations: A more recently published study was also identified: a Japanese retrospective observational study evaluating the therapeutic efficacy of ABA in 38 patients with RA-ILD treated between 2012 and 2021, including treatment response as measured using chest CT<sup>187</sup>. At 1 year of follow-up, significant improvements were observed in RA activity indices, as well as decreases in ground-glass opacity scores in patients with both UIP-like and non-UIP-like patterns ( $p = 0.008$  and  $p < 0.002$ , respectively). In the UIP-like pattern group, the total fibrosis scores also decreased ( $p < 0.042$ ). FVC remained stable.

#### Rituximab

The review identified one meta-analysis of 15 studies, including 314 patients with RA-ILD<sup>188</sup>. It found that ILD remained stable or improved at 1 year of follow-up in 88% of patients. Further, RTX was associated with significant improvements in FVC and DLCO in 7.5% and 6.39% of patients, respectively.

Other considerations: The review identified one relevant SR and meta-analysis assessing the efficacy of biologics (ABA, RTX and TCZ), JAK inhibitors and TNF inhibitors in patients with RA-ILD, as monotherapy or in combination with slow-acting csDMARDs or immunosuppressants<sup>189</sup>. It analysed 17 clinical studies, including a total of 1315 patients. In the overall analysis, there were no significant changes in FVC ( $p=0.36$ ) or DLCO ( $p=0.46$ ) after treatment. In the subgroup analysis, only RTX was associated with significant improvement in FVC (mean difference: -4.62; 95% CI: -8.90 to -0.33;  $p=0.03$ ). Radiological findings were stable or improved in the majority of patients, with a non-progression rate of 79.2% (95% CI: 74.6 to 83.4%;  $p = 0.015$ ). The mortality rate attributed to ILD progression was 4.9% (95% CI: 3.5 to 6.5%;  $p < 0.001$ ), reaching as high as 16.5% in patients treated with RTX and 6.4% in those treated with TNF inhibitors.

In the first meta-analysis mentioned above, authors also performed a sensitivity analysis of the effects of RTX, considering only studies reporting data on patients with RA-ILD separately. Two outcomes were analysed: the percentage of patients in whom lung function stabilised or improved and mean change in FVC (both types of data were included in the evidence table; see Appendix 4)<sup>188</sup>. In the second meta-analysis, sensitivity analysis was only performed for mean change in DLCO<sup>189</sup>.

### **JAK inhibitors**

The review identified seven observational studies assessing the safety and efficacy of JAK inhibitors in patients with RA-ILD<sup>190-196</sup>, comparing JAK inhibitors with ABA in four cases<sup>192, 194, 196</sup> and with RTX in one<sup>190</sup>.

In terms of safety, JAK inhibitors seem to be well-tolerated in patients with RA-ILD. Between 4.5% and 25% of patients developed clinically relevant infections. In comparison studies, JAK inhibitors showed comparable efficacy and safety to those of ABA and RTX<sup>190, 192, 194, 196</sup>.

Other considerations: Other studies were identified on the safety of various JAK inhibitors for treating patients with RA. Three studies evaluated the risk of incident ILD in patients with RA treated with JAK inhibitors. Two of these were post-hoc analyses conducted using aggregated data from RCTs (phases 1, 2 and 3) and long-term extension studies with TOF<sup>197</sup> or BAR<sup>198</sup>. The reported incidence rates were 0.18 per 100 patient-years for TOF and 0.17 per 100 patient-years for BAR. These figures do not exceed those estimated for the general population with RA, which range between 1.05 and 4.1 cases of ILD per 1,000 patients.

The most robust evidence supporting the possible beneficial role of JAK inhibitors in RA-ILD comes from a retrospective cohort study performed in more than 28,000 patients with RA in the USA<sup>199</sup>. Among all bDMARDs, patients treated with TOF showed the lowest incidence of ILD, with a crude incidence rate of 1.47 per 1,000 person-years. After adjusting for covariates, TOF was associated with a 69% lower risk of ILD than ADA (adjusted HR: 0.31).

The review also identified a meta-analysis based on 10 of the aforementioned studies, in which most patients received TOF or BAR, although they also included patients treated with UPA or FIL<sup>200</sup>. The data suggest that JAK inhibitors lead to modest but significant improvements in lung function, as measured by FVC and DLCO. The pooled analysis showed a 2.07% increase in FVC (95% CI: 0.57 to 3.58;  $p = 0.007$ ) and a 3.12% increase in DLCO (95% CI: 2.11 to 4.12;  $p < 0.001$ ). Further, improvements were observed on chest CT in at least 11% of patients. An estimated 5% of patients (95% CI: 0.01 to 0.11) experienced worsening of existing ILD, and the risk of developing de novo ILD was low, with a pooled incidence of 0.2 per 1,000 person-years. Adverse effects were reported in 14% of patients (95% CI: 0.08 to 0.21), and clinically significant infections in between 4.5% and 25%.

Considering all these results, it has not been demonstrated that RTX, ABA, IL-6R inhibitors or JAK inhibitors increase the risk of exacerbation or progression of RA-ILD. Their adverse effect profile in patients with existing RA-ILD is similar to that already known in the general population of patients with RA.

The overall quality of the evidence was rated as low to very low for the observational studies without comparators, most of which did not control for confounding and had limited sample sizes.

The GDG highlights that the lack of systematic data on pulmonary function from tests before starting biological therapy, together with the lack of follow-up data in many of the patients included, means that it cannot be assumed that all of them have active and progressive ILD. This methodological weakness leads to a high degree of uncertainty and variability in the assessment of treatment efficacy, making it difficult to draw robust conclusions. Therefore, the recommendations are primarily based on the safety profile of the drugs.

After weighing the benefits and risks, ABA, RTX, IL-6R inhibitors and JAK inhibitors are considered safe options for the management of patients with RA-ILD. Although one meta-analysis identified RTX as the only biologic that improves FVC, and some observational studies support its efficacy in patients with active and progressive disease, the GDG considers that, given its overall efficacy and safety profile, it should not be preferred over ABA, JAK inhibitors and IL-6R inhibitors.

To conclude, based on the group's experience and pooled analysis of the available data, the GDG considers that there is insufficient evidence to rank these treatments for use in patients with RA-ILD.

Nevertheless, the GDG also points out that according to the latest safety alert from AEMPS<sup>144</sup> on the use of JAK inhibitors, issued after publication of the final results of the ORAL Surveillance study<sup>142</sup>, new recommendations have been made concerning all their indications.

### **Antifibrotics**

Three studies were identified assessing the efficacy and safety of antifibrotics nintedanib (NTB) and pirfenidone (PFN) in patients with RA-ILD in recent years<sup>201-203</sup>.

NTB has been formally approved by healthcare authorities for the treatment of idiopathic pulmonary fibrosis, regardless of the underlying condition, based on the INBUILD trial, which showed a significant reduction in the annual rate of FVC decline in these patients. In a specific analysis of the subgroup of 89 patients with RA-ILD, the efficacy of the drug was comparable to

that observed in other diseases<sup>201</sup>. Specifically, after 52 weeks of treatment, the mean rate of decline in FVC was -82.6 ml/year in the group treated with NTB, compared to -199.3 ml/year in the placebo group, with a difference of 116.7 mL/year (95% CI: 7.4 to 226.1;  $p = 0.037$ ).

The efficacy of PFN as a treatment for RA-ILD was assessed in the TRAIL1 RCT, but the study's statistical power was limited as recruitment stopped early due to the COVID-19 pandemic, and hence, the desired sample size was not attained<sup>203</sup>. Although the primary endpoint was not achieved ( $\geq 10\%$  reduction in predicted FVC or death within 1 year), PFN was associated with a significant decrease in the rate of FVC decline compared to placebo. The rate of pulmonary progression was 25% in the PFN group compared to 32% in the placebo group, although the difference was not statistically significant ( $p=0.35$ ). In a post hoc analysis, its therapeutic effect was particularly clear in patients with a UIP-like pattern, the difference reaching significance in this group.

In another observational study<sup>204</sup>, both NTB and PFN slowed the decline in FVC and DLCO at 18 months, with a significant reduction in the annual rate of predicted FVC decline (0.3% per year after initiation vs. 6.2% per year before initiation;  $p = 0.03$ ), although no significant impact was observed on absolute FVC or DLCO.

Other considerations: The 2023 ACR and the American College of Chest Physicians (CHEST) guidelines conditionally recommend PFN as a second-line treatment in patients with progressive RA-ILD who do not respond to their first-line treatment<sup>205</sup>.

Three other observational studies have provided complementary data on the efficacy and safety of antifibrotics in clinical practice. In contrast with the RCTs, in which antifibrotics only slowed the rate of FVC decline without stopping or reversing the fibrotic process<sup>197, 206</sup>, real-world studies have observed stabilisation or even a slight improvement in this parameter. One study reported stabilisation of lung function after 6 months, with non-significant increases in FVC ( $62.5 \pm 20.04$  to  $63.2 \pm 18.2$ ;  $p = 0.3$ ) and DLCO ( $70.1 \pm 15.2$  to  $72.1 \pm 12.4$ ;  $p = 0.15$ )<sup>207</sup>. Another study described an initial stabilisation of FVC at 6 months, followed by a modest improvement (+4.7%;  $p = 0.023$ ) after 1 year, while there was a slight, non-significant decrease in DLCO (-3.8%;  $p = 0.175$ )<sup>202</sup>. Similarly, a third study reported that the antifibrotic therapy stopped FVC decline, the rate changing from a decrease of  $300 \pm 500$  mL/year before the treatment to an improvement of  $200 \pm 400$  mL/year ( $p = 0.336$ ), while DLCO showed a slight downward trend, though it did not

reach significance (3% before the treatment vs 2.9% after the treatment;  $p=0.75$ )<sup>208</sup>. In all the observational studies, changes in FVC were similar for NTB and PFN.

These observational studies confirm the safety of antifibrotics in combination with glucocorticoids, csDMARDs/immunosuppressants (LEF, MTX and mycophenolate mofetil [MMF]) or biologics, in particular ABA, RTX and JAK inhibitors.

Adverse effects were common, with higher rates in the RCTs (100%) than the observational studies (25 to 81.5%), likely due to closer monitoring. The most common were gastrointestinal symptoms and liver toxicity. Treatment discontinuation due to adverse effects was also somewhat more common in observational studies (30 to 46%) than RCTs (23.8% in INBUILD and 24% in TRAIL1). Permanent dose reduction was common, reported in 21.4 to 40% of cases for NTB and 14% for PFN.

Lastly, two studies suggest that switching to PFN could be a viable option in patients with intolerance to NTB, although the evidence is limited to 19 cases, among which 13 patients (68.4%) were successfully able to continue the second antifibrotic treatment<sup>202, 204</sup>.

The quality of the evidence was rated as moderate for the outcome variables assessed in the RCTs, and very low for those for which data came from observational studies without comparators or control of potential confounding, and with small sample sizes.

After weighing the benefits and risks, the evidence indicates that NTB is effective in RA-ILD, demonstrating a significant reduction in the annual rate of FVC decline. In the case of PFN, results suggest that it may be a good alternative to NTB in people with intolerance to this drug. Based on the group's experience and considering the larger body of evidence available on efficacy, the GDG considers that preference should be given to NTB as an antifibrotic agent in patients with RA-ILD.

### **Immunosuppressants**

Only one study has been identified assessing the efficacy of csDMARDs and immunosuppressants for the treatment of RA-ILD. This multicentre study, based on the Korean RA-ILD cohort, assessed the relationship between disease progression and the use of MTX, LEF or tacrolimus<sup>209</sup>. Between 2015 and 2018, 143 patients were prospectively recruited and followed up for 3 years. ILD progression was defined as a  $\geq 10\%$  decline in FVC, a  $\geq 15\%$  decline in DLCO and/or death due to respiratory failure.

During the mean follow-up of 33 months, 64 patients experienced ILD progression. Overall, none of the drugs were associated with an increased risk of ILD progression, with adjusted hazard ratios (HRs) of 1.06 (95% CI: 0.59 to 1.89) for MTX, 1.75 (95% CI: 0.88 to 3.46) for LEF, and 0.94 (95% CI: 0.52 to 1.72) for tacrolimus. On the other hand, in the subgroup with severely impaired lung function, LEF was associated with a greater risk of progression (adjusted HR 8.42; 95% CI: 2.61 to 27.15).

Other considerations: it should be noted that the 2023 ACR/CHEST guidelines also prefer MMF as the immunosuppressant of choice<sup>205</sup>. Nonetheless, there are not yet any data from RCTs supporting its use in RA-ILD, and the evidence remains scarce. One study described functional and radiological improvements in a series of three patients<sup>210</sup>.

A multicentre study in the United Kingdom assessed mortality over 25 years in a cohort of 290 patients with RA-ILD, compared to 290 age- and sex-matched controls with RA but without this complication. It found greater all-cause and respiratory mortality in patients treated with CP or AZA than those treated with MMF<sup>211</sup>.

Lastly, a study compared AZA and MMF in patients with fibrosing connective tissue disease-related ILD, including 15 with RA-ILD. In both groups, lung function remained stable over time. The AZA group showed marginal improvements but a higher rate of adverse events<sup>212</sup>.

The quality of the evidence was rated as very low for observational studies with no comparator group, most of which did not control for confounding and had limited sample sizes.

Based on the group's experience and the aforementioned data, the GDG considers that the previous recommendations for ILD regarding this group of drugs made by the SER Research Unit remain valid. These can be consulted in Appendix 2 and on the SER website.

### **Specific considerations concerning TNF inhibitors**

Although TNF inhibitors were not included in the research question, the GDG considers it necessary to provide some data concerning these drugs. Their use in patients with RA-ILD remains controversial. A retrospective study based on United States Department of Veterans Affairs health records compared outcomes in patients with RA-ILD treated with TNF inhibitors versus other biologics<sup>213</sup>. A total of 237 patients starting TNF inhibitor therapy were matched with 237 patients starting other treatments, and followed up for 3 years. No significant between-

group differences were observed in hospitalisation rates for respiratory causes or all-cause or respiratory mortality.

Another study, conducted in an Asian population (Taiwan) using the TriNetX database, retrospectively compared mortality in patients with RA-ILD treated with ABA versus TNF inhibitors. A total of 895 patients were included in each group. The ABA group had a higher risk of mortality and a greater need for mechanical ventilation<sup>214</sup>.

An SR and meta-analysis has also been published investigating the association between various treatments and the risk of developing RA-ILD, based on data from 40 studies (24 RCTs), including 486,465 patients with RA and 3,928 cases of incident ILD. The trial results did not show significant differences in the risk of developing ILD with any of the drugs analysed: MTX, TNF inhibitors, TCZ, TOF (ORAL Surveillance) or BAR. Observational studies suggested that MTX may be protective, with the likelihood of developing ILD being 51% (OR 0.49; 95% CI: 0.32 to 0.76) lower in patients receiving MTX than in other groups. Moreover, as mentioned above, comparing TOF with ADA, the likelihood of developing ILD was found to be 69% lower<sup>199</sup>.

Lastly, an SR and meta-analysis mentioned above also assessed the efficacy of bDMARDs (ABA, RTX, TCZ, JAK inhibitors and TNF inhibitors) in patients with RA-ILD, alone or combined with csDMARDs or immunosuppressants<sup>189</sup>. The analysis was based on 17 clinical studies including 1315 patients. Overall, no significant differences were observed in FVC ( $p=0.36$ ) or DLCO ( $p=0.46$ ) after treatment, while in subgroup analysis, only RTX was associated with significant improvement in FVC (mean difference  $-4.62$ ; 95% CI:  $-8.90$  to  $-0.33$ ;  $p = 0.03$ ). Radiological findings showed stability or improvement in most cases, with a chest CT non-progression rate of 79.2% (95% CI: 74.6 to 83.4%;  $p = 0.015$ ). The rate of mortality associated with ILD progression was 4.9% (95% CI: 3.5 to 6.5%;  $p < 0.001$ ) overall and higher in the RTX group (16.5%) than the TNF inhibitor group (6.4%).

Other considerations: Although recent studies on the risk of ILD development or exacerbation are encouraging, cases described in patients on TNF inhibitor monotherapy or treated for ulcerative colitis or spondyloarthritis<sup>180, 181</sup> mean that caution must be exercised, since an as-yet poorly defined –though likely overestimated risk– cannot be ruled out. For this reason, based on the group’s experience, the GDG still recommends minimising risks and preferring other treatment options in patients with RA-ILD who are going to start biological therapy.

In patients with RA and ILD already treated with TNF inhibitors, the current evidence does not support their withdrawal if joint disease is well controlled and ILD remains stable, given that there are no well-founded arguments for a blanket contraindication of these drugs.

### **Equity, acceptability and feasibility of the implementation**

The GDG considers that, in our setting, there are no marked inequities in access to bDMARDs, JAK inhibitors and antifibrotic agents. Further, it judges that, given the experience accumulated over recent years, the use of these drugs in clinical practice is likely to be deemed acceptable by all parties involved (healthcare authorities, specialists and patients).

Additionally, in the view of the GDG, the presence of prognostic factors does not seem to significantly influence the equity in response to these drugs, their acceptability or the feasibility of implementation of these therapies.

### **Outcome assessment by patients**

In the view of the GDG, it is unlikely that there is significant variability in how patients rate the main outcomes.

### **Resource use**

No specific search has been conducted for data on drug costs, as this topic is usually deemed to be beyond the scope of CPGs. Therefore, the GDG believes that it has insufficient information to make any recommendations regarding resource use.

Nevertheless, it considers it reasonable to assume that investments in these treatments may be justified if they help reduce hospitalisations for exacerbation or respiratory causes, avoid the need for lung transplantation and reduce overall use of healthcare resources.

## 9.4. Cardiovascular risk

Cardiovascular mortality has been shown to be higher in patients with RA than in the general population of the same age and sex<sup>216, 217</sup>. This is due to the rapid development of accelerated atherogenesis<sup>218</sup>. Specifically, the relative risk of a cardiovascular event in patients with RA is 2-fold higher than in age- and sex-matched individuals without this condition<sup>219</sup>. Furthermore, 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<sup>219</sup>. 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<sup>220</sup>.

### **Subclinical cardiovascular disease in patients with RA**

Patients with RA have a higher risk of heart failure<sup>221</sup> and of subclinical atherosclerosis<sup>222</sup>, 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 are more likely to have left ventricular diastolic dysfunction and subclinical pulmonary hypertension<sup>223</sup>. These findings may explain the higher rate of congestive heart failure observed in this population.

Various tests used for detecting subclinical atherosclerosis have also been shown to be useful for confirming accelerated atherogenesis in patients with RA<sup>222</sup>. These include brachial artery ultrasound imaging to assess endothelial function, a marker of early atherosclerosis<sup>224</sup>, which revealed endothelial dysfunction in patients with long-standing RA who did not have traditional cardiovascular risk factors<sup>225</sup> and in young patients with early RA<sup>226</sup>.

Another non-invasive marker of atherosclerosis useful in RA is carotid intima-media thickness (CIMT) measured using common carotid artery ultrasound imaging<sup>222</sup>. In another study, the same research group observed abnormally high CIMT in a series of patients with long-standing RA who had no traditional risk factors for atherosclerosis and no history of cardiovascular events compared to that in a control population<sup>227</sup>. It was also found that these patients with no traditional cardiovascular risk factors had a higher prevalence of carotid atheromatous plaques, and that this was correlated with longer disease duration and the presence of extra-articular manifestations of RA<sup>227</sup>. In addition, it has been reported that persistently high CRP levels are associated with higher CIMT in patients with long-standing RA<sup>228</sup>. Lastly, the presence of subclinical carotid atherosclerosis was prognostically associated with 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, thicknesses greater than 0.90 mm being associated with a higher risk of cardiovascular events during follow-up<sup>229</sup>.

Carotid atheromatous plaques were found to be independent predictors of acute coronary syndrome in patients with RA. Furthermore, the incidence of this syndrome was 2.5-fold higher if plaques were observed in only one carotid artery and 4.3-fold if observed in both<sup>230</sup>.

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 of advanced atherosclerosis and has been 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 matched controls, especially in those with long-standing disease (>10 years)<sup>231</sup>.

### **Impact of RA treatment on cardiovascular risk**

Once patients with RA have been shown to have a higher cardiovascular risk, the next step is to establish a treatment strategy focused on reducing this risk. In relation to this, it has been confirmed that active treatment of RA reduces the risk of cardiovascular death<sup>218</sup>. Recent research has demonstrated a reduction in mortality in RA associated with a decrease in the incidence of myocardial infarction (MI) attributable to more intense treatment of the rheumatic disease<sup>232</sup>.

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<sup>233</sup>. Choi *et al.* showed that, despite poorer prognostic factors for mortality, patients treated with MTX did not have a higher rate of cardiovascular events during follow-up<sup>234</sup>. 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, lower cardiovascular mortality in patients with RA during follow-up.

Recent population studies have shown that the use of biological therapies in patients with RA who have an inadequate response to conventional therapy reduces all-cause mortality, and in particular, cardiovascular mortality<sup>235</sup>. Biological therapy with TNF inhibitors improves endothelial function in patients with RA who have an inadequate response to MTX<sup>236-238</sup>. Similarly, in patients with an inadequate response to TNF inhibitors, RTX has been shown to achieve rapid and lasting improvement in endothelial function<sup>239</sup>. Given that endothelial dysfunction is a key mechanism in the development of atherosclerosis, the improvement in endothelial function achieved with these drugs may serve as a future treatment target in patients with severe RA. On the other hand, although one study did not show regression of subclinical carotid atherosclerosis with TNF inhibitor therapy in a series of patients with long-

standing severe RA over a 3-year follow-up<sup>240</sup>, a later study described a beneficial effect of these drugs in patients with RA, namely, a significant reduction in CIMT<sup>241</sup>.

In patients with RA, biologics, in particular TNF inhibitors, have 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 MI<sup>242</sup>. Further, the risk of cardiovascular events (acute MI, stroke and cardiovascular-related death) in patients enrolled in the CORRONA registry was lower in the group that received TNF inhibitors than in those who received MTX or another DMARD (HR 0.39)<sup>243</sup>. This effect was likely due to a reduction in the inflammatory load associated with RA.

Given the effect of TCZ on lipid levels (elevation of total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL] and triglyceride levels), it has been suggested that this drug may increase cardiovascular risk, although this has not been demonstrated in clinical trials<sup>244</sup>. On the other hand, by reducing the inflammatory burden of the disease, TCZ was found to reduce pro-atherothrombotic risk through the restoration of endothelial function, reduction in oxidative stress and inhibition of the pro-thrombotic and inflammatory properties of monocytes<sup>245</sup>.

The ENTRACTE study, a safety clinical trial in patients with RA and cardiovascular risk factors, assessed the occurrence of major adverse cardiovascular events (MACE: fatal and non-fatal myocardial infarction, sudden cardiac death and death of unknown cause), and found that TCZ was not inferior to ETN after a mean follow-up of 3.2 years<sup>246</sup>.

Regarding JAK inhibitors, neither clinical trials nor extension studies have found higher rates of severe adverse effects, including MACE and cancer, than would be expected considering comparison populations treated with other drugs. TOF in particular has been associated with a low incidence of cardiovascular events<sup>247</sup>. Nonetheless, in the ORAL SURVEILLANCE<sup>142</sup> study, a safety clinical trial in patients with RA and cardiovascular risk factors, TOF failed to demonstrate non-inferiority compared to TNF inhibitors; it was associated with a higher rate of MACE, cancer, thromboembolic events, infections and mortality, in general, and especially in over-65-year-olds, smokers and patients with a history of MACE.

These findings have led the ACR, as well as the EMA<sup>143</sup> and AEMPS<sup>144</sup>, to issue recommendations on the use of JAK inhibitor therapies in inflammatory diseases, limiting their use in people with the aforementioned risk factors. Given the importance and implications of these mandatory measures, this recommendation has been updated.

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, they should be prescribed with caution, especially in patients with a history of cardiovascular disease or traditional cardiovascular risk factors<sup>248</sup>.

Glucocorticoids also have a dual effect. On the one hand, they promote atherogenesis, because they negatively influence lipid profile, glucose metabolism and blood pressure, especially when used for a long time. On the other, when used acutely (for short periods), these drugs can be beneficial in reducing inflammation and improving mobility, especially in the early stages of the disease. Given that cardiovascular risk increases with the cumulative dose of glucocorticoids<sup>249</sup>, they must be prescribed at the lowest possible effective dose and for the shortest possible time<sup>248</sup>.

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

Strict control of traditional cardiovascular risk factors is essential in patients with RA for reducing the high overall cardiovascular risk associated with this disease. These patients tend to have abnormal lipid profiles as a result of the chronic inflammation associated with RA<sup>218</sup>, and the monitoring of lipid levels is a key component of the therapeutic management of the disease. In a long-term clinical trial, clinical and biological markers of inflammation decreased in patients with long-standing RA treated with statins<sup>250</sup>. Moreover, their use has been associated with an improvement in endothelial function in patients with RA<sup>251, 252</sup>. Similarly, the RORA-AS study found atherosclerotic regression (as assessed by carotid plaque height) in patients with RA treated with rosuvastatin for 18 months<sup>252</sup>. The ORAL Surveillance study showed that, in patients treated with TOF with a history of atherosclerotic disease, statins reduce the risk of MACE to levels comparable to those in patients treated with TNF inhibitors<sup>253</sup>.

### **Stratification of cardiovascular risk in patients with RA**

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

The use of Systematic *CO*ronary 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 consensus across clinical practice guidelines on what to recommend concerning this key clinical aspect of the care of these patients. In Spain, statin therapy should be started in line with the Spanish guidelines on cardiovascular risk, which are adapted for southern European populations according to the SCORE guidelines and allow estimation of the 10-year risk of cardiovascular death as a function of sex, age, systolic blood pressure, smoking habits and total cholesterol<sup>254</sup>. Notably, the cardiovascular risk associated with RA is similar to that observed in patients with type 2 diabetes<sup>255</sup>. For this reason, to assess cardiovascular risk properly 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.

Notably, RF- or anti-CCP-positive individuals were found to have more severe disease and a poorer cardiovascular prognosis<sup>256</sup>. Additionally, anti-CCP positivity was commonly associated with HLA-DRB1\*04 alleles, which are related to an elevated cardiovascular risk<sup>257</sup>. In line with this, the prognostic value of anti-CCP positivity is underlined by evidence of associations of HLA-DRB1\*0401 and HLA-DRB1\*0404 with the development of endothelial dysfunction<sup>225</sup>, and with an elevated risk of cardiovascular events<sup>220</sup>.

Lastly, longer disease duration and more severe clinical signs and symptoms (specifically, extra-articular manifestations) are other cardiovascular risk factors in RA<sup>227, 228</sup>. For this reason, the EULAR Standing Committee for International Clinical Studies Including Therapeutics recommended multiplying the estimated SCORE cardiovascular risk value by a factor of 1.5<sup>248</sup>. Unfortunately, this multiplying factor in RA is insufficient in many cases<sup>258, 259</sup> and the EULAR consensus advocates for 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 cardiovascular risk, this technique may be particularly appropriate in patients with RA in the moderate risk category according to the SCORE charts<sup>248</sup>.

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, specifically, encouraging regular moderate physical activity and a heart-healthy diet low in

saturated and hydrogenated fats, cholesterol and refined sugars, as well as control of body weight and blood pressure, and smoking cessation. Recommendations for the management of hypertension in patients with RA are the same as for the general population<sup>248</sup>. 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%), seeking to attain the LDL cholesterol target (< 70 mg/dl) or at least achieve a greater than 50% reduction in LDL cholesterol<sup>260</sup>.

### Cardiovascular comorbidity

#### Clinical question 14 (new)

In patients with RA, what is the risk of cardiovascular events and thromboembolic disease associated with bDMARDs and tsDMARDs?

### Context/Background

Several epidemiological studies have shown that patients with a diagnosis of RA have a greater risk of experiencing cardiovascular events than people in the general population with similar characteristics<sup>261</sup>.

Evidence suggests that chronic inflammation is associated with accelerated progression of atherosclerosis, which increases the risk of cardiovascular events such as MI and ischaemic stroke<sup>262, 263</sup>. Considering this relationship, it can be inferred that the use of drugs able to control inflammation caused by the disease would reduce the risk of cardiovascular events. Several studies have demonstrated that this is true, but the findings do differ. Given this, to optimise patient care, we need to analyse the evidence on the various biological and targeted DMARDs available.

#### Recommendations

**Recommendation 18:** In patients with RA who do not have related cardiovascular or thromboembolic risk factors, use either bDMARDs or tsDMARDs (Strong recommendation, in favour)<sup>U</sup>.

**Recommendation 19:** In patients with RA aged ≥65 years and those with cardiovascular or thromboembolic risk factors, consider avoiding tsDMARDs unless no other treatment options

are available. If these drugs are required, the lowest possible effective dose should be used and cardiovascular risk factors closely monitored ([Weak recommendation, in favour](#)) <sup>U</sup>.

<sup>U</sup> Recommendation related to a question in the previous GUIPCAR guideline that has been updated.

#### Important clinical considerations

- Pretreatment assessment- and monitoring-related factors
  - Before and after starting bDMARD or tsDMARD therapy, potentially modifiable cardiovascular and thromboembolic risk factors should be assessed.

### Rationale

The recommendations have been formulated based on the results of RCTs and observational studies on cardiovascular and thromboembolic events in patients with RA receiving bDMARDs or tsDMARDs.

Studies on bDMARDs have consistently shown a similar risk of cardiovascular and thromboembolic events to that in patients receiving placebo or csDMARDs. Studies on tsDMARDs describe similar findings to those in the general population, although incidence rates are non-significantly higher in groups of patients on high doses who also have cardiovascular risk factors.

The recommendations made are weak, given the poor quality of the evidence available. These drugs may be beneficial in patients with no cardiovascular risk factors or controlled risk factors, or when no alternative treatment options are available.

### Detailed rationale

#### **bDMARDs**

##### bDMARDs vs csDMARDs

The review identified three SRs<sup>264-266</sup> evaluating the safety of bDMARDs for treating patients with RA compared to csDMARDs.

The first SR based on 31 observational studies including patients with RA receiving bDMARDs, and compared adverse events in this group with those in patients not treated with bDMARDs<sup>264</sup>.

The second SR was based on 10 RCTs and 8 observational studies. This review included studies in patients with RA, but also with psoriatic arthritis or systemic lupus erythematosus, and assessed cardiovascular adverse events occurring in bDMARD versus csDMARD users<sup>265</sup>. The

third SR was conducted to inform an update of the EULAR recommendations for the management of patients with RA. It included eight RCTs and five non-systematic reviews

reporting the occurrence of adverse events in patients with RA treated with bDMARDs or csDMARDs<sup>266</sup>.

The quality of the evidence was rated as low or very low, given that the body of evidence is mainly from non-randomised studies, and due to imprecision associated with 95% CIs crossing either the line of no effect or the threshold of clinical significance, heterogeneity among studies, and potential publication bias.

The GDG considers that the influence of bDMARDs on the risk of cardiovascular events compared to that of csDMARDs is small, since no substantial between-group differences were observed despite the inclusion of a relatively large number of patients from the SRs identified. Regarding the development of MACE and heart failure, the event rate is higher in the group treated with csDMARDs, but the studies identified are very heterogeneous, comparing multiple drugs, with a high risk of bias due to imprecision, and in the case of mortality, very few events. In this context, note that disease activity may be a confounding factor, as inflammation is better controlled in patients treated with bDMARDs. The use of TNF inhibitors is not recommended in patients with grade 4 heart failure.

Weighing benefits and risks, the evidence indicates that bDMARDs are as safe as csDMARDs.

Other considerations: German (RABBIT) and French national registries and large studies based on databases from American insurance companies (STAR-RA) have not shown differences in the development of cardiovascular and thromboembolic events between csDMARDs and bDMARDs<sup>267-269</sup>.

Based on the group's experience and analysis of the available evidence, the GDG considers that bDMARDs may be used in patients with RA who have no major cardiovascular risk factors.

### IL-6R inhibitors

#### *Tocilizumab vs. TNF inhibitors*

The review identified two SRs<sup>266, 270</sup> comparing TCZ with other bDMARDs. The first one<sup>266</sup> included a non-randomised study (cohort follow-up)<sup>271</sup> that analysed the safety of TNF inhibitors compared to TCZ for the treatment of RA, assessing the risk of MACE, MI and stroke, with more than 40,000 person-years of follow-up. This SR also included one RCT (the ENTRACTE study) that

assessed the rate of MACE associated with TCZ compared to ETN. The second SR<sup>270</sup> included two non-randomised studies<sup>272, 273</sup> that compared TCZ with TNF inhibitors in relation to the development of MACE.

The quality of the evidence was rated as moderate (e.g., for the ENTRACTE study, an RCT whose primary objective was to assess safety) and very low for the non-randomised studies. All the studies were at risk of bias due to imprecision associated with wide 95% CIs and small event numbers.

Weighing the expected desirable and undesirable effects, the evidence indicates that TCZ is at least as safe as TNF inhibitors in relation to the risk of cardiovascular/thromboembolic events.

Other considerations: Similar conclusions were drawn in a study analysing data from the Swedish Rheumatology Quality Register, which did not show a higher risk of thromboembolic events in patients receiving IL-6R inhibitors (TCZ or SAR) than those receiving other bDMARDs<sup>274</sup>.

Based on the evidence available and the group's experience, the GDG considers that there is a negligible difference in the risk of developing cardiovascular and thromboembolic adverse events in patients with RA receiving TCZ compared to that in those receiving other bDMARDs.

### Rituximab

#### *Rituximab vs tocilizumab*

One of the aforementioned SRs<sup>266</sup> assessed the safety of RTX compared to TCZ based on two non-randomised studies. One of these studies assessed the risk of MACE, MI and stroke in patients receiving RTX or TCZ, with a follow-up of more than 14,000 person-years<sup>271</sup>. A smaller study (n=1,207) reported the hazard ratio for MACE, MI, stroke, and heart failure after a 2-year follow-up<sup>275</sup>. In this case, patients included had previously been treated with a TNF inhibitor.

These studies did not find significant differences regarding the development of cardiovascular or thromboembolic events.

The quality of the evidence was rated as low or very low, given that the body of evidence comes from non-randomised studies and imprecision associated with wide 95% CIs. Further, it should be noted that some patients had been exposed to TNF inhibitors previously, and hence, the effects observed might have been influenced by these earlier treatments.

Weighing the expected desirable and undesirable effects, the evidence indicates that the risk of cardiovascular/thromboembolic events in patients receiving RTX does not differ significantly from that in those receiving TCZ. Therefore, based on the evidence reviewed and the group's experience, the GDG considers that patients with RA given RTX are not at a higher risk of cardiovascular or thromboembolic events than those given TCZ.

### Abatacept

#### *Abatacept vs. TNF inhibitors*

Two of the aforementioned SRs<sup>264, 270</sup> also assessed the risk of MACE associated with ABA compared to TNF inhibitors. The second review<sup>270</sup> included two non-randomised studies<sup>276, 277</sup>, and the first review three studies published more recently<sup>278-280</sup>.

Another of the aforementioned SRs<sup>266</sup> assessed the safety of ABA compared to TCZ based on one of the studies included<sup>271</sup>, finding no differences in the risk of cardiovascular events (MACE, MI or stroke). Lastly, this same SR<sup>266</sup> assessed the safety of RTX compared to ABA, based on one of the studies, considering MACE, MI, stroke, congestive heart failure and cardiovascular mortality<sup>275</sup>.

The comparisons made in these studies did not reveal higher cardiovascular risk in patients treated with ABA than that observed when other drugs were used.

The quality of the evidence was rated as very low, given the non-randomised nature of the research, the heterogeneity of the studies, and bias due to imprecision associated with wide 95% CIs, even in the case of research including a large number of patients (comparisons of ABA with TNF inhibitors or TCZ).

Weighing the expected desirable and undesirable effects, the evidence did not show that patients treated with ABA were at higher risk than those treated with TNF inhibitors, TCZ or RTX.

Based on the evidence and the group's experience, the GDG considers that the effect of ABA on the risk of cardiovascular and thromboembolic events is negligible compared to that of other bDMARDs.

## JAK inhibitors

### *tsDMARDs vs TNF inhibitors*

The review identified one SR<sup>281</sup> that carried out a network meta-analysis of 40 studies (RCTs and cohort studies) assessing cardiovascular risk in patients with immune-mediated inflammatory disease. For this comparison, four RCTs were included<sup>142, 282-284</sup>. These trials compared the risk of MACE in patients receiving tsDMARDs to that in those receiving TNF inhibitors, and no between-group differences were observed in rates of cardiovascular or thromboembolic events.

One aforementioned SR<sup>266</sup>, which included one RCT<sup>142</sup> and three non-randomised studies, evaluated the safety of TOF compared to bDMARDs in relation to the following outcomes: MACE, MI, stroke, congestive heart failure, revascularisation and venous thromboembolism<sup>268, 285, 286</sup>.

The review also identified one meta-analysis of data on patients from 14 databases (registries) using propensity score matching to evaluate the safety of BAR compared to TNF inhibitors for treating patients with RA<sup>287</sup>.

The quality of the evidence was rated as low, due to imprecision associated with wide 95% CIs and because the occurrence of cardiovascular events was not the primary endpoint of many of these RCTs.

Weighing the expected desirable and undesirable effects, the available evidence shows that the risk of developing pulmonary embolism was higher in patients treated with TOF than those treated with TNF inhibitors (ADA and ETN), when using TOF at a dose of 10 mg twice daily<sup>142</sup>.

Other studies have attempted to replicate the conditions of the ORAL Surveillance study and have not found similar results. In a subsequent sub-analysis of the Ytterberg study, it has been shown that although this increased risk may be associated with TOF, the presence of other factors such as age >65 years, smoking, a history of CV events, and/or disease activity may amplify the risk<sup>267, 271, 287-292</sup>.

Other considerations: Along similar lines, evaluations of populations from various national registries have yielded mixed results. Data from the Swedish and German registries have not shown a higher cardiovascular or thromboembolic risk in patients with RA treated with tsDMARDs than in those treated with TNF inhibitors, whereas data from the French registry

indicated a numerically –though not significantly– higher risk in patients treated with JAK inhibitors<sup>267, 291, 293</sup>.

Based on clinical trials and observational studies and the group's experience, the GDG considers that although the effect size is small, there may be a higher risk in patients with a history of cardioembolic events.

### **Equity, acceptability and feasibility of the implementation**

In the opinion of the members of the GDG, in our setting, there are no inequities in access to bDMARDs and tsDMARDs as a function of geographical location, economic status, race or ethnic origin. It also considers that, given the good efficacy of all the drugs, the experience accumulated over the years in the use of bDMARDs and tsDMARDs in patients with RA, and the good risk/benefit balance observed, their use in clinical practice following EMA and AEMPS recommendations is likely to be accepted by all the parties involved (healthcare authorities, specialists and patients).

Moreover, targeted treatments, including bDMARD and tsDMARD therapy, are commonly used in our healthcare setting. The experience accumulated over the years by rheumatologists facilitates the introduction and use of the new therapeutic targets.

### **Outcome assessment by patients**

Based on the members' own judgement, the GDG considers it unlikely that there is variability in how patients rate the main outcomes.

### **Resource use**

No search has been conducted specifically for data on drug costs, as this topic is usually deemed to be beyond the scope of CPGs. Therefore, the GDG considers the available information insufficient to make any recommendations regarding resource use.

### **Monitoring and evaluation**

Monitoring and clinical follow-up required for these therapies are similar to those in routine clinical practice: a first clinical assessment and blood test at 6 to 8 weeks after starting

treatment, followed by check-ups every 3 to 6 months, depending on disease activity. All these treatments generally have a rapid effect, their efficacy being assessable between 12 and 24 weeks after initiation.

## 9.5. Serious infections

### **Clinical question 15** (valid)

In patients with RA treated with bDMARDs who have had a serious infection, is it safe to restart the biological therapy?

Regarding the safety of starting biological therapy in patients who have experienced a serious infection, the GDG considers that no significant changes are needed to the corresponding section in GUIPCAR d2019<sup>7</sup>. Nonetheless, it is acknowledged that this question should be prioritised in the next review of the guideline, given that there are already new interventions on which studies are ongoing, and further evidence that emerges about these interventions may influence the recommendations. Additionally, it should be underlined that the current general recommendations on safety are considered to be still valid, and when assessing which factors to consider concerning the risk of serious infection in patients with RA associated with bDMARD or tsDMARD therapy, the GDG points out that the SER Research Unit has recently formulated recommendations on treatment-related risk management in patients with RA<sup>294</sup>.

The corresponding recommendations in the aforementioned publication are as follows:

**Recommendation 20:** Before initiating bDMARD or tsDMARD therapy in patients with RA, a comprehensive assessment of the risk of infection should be performed, considering factors such as age, concomitant treatments, comorbidities and vaccination status, to accurately identify potential risk factors for serious infection ([Good clinical practice](#))<sup>v</sup>.

**Recommendation 21:** In patients with RA and no risk factors for infection, consider using bDMARDs or tsDMARDs as safe options ([Weak recommendation, in favour](#))<sup>v</sup>.

**Recommendation 22:** In patients with RA aged  $\geq 65$  years with concomitant lung disease or a history of smoking, JAK inhibitors should only be used if no suitable alternative treatments are available\* (Good clinical practice)<sup>v</sup>.

<sup>v</sup> Recommendation related to a question in the previous GUIPCAR guideline considered still valid.

#### Important clinical considerations

- Implementation-related factors

Based on the results of the ORAL Surveillance study on TOF<sup>142</sup> and data on the other three JAK inhibitors available in the EU, the EMA<sup>143</sup> and AEMPS<sup>144</sup> have issued recommendations to minimise the risk of major adverse events associated with this class of drugs in the treatment of various chronic diseases. These adverse effects include cardiovascular events, thrombosis, malignancies, and infections.

For more information, please consult the corresponding document on the SER website<sup>295</sup>.

## 9.6. Cancer

### **Clinical question 16** (new)

In patients with RA, what is the risk of new or recurrent cancer (melanoma or nonmelanoma skin cancer, solid tumours or haematological cancer) associated with bDMARD or tsDMARD therapy?

### **Context/Background**

Characterised by joint pain, swelling, and stiffness, RA is an autoimmune inflammatory disease that affects approximately 0.82% of the adult population in Spain<sup>296</sup>. If left untreated, it may lead to substantial disability and increased morbidity and mortality due to its association with an elevated risk of certain types of cancer, among other factors.

In recent years, the therapeutic approach to RA has evolved considerably, incorporating a more intensive treat-to-target strategy from the outset, as well as targeted biological and synthetic therapies. Although RA is still incurable, good control can delay disease progression, prevent structural damage to bone and cartilage, and reduce mortality<sup>297</sup>.

Nonetheless, there are still questions concerning the impact of these new therapies on the development of comorbidities, particularly cancer. It is essential to assess the risk of cancer

associated with each therapy to be able to provide tailored treatments for patients with an elevated baseline risk of developing cancer.

Furthermore, some patients with RA have a history of cancer, which poses additional challenges when selecting the most appropriate treatment if advanced therapies are required. In such cases, treatment must be chosen with caution, taking into account not only RA activity but also the risk of cancer recurrence. In relation to this, recent EULAR recommendations provide guidance on the management of patients with a history of cancer<sup>298</sup>. Nonetheless, the lack of robust evidence leaves many questions unanswered.

It is essential to continue investigating the relationship between RA therapies and the risk of cancer to provide patients with treatments that are the most effective and safest based on each patient's risk profile.

### Recommendations

**Recommendation 23:** In patients with RA, the drugs with the best safety profiles in relation to cancer risk are TNF inhibitors, IL-6R inhibitors and RTX. Do not use tsDMARDs unless no alternative treatments are available ([Strong recommendation, against](#))<sup>U</sup>.

**Recommendation 24:** In patients with RA and a history of solid tumours who require bDMARD or tsDMARD therapy, TNF inhibitors, IL-6R inhibitors, or RTX should be preferred ([Good clinical practice](#))<sup>U</sup>.

**Recommendation 25:** In patients with RA and a history of haematological cancer or lymphoma who require bDMARD or tsDMARD therapy, RTX should be preferred ([Good clinical practice](#))<sup>U</sup>.

<sup>U</sup> Recommendation related to a question in the previous GUIPCAR guideline that has been updated.

### Important clinical considerations

- Subgroups to consider:
  - Give preference to options other than JAK inhibitors in ≥65-year-olds, current smokers (and former smokers who have a long history of smoking or have been heavy smokers), and individuals with an elevated risk of cancer or other risk factors for cardiovascular disease. If JAK inhibitors are required in such patients, use the lowest possible effective dose.
  - Drug class: Although there are some differences between the various TNF inhibitors and JAK inhibitors, the GDG has decided that recommendations should be made by drug class, as it is not currently possible to demonstrate that small differences in the mechanism of action between drugs in the same class lead to significant differences in safety profile. Nonetheless,

it should be recalled that TOF is the only drug for which an increased cancer risk has been demonstrated.

## Rationale

These recommendations are based on the results of observational studies (large registries) on various bDMARDs and tsDMARDs and one RCT comparing TOF with TNF inhibitors with cancer as a primary endpoint. Given that nearly all the studies were observational in design, the quality of the evidence for most of the comparisons was low or very low. The observed effects were negligible in most cases, the exceptions being an increased risk of nonmelanoma skin cancer (NMSC) and melanoma with ABA and NMSC and lung cancer with TOF.

## Detailed rationale

### **TNF inhibitors**

The review identified 19 observational studies<sup>299-314</sup>, corresponding to large cohort studies (mostly based on registries), assessing the risk of different types of cancer in patients with RA treated with TNF inhibitors compared to csDMARDs.

One of these studies was based on South Korea's Health Insurance Review and Assessment Service (HIRA) database<sup>302</sup>. All patients with RA treated with csDMARDs or TNF inhibitors between 2010 and 2014 were selected, and cancer incidence rates were calculated for each group. The study included 43,086 patients who received csDMARDs and 2,337 patients who received TNF inhibitors. In these groups, the mean ages were 57.7 and 53.6 years, 79.8% and 78.3% of patients were women, and 72.8% and 85.9% of patients were also taking MTX, respectively.

Another study assessed the risk of cancer in patients with RA treated with TNF inhibitors or other bDMARDs, compared to biologic-naïve patients and the general population<sup>306</sup>. It included 15,129 people receiving TNF inhibitors (10,782 as the first biologic), 6,358 receiving other bDMARDs, 46,610 receiving csDMARDs and 107,491 from the general population. The mean age of patients in the TNF inhibitor group was 58 years, compared to 64 and 59 years old in the csDMARD and general population groups, respectively, and 26%, 29% and 24% of participants were men, respectively.

A third study compared the rates of cancer associated with MTX, other csDMARD and bDMARD therapy<sup>304</sup>. It included 1,566 patients receiving MTX, 904 receiving other csDMARDs, 3,761

receiving TNF inhibitors, 167 receiving RTX and 408 receiving ABA. Across the groups, between 72% (MTX) and 84% (ABA) of patients were women. No significant between-group differences were observed in age distribution or percentage of smokers (around 20%).

A risk analysis of cases of serious infection and cancer was conducted based on patients with RA who received TNF inhibitors or RTX from the Finnish National Registry for Biologic Treatment<sup>299</sup>. It compared 3,094 patients treated with TNF inhibitors (438 patients receiving RTX and 1,400 receiving bDMARDs). The mean age was 54 years in the TNF inhibitor group, 59 years in the RTX group and 62 in the csDMARD group, and in these groups, 75%, 77% and 69% of patients were women, respectively.

A safety analysis of ETN based on data from the BSRBR<sup>303</sup> analysed the risk of cancer, serious infections, MACE and other serious adverse events. It included 3,529 patients treated with ETN and 2,864 patients treated with csDMARDs, with mean ages of 55 and 60 years, respectively, and 77% and 75% of patients were women.

The risk of cancer has also been assessed in patients with different rheumatic diseases exposed to TNF inhibitors<sup>301</sup>. The study included 2,531 patients with RA from the BIOBADASER registry treated with TNF inhibitors and 789 patients with RA from the EMECAR cohort treated with csDMARDs. The mean age was 58 years in the TNF inhibitor group and 61 years in the csDMARD group, while 80% and 72% of patients were women in these groups, respectively. Patients were also compared with the general population.

A study based on the German RABBIT registry for patients with RA exposed to biologics (TNF inhibitors and anakinra) assessed the incidence of new and recurrent cancer<sup>305</sup>. The cohort of patients with prior malignancy included 67 patients treated with bDMARDs and 55 controls treated with csDMARDs, while that of patients with no prior malignancy included 3,279 patients treated with bDMARDs and 1,719 treated with csDMARDs. In the prior malignancy group, patients with and without exposure to biologics had a mean age of 64 and 63 years, and 67% and 75% were women, respectively. In the no prior malignancy group, the mean age was 54 years among those who had received biologics and 56 years among those who had not, and women accounted for 78% of patients in both groups.

One study assessed the incidence of cancer in patients with RA from Swedish registries, comparing patients receiving TNF inhibitors with those receiving csDMARDs in general, and MTX in particular<sup>300</sup>. It included 6,604 patients treated with TNF inhibitors and 61,160 patients treated with csDMARDs (5,989 with MTX). Among those receiving TNF inhibitors, the mean age was 55 years, and 75% were women.

Another study on the risk of cancer in patients with different rheumatic diseases<sup>308</sup>, treated with TNF inhibitors compared to csDMARDs, reported the results separately for each disease. The sample included 29,555 patients with RA: 19,750 patients treated with TNF inhibitors and 9,805 with csDMARDs. In these groups, age and race distributions were similar, and 85% and 86% of patients were women, respectively.

Another study compared the risk of cancer between patients with RA starting their first biologic (n=19,869) and those continuing treatment with csDMARDs (n=63,837)<sup>314</sup>. It conducted a propensity score analysis with 19,727 patients in each group. The mean age was 52 years in the bDMARD group and 51 years in the csDMARD group. The percentage of women was 74% in both propensity score-matched groups.

Further, cancer risk was analysed in patients with RA receiving various bDMARDs or csDMARDs using data from the Swedish Rheumatology Quality Register, linking it with other registries such as that for cancer<sup>309</sup>. It included 69,308 patients: 21,365 patients treated with TNF inhibitors, 4,123 with RTX, 3,306 with ABA, 2,689 with TCZ, 1,289 with JAK inhibitors and 56,233 with csDMARDs. A cohort of 109,532 from the general population was used for comparison. Across the cohorts, the mean age ranged from 56 and 63 years, and between 19 and 30% of patients were men.

The review found two studies based on the BSRBR/BSRBR-RA. One compared cancer risk in patients with RA treated with TNF inhibitors to that in patients who continued on csDMARDs<sup>312</sup>. It included 11,767 patients who received TNF inhibitors and 3,249 patients who received csDMARDs. In these groups, respectively, the mean ages were 56 years and 60 years, while 76% and 73% of patients were women. The other study analysed the risk of NMSC<sup>311</sup> in 11,881 patients treated with TNF inhibitors and 3,629 patients treated with csDMARDs. In these groups, respectively, the mean ages were 56 and 60 years, while 76% and 72% of patients were women. Another study analysed the US Department of Veterans Affairs databases, comparing the risk of NMSC in patients with RA who received TNF inhibitors and those who received csDMARDs<sup>307</sup>. It included 4,088 patients treated with TNF inhibitors and 18,396 patients treated with csDMARDs, with a mean age of 60 and 63 years, respectively, and 90% of patients in both cohorts were men. Based on the Swedish registries, the risk of melanoma in patients with RA treated with TNF inhibitors or csDMARDs was compared with that in the general population<sup>313</sup>. The study included 10,878 patients treated with TNF inhibitors, 42,198 patients treated with csDMARDs and 162,743 individuals from the general population. The median age was 57 years in the TNF

inhibitor group and 62 years in the other two groups. In the TNF inhibitor, csDMARD and general population groups, respectively, 76%, 72% and 71% of participants were women.

Another study analysed the risk of melanoma using data from 11 European registries<sup>310</sup>. It compared the incidence of melanoma associated with various biological therapies and csDMARDs with that in the general population. It included 68,411 bDMARD-naïve patients, as well as 48,304 patients treated with TNF inhibitors, 9,431 with RTX, 2,606 with TCZ, and 1,563 with ABA. Across the cohorts, the mean age ranged from 55 to 61 years, and 72% to 79% of patients were women.

In addition, the risk of lymphoma was assessed in patients with RA treated with TNF inhibitors or csDMARDs using 2001 to 2013 data from the BSRBR-RA<sup>315</sup>. Researchers selected bDMARD-naïve patients receiving their first TNF inhibitor who had no history of lymphoproliferative or myeloproliferative syndrome and at least 6 months of follow-up. They included 11,931 patients treated with TNF inhibitors and 3,367 with csDMARDs. In the TNF inhibitor and csDMARD groups, respectively, the mean ages were 56 and 60 years, the mean disease durations were 11 and 6 years, and 76% and 74% of patients were women. In the TNF inhibitor group, 4,288 patients received ADA, 4,144 ETN, and 3,499 IFX.

Lastly, one study assessed the incidence of breast cancer in 9,629 patients with RA starting TNF inhibitors, compared to 34,984 biologic-naïve patients with RA and 3,003,331 women from the general population<sup>316</sup>. The mean ages were 56, 62 and 61 years in the biological therapy, biologic-naïve, and general population groups, respectively. The comorbidity profile was similar across the groups.

The quality of the evidence for this outcome was rated as low, given that it was all from observational studies (cohorts).

Amongst all the studies, only one<sup>304</sup> reported significant differences between treatment groups in favour of TNF inhibitors (a lower risk of cancer than with csDMARDs). No significant differences were observed in any of the other studies. Therefore, the GDG considers that these findings are not clinically relevant and concludes that TNF inhibitor and csDMARD therapies in RA are associated with a similar cancer risk.

Other considerations: The review also identified one SR<sup>317</sup> on the risk of NMSC in patients with RA who had received TNF inhibitors, based on 6 studies including 123,031 patients with RA. Of these, 5,090 patients developed NMSC (1,941 treated with TNF inhibitors). The RR was 1.28 (95%

CI: 1.19 to 1.38), leading to the conclusion that TNF inhibitor therapy in patients with RA does increase the risk of NMSC.

The quality of the evidence was rated as low, given that it was from non-randomised studies that have an inherently high risk of bias.

After weighing the benefits and risks, the evidence indicates that TNF inhibitors may increase the risk of NMSC compared to csDMARDs.

Based on the group's experience, the GDG considers that patients with an increased risk of NMSC treated with TNF inhibitors should receive particularly close dermatological follow-up.

### Abatacept

#### *Abatacept vs. bDMARDs/tsDMARDs*

The review identified seven studies<sup>306, 318-323</sup> comparing the incidence of cancer in patients with RA treated with ABA and those treated with other bDMARDs or tsDMARDs.

One study assessed cancer risk in patients with RA treated with ABA or other bDMARDs<sup>319</sup>. It included patients treated with bDMARDs for at least 6 months, 4,328 patients who had received ABA and 59,860 other biologics. In these groups, respectively, the mean ages were 56 and 52 years, and 84% and 77% of patients were women.

Another study analysed data from Vigibase, the WHO's global database of individual case safety reports, comparing cancer risk in patients treated with ABA and other bDMARDs<sup>318</sup>. It included 15,846 cases of patients treated with ABA and 290,568 treated with other bDMARDs. In these groups, respectively, the mean ages were 60 and 58 years, and 83% and 80% of cases were in women.

The risk of cancer and infections was also evaluated in patients with RA initiating ABA compared to other bDMARDs or TOF<sup>321</sup>. The study included 32,991 patients treated with ABA and 59,026 treated with other biologics who had no history of cancer documented in the previous 6 months. The patients' mean age was 54 years, and 82% of them were women.

In addition, data from the DANBIO registry from 2006 to 2020 were used to investigate the risk of cancer (excluding NMSC) in patients with RA initiating bDMARDs, compared to that in those receiving TNF inhibitors and bDMARD-naïve patients<sup>323</sup>. The bDMARD-naïve group also included patients initiating a second csDMARD. Overall, 21,982 treatment initiation episodes were

identified in 14,944 patients with RA. Specifically, there were 1,457 cases of patients initiating IL-6R inhibitors (TCZ or SAR), 1,016 initiating ABA, 690 initiating RTX, 7,458 initiating TNF inhibitors, and 11,361 initiating csDMARDs. Across the groups, the mean age ranged from 57 to 59 years, the mean disease duration ranged from 2 to 8 years, and 72 to 78% of cases were in women.

Another study analysed cancer risk in patients with RA treated with ABA compared to other bDMARDs based on data from the FORWARD registry<sup>320</sup>. It included 1,496 patients treated with ABA, 3,490 with other bDMARDs and 1,520 with csDMARDs. In these groups, respectively, the mean ages were 62, 61 and 63 years old, and 86%, 84% and 81% were women.

Another study assessed cancer risk in patients with RA treated with TNF inhibitors or other bDMARDs compared to that in biologic-naïve patients and the general population<sup>306</sup>. It included 15,129 patients treated with TNF inhibitors, 6,358 treated with other bDMARDs (2,021 with ABA), and 46,610 treated with csDMARDs, as well as 107,491 individuals from the general population. The mean age in the ABA group was 61 years compared to 64 and 59 years in the csDMARD group and the general population sample, respectively. Across these groups, respectively, 20%, 29% and 24% of patients were men.

Lastly, one study compared the risk of cancer in general, including breast cancer, lung cancer and lymphoma, between patients with RA who had received ABA, other bDMARDs and csDMARDs<sup>322</sup>. It analysed data from 5,182 patients treated with ABA from four registries: ARTIS (Sweden), RABBIT (German), FORWARD (USA) and BC (Canada). Across the registries, the mean age ranged from 58 to 62 years, and 76% to 85% of patients were women.

The quality of the evidence for this outcome was rated as low, given that it was all from observational studies.

#### *Abatacept vs. csDMARDs*

Seven of the aforementioned studies also assessed the incidence of cancer in patients with RA who received ABA compared to csDMARDs<sup>304, 306, 309, 310, 320, 322, 323</sup>.

The quality of the evidence was rated as low or very low, given that it was from uncontrolled observational studies.

After weighing the benefits and risks, the evidence indicates that treatment with ABA may increase the risk of NMSC compared to treatment with either other bDMARDs or other csDMARDs, and to a lesser extent, the risk of melanoma compared to that with other bDMARDs. Based on the evidence and the group's experience, the GDG considers that ABA may only be used in patients with an increased risk of skin cancer if no safer options are available.

### Tocilizumab

#### *Tocilizumab vs TNF inhibitors*

The review identified two studies<sup>306, 324</sup> assessing the development of cancer in patients with RA treated with TCZ compared to TNF inhibitors. One analysed the incidence of cancer –excluding NMSC– in patients with RA treated with TCZ compared to other bDMARDs (TNF inhibitors and ABA)<sup>325</sup>, based on 12,832 patients treated with TCZ and 26,727 patients treated with TNF inhibitors between 2010 and 2015. It excluded patients with a history of cancer and/or treatment with RTX. The other study was based on data from the Swedish ARTIS registry<sup>306</sup> on patients with RA treated with TNF inhibitors, other bDMARDs or csDMARDs between 2006 and 2015. It compared cancer risk in patients treated with bDMARDs to that in patients treated with csDMARDs and the general population. It included 18,187 patients who had received bDMARDs, broken down into 10,782 treated with TNF inhibitors, 3,586 with RTX, 1,798 with TCZ and 2,021 with ABA, as well as 46,610 patients treated with csDMARDs, and 107,491 individuals from the general population. In these groups, respectively, the mean ages were 58, 63, 59, 61, 64 and 49 years, and 74%, 76%, 78%, 80%, 71% and 76% of participants were women. In the first 4 groups of patients, RA duration was 6, 13, 12 and 11 years, respectively.

#### *Tocilizumab vs. csDMARDs*

Two of the aforementioned studies also assessed the development of cancer in patients with RA treated with TCZ compared to csDMARDs<sup>306, 309</sup>.

The quality of the evidence was rated as low or very low, given that it was from uncontrolled observational studies.

After weighing the benefits and risks, the evidence does not show that TCZ increases the risk of any type of cancer in patients with RA.

Based on the evidence and the group's experience, the GDG considers that TCZ may be used without restrictions in patients with RA.

### Rituximab

#### *Rituximab vs. TNF inhibitors*

Just one study, already cited above, was found assessing cancer risk in patients treated with RTX compared to TNF inhibitors<sup>323</sup>.

#### *Rituximab vs. csDMARDs*

Three of the aforementioned studies also assessed cancer risk in patients treated with RTX and csDMARDs<sup>299, 306, 323</sup>.

The quality of the evidence was rated as low, given that it was from uncontrolled observational studies.

After weighing the benefits and risks, the evidence does not show that RTX increases the risk of any type of cancer in patients with RA.

Based on the evidence and the group's experience, the GDG considers that RTX may be used without restrictions in patients with RA.

Other considerations: The review also identified three observational studies that assessed all bDMARDs as a single group, without differentiating between mechanisms of action, which means their results are of very little relevance to clinical practice. One study compared cancer risk in patients with RA who started their first biologic (n=19,869) with that in patients who stayed on csDMARDs (n=63,837)<sup>314</sup>. Another study<sup>324</sup> assessed whether the incidence of cervical cancer was higher in women with RA treated with bDMARDs than those treated with csDMARDs, based on data from 22,267 patients in each group retrieved from Medicaid and commercial databases. Lastly, a case-control study<sup>326</sup> that included 4,738 patients with RA explored the influence of bDMARDs on the development of cancer. None of these three studies found bDMARDs as a group to be associated with a higher risk of cancer than csDMARDs in patients with RA.

### **JAK inhibitors**

In November 2022, the AEMPS<sup>144</sup> issued an alert concerning the use of JAK inhibitors in patients with chronic inflammatory diseases, warning of a high risk of cancer, MACE, serious infections, venous thromboembolism and increased mortality. This conclusion was drawn from the final results of the ORAL Surveillance study<sup>142</sup> that compared TOF with TNF inhibitor therapy in over-50-year-olds with RA and at least one cardiovascular risk factor. Following this alert, the AEMPS made new recommendations regarding treatment with TOF and other JAK inhibitors for all their indications. In particular, it stated that in over-65-year-olds, current smokers and former smokers with a long history of smoking, and people with other cardiovascular/thromboembolic and cancer risk factors, JAK inhibitors should only be used when no suitable alternative treatments are available. In addition, if used in these patients, the therapy should be tapered. Further, all such patients should be closely monitored, and this monitoring should include regular dermatological examinations.

The ORAL Surveillance study, a non-inferiority RCT focusing on primary safety outcomes (cancer and MACE), compared TOF with TNF inhibitors in the treatment of patients with RA. Patients included were at least 50 years old, had at least one cardiovascular risk factor and had active RA despite treatment with MTX. The study included 1,455 patients who had received TOF 5 mg and 1,456 who had received TOF 10 mg (in both cases, twice daily), as well as 1,451 treated with TNF inhibitors (ADA or ETN). Across the groups, the mean age was 61 years, and in the three groups, respectively, 80%, 77% and 77% of the patients were women, and 50%, 48% and 47% were current or former smokers.

As well as ORAL Surveillance, the review identified six observational studies<sup>327-332</sup> that assessed the risk of cancer in patients with RA treated with a JAK inhibitor compared to TNF inhibitors. One compared cancer risk in patients with RA or psoriatic arthritis receiving JAK inhibitors to that in patients receiving bDMARDs (TNF or non-TNF inhibitors) and the general population<sup>327</sup>. The data for each disease were presented separately. The study included 2,143 patients treated with JAK inhibitors, 8,580 with TNF inhibitors and 4,128 with non-TNF-inhibitor bDMARDs, while the control cohort included 48,318 individuals from the general population. Across the cohorts, the mean age ranged from 56 to 60 years and the mean disease duration from 7 to 13 years, while 78 to 82% of participants were women. The rates of cancer were analysed for JAK inhibitors taken together and separately (TOF, BAR).

Another study compared the safety (in relation to cancer, infections, and MACE) of JAK and TNF inhibitors in patients from the Hong Kong Biologics Registry<sup>330</sup>. It included 551 patients treated with JAK inhibitors and 1,920 treated with TNF inhibitors. In these groups, respectively, the mean ages were 58 and 53 years, 82% and 84% of patients were women, and mean disease durations were 127 and 89 months.

Similarly, another study analysed the safety of JAK inhibitors (in relation to cancer, cardiovascular disease, thromboembolism and death) based on data from South Korea's National Health Insurance Service database<sup>329</sup>. It compared the safety of JAK inhibitors with that of TNF inhibitors, using two sets of data: one on patients initiating JAK or TNF inhibitors, and the other on all patients who had received JAK or TNF inhibitors. The first set comprised 645 patients receiving JAK inhibitors (76% women) and 951 receiving TNF inhibitors (72% women), with mean ages of 52 and 50, respectively; while the second set contained 2,498 patients receiving JAK inhibitors (83% women) and 9,267 receiving TNF inhibitors (82% women), with a mean age of 52 years in both groups.

Further, a retrospective study of 499 patients with RA treated with TOF (192), BAR (104) or a TNF inhibitor (203)<sup>332</sup> reported standardised incidence ratios for cancer. In the TOF, BAR and TNF inhibitor groups, respectively, the mean ages were 67, 68 and 51 years old, and disease durations were 11, 12 and 6 years.

Another study analysed cancer risk in patients with RA treated with TOF compared to TNF inhibitors, based on data from three US databases, Optum Clinformatics, IBM MarketScan and Medicare<sup>328</sup>. Searches of these databases yielded, respectively, 3,301, 4,499 and 2,689 patients treated with TOF and 21,934, 24,960 and 25,673 patients treated with TNF inhibitors. The mean ages were 54 and 56 years in the Optum and MarketScan databases, respectively, and somewhat higher, 71 years, in Medicare. Across the three databases, between 82% and 86% of patients were women.

Lastly, another study based on South Korea's National Health Insurance System database analysed cancer risk in patients with RA treated with JAK or TNF inhibitors<sup>331</sup>. It included 1,064 patients treated with JAK inhibitors and 3,865 with TNF inhibitors. In these groups, respectively, the mean ages were 56 and 54 years, and 83% and 79% of patients were women.

None of these six observational studies comparing JAK inhibitors (TOF, BAR and UPA) with TNF inhibitors in patients with RA observed increases in cancer overall, or in specific types, such as haematopoietic, breast or lung cancer. Of the four studies evaluating NMSC, only that of Huss et al. found a slight increase. These results contrast with those from the ORAL Surveillance study, which detected significant increases in NMSC and lung cancer.

The quality of the evidence was rated as high for the results of the RCT and low to very low for the observational studies.

After weighing the benefits and risks, the evidence indicates that TOF does increase the risk of NMSC in patients with RA, and when used at a dose of 10 mg twice daily, may increase the risk of lung cancer, compared to that with TNF inhibitors. It should be recalled that TNF inhibitors are themselves associated with a higher risk of NMSC than csDMARDs, and hence, the risk associated with TOF is considered moderate.

Based on the evidence and the group's experience, the GDG considers that older patients and those with an increased risk of cancer should not be treated with JAK inhibitors.

### **Patients with a history of cancer**

The review identified five studies<sup>305, 333-336</sup> evaluating the risk of cancer recurrence or new cancer in patients with RA and a history of cancer who had been treated with bDMARDs compared to those treated with csDMARDs.

One of these studies<sup>334</sup> analysed the risk of new or recurrent cancer in patients with RA and prior malignancy, based on the BSRBR-RA. It included 177 patients who initiated TNF inhibitors and 117 patients who stayed on csDMARDs. In these groups, respectively, the mean ages were 62 and 66 years, and 81% and 74% of patients were women.

Another study<sup>305</sup> assessed the risk of new or recurrent cancer in patients with RA and prior malignancy who had received treatment with bDMARDs (TNF inhibitors or anakinra) based on the German RABBIT registry. The prior malignancy cohort included 67 patients treated with bDMARDs and 55 control patients who had remained on csDMARDs, and the comparison cohort without prior malignancy included 3,279 patients treated with bDMARDs and 1,719 who had remained on csDMARDs. Among patients with prior malignancy who did and did not receive biologics, respectively, the mean ages were 64 and 63 years, and 67% and 75% were women, while among those with no prior malignancy who did and did not receive biologics, respectively, the mean ages were 54 and 56 years, and 78% of patients were women in both groups.

Another study<sup>333</sup> evaluated the incidence of cancer in patients from the BSRBR-RA. It compared patients with prior malignancy treated with TNF inhibitors or RTX. This study was an update of an earlier study based on the British register<sup>334</sup>. It included 243 patients treated with TNF

inhibitors, and 23 treated with RTX, as well as 159 control patients who had remained on csDMARDs. In these groups, respectively, the mean ages were 63, 67 and 66 years, and 82%, 65% and 74% of patients were women.

The risk of cancer recurrence and death in patients with RA treated with bDMARDs was also assessed based on data from the DANBIO registry<sup>335</sup>. Of the 15,286 patients recorded in the DANBIO registry, 1,678 had had cancer, and of these, 1,176 had never been treated with biologics, while the others had received bDMARDs either before, after, or both before and after their primary cancer diagnosis. The mean age of patients was 70 years, and 32% were men.

Lastly, another study assessed the risk of cancer recurrence in patients with RA and a history of cancer who had received TNF inhibitors and compared it with the risk in patients with the same cancer history but who had never received bDMARDs<sup>336</sup>. For this study, two samples were identified from Swedish registries. Sample A included all patients with RA and a history of cancer, 467 who had been treated with TNF inhibitors and 2,164 who were bDMARD naïve. In these groups, respectively, the mean ages were 67 and 69 years, and 79% and 80% of patients were women. Sample B only included patients diagnosed with cancer after 2001, 223 who were treated with TNF inhibitors and 1,070 who were bDMARD naïve. In these groups, respectively, the mean ages were 67 and 69 years, and 70% and 71% of patients were women.

The quality of the evidence was rated as low.

Weighing the benefits and risks, the evidence indicates that, in the way bDMARDs are currently used in patients with RA and a history of cancer, this treatment is not associated with an increased risk of recurrent or new cancer. Nonetheless, this information is based on observational studies with an inherent risk of confounding by indication.

Based on the evidence, the GDG considers that no specific bDMARD can be recommended for treating patients with RA and a history of cancer. Nonetheless, based on the group's experience and given the evidence from the treatment of lymphoma, it recommends using RTX as the treatment of choice in patients with RA and a history of lymphoma.

The SER Research Unit has recently formulated recommendations on treatment-related risk management in patients with RA treated with bDMARDs or tsDMARDs<sup>294</sup>.

The corresponding recommendations are as follows:

In patients with RA who are about to start treatment with bDMARDs or tsDMARDs, a history of cancer should be taken into account ([Good clinical practice](#)).

In patients with RA and a history of NMSC who need treatment with bDMARDs or tsDMARDs, regular dermatological follow-up is recommended to detect recurrences ([Good clinical practice](#)).

In patients with RA and advanced age, where it is considered necessary to initiate treatment with tsDMARDs, a regular medical check-up is recommended to rule out the development of NMSC\* ([Good clinical practice](#)).

\*This recommendation is based on the statement of the AEMPS issued after the recommendations of the European Pharmacovigilance Risk Assessment Committee. Although the statement expressly refers to dermatologists, the panel believed this was not operational as it would place an unmanageable burden on dermatology departments. Since this lesion is easily identifiable, it recommended that both primary care physicians and specialists refer all patients with lesions they consider suggestive of skin cancer to a dermatologist.

Current evidence is insufficient to recommend the use of TNF inhibitors or tsDMARDs in patients with a history of blood cancer ([Good clinical practice](#)).

For further information, please consult the published article<sup>294</sup> on the recommendations or corresponding document on the SER website (in Spanish)<sup>295</sup>.

### **Equity, acceptability and feasibility of the implementation**

Based on the members' own judgement, the GDG considers that, in our setting, there are no inequities in access to bDMARDs and tsDMARDs as a function of geographical location, economic status, race or ethnic origin.

It also considers that, given the good efficacy of all these drugs, the experience accumulated over the years, and the limited associated adverse effects, their use in clinical practice is likely to be accepted by all the parties involved (healthcare authorities, specialists and patients).

On the other hand, bDMARDs and tsDMARDs are commonly used in our healthcare setting.

The experience accumulated over the years by rheumatologists facilitates the introduction and use of the new therapeutic targets.

### **Outcome assessment by patients**

Based on the members' own judgement, the GDG considers it unlikely that there is variability in how patients rate cancer recurrence as an outcome.

### **Resource use**

No search has been conducted specifically for data on drug costs, as this topic is usually deemed to be beyond the scope of CPGs. Therefore, the GDG believes that it has insufficient information to make any recommendations regarding resource use.

### **Monitoring and evaluation**

Monitoring and clinical follow-up required for these therapies are similar to those in routine clinical practice: a first clinical assessment and blood test at 6 to 8 weeks after starting treatment, followed by check-ups every 3 to 6 months, depending on disease activity. Closer follow-up, including additional assessments such as dermatological examinations, may be appropriate in patients with an increased risk of cancer.

## 10. Management of risk in the treatment of RA

### 10.1. Screening

The treatment of RA has changed dramatically over the last 20 years. The availability of new biologics, used as monotherapy or in combination therapy, has allowed us to reduce the harmful effects 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<sup>337, 338</sup>. Furthermore, this risk is related to other coexisting factors such as comorbidities, steroid treatments, previous 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 csDMARDs as well as with bDMARDs or tsDMARDs, the following tests should be performed<sup>339</sup>:

- Blood tests including a complete blood count, assessment of kidney function, and measurements of transaminase, ESR and CRP levels. The results allow us to rule out active infections that would contraindicate treatment, cytopaenia that might restrict the use of combined therapies or certain drugs, and renal or hepatic 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, respectively). All patients with no known history of hepatitis must be screened for HBV core and surface antigens before starting treatment with prednisone doses above 20 mg/day, csDMARDs, bDMARDs, or tsDMARDs. 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 high-risk sexual behaviour 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 (for further information on this issue, please consult the recommendations developed by the SER research unit on the management of the risk of treatment with bDMARDs or tsDMARDs in patients with RA<sup>294</sup>). The presence of latent infection should be considered when selecting the drug, and among the options available, TNF inhibitors have been the most widely studied. In the case of chronic HBV infection, the results are contradictory, varying from reactivation of the virus, which may even be

associated with liver failure<sup>340</sup>, through unchanged liver function<sup>341, 342</sup>, to a reduction in viral load<sup>343</sup>. Regarding HCV infection, reported cases suggest that TNF inhibitors may be safe<sup>344, 345</sup>. 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 bDMARDs or JAK inhibitors. Proper screening before starting treatment has been associated with up to a 7-fold reduction in the risk<sup>346</sup> of reactivation of latent tuberculosis<sup>337, 347</sup>. 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 screen for lesions suggestive of 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, patients should be started on isoniazid (5 mg/kg/day up to a maximum of 300 mg/day) and prophylactic vitamin B6 for a period of 9 months<sup>348</sup>.
- 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<sup>349, 350</sup> in this population.

## 10.2. Treatment monitoring

According to experts, regular monitoring of patients treated with csDMARDs, bDMARDs or tsDMARDs allows assessment of treatment response and the development of potential adverse effects. The goal of current treatment strategies is to achieve clinical remission, or if not, the lowest possible level of disease activity. If the patient has moderate-to-severe disease activity, assessments should be regular (every 1 to 2 months), to consider potential changes in treatment that might improve control of the inflammation. On the other hand, they can be spaced out to every 3 to 6 months in patients in remission or with low disease activity<sup>44</sup>.

International consensus statements conclude that patient assessment should involve:

- *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, and splenomegaly) and drug-related adverse effects (e.g., drug-induced skin reactions, aphthous ulcers, or hepatomegaly)
- *Blood tests:* during routine assessments, request tests including:
  - a) Measurement of ESR and CRP levels, to allow us to assess inflammatory status and calculate composite indices
  - b) A complete blood count to rule out drug-related bone marrow toxicity or changes indicative of disease activity (anaemia) or secondary complications (neutropaenia, thrombocytopaenia)
  - c) Assessment of hepatic function, through transaminase levels, to rule out liver toxicity
  - d) Measurement of electrolyte and creatinine levels, to assess renal function
  - e) Measurement of the lipid profile, to assess cardiovascular risk and the potential effects of some biologics
- *Imaging tests:* in patients with early RA, obtain annual anteroposterior radiographs of the hands and feet for the first 3 years to monitor for progression. Radiological abnormalities are clearly associated with persistent inflammatory activity, especially early in the disease, and a moderate correlation with physical disability, which strengthens over time<sup>351, 352</sup>. As has been described, it is currently possible to detect radiological progression in patients with RA after intervals of as short as 6 months<sup>353</sup>.

### 10.3. Vaccinations

Infectious morbidity and mortality are higher in patients with RA than in the general population. Although there are numerous reasons, among the most important are the autoimmune nature of the disease itself, abnormal blood counts and the drugs administered. According to experts, preventive measures should be taken to avoid infections, and efforts should be made to achieve early diagnosis and treatment of any infections that do occur. In patients with RA, especially those treated with biologics, adequate vaccination may be extremely useful for preventing various infectious diseases<sup>354</sup>.

Experts agree that, as well as being aware of the range of vaccines available both for the general population and immunosuppressed patients, rheumatologists should implement the current recommendations concerning the vaccines most widely used in these patients, especially for influenza, pneumococcus and hepatitis B. In 2022, the ACR updated its recommendations on the use of vaccines in patients with rheumatic disease, taking into account the disease itself, the type of vaccine and the treatments received<sup>355</sup>. Table 9 summarises the vaccines currently used and their applicability in rheumatology following the recommendations of the ACR<sup>355</sup> and the SER consensus on risk management in the use of biological therapy in rheumatic patients<sup>348</sup>, especially the vaccines for pneumococcus, influenza, hepatitis B, human papilloma virus, herpes zoster and SARS-CoV-2. As can be seen from these tables, live-attenuated vaccines are contraindicated in patients on immunosuppressive drugs, given the risk of disease reactivation, and should be administered before starting bDMARDs or tsDMARDs, when possible. In general, the recombinant zoster vaccine is recommended for patients receiving JAK inhibitors, regardless of age, due to the higher rates of this viral infection associated with this type of therapy. In situations in which there are barriers to universal vaccination in these patients, give preference to those at the highest risk due to age, combination therapy with glucocorticoids, and other comorbidities and concomitant treatments, as well as a history of herpes zoster infection.

The efficacy of certain vaccines may decrease in patients on RTX or MTX<sup>356</sup>, and therefore, the vaccination programme should be started before prescribing these drugs. Table 9 summarises the main characteristics of the vaccines available in Spain<sup>348</sup>.

**Table 9. Vaccines available in Spain**<sup>348</sup>

Vaccine	Type of vaccine	Active ingredient	Recommendation
Chicken pox	Live-attenuated	Live-attenuated varicella virus, OKA strain	Contraindicated
Mumps, measles, rubella	Live-attenuated	Live-attenuated mumps virus, live-attenuated measles virus, live-attenuated rubella virus	Contraindicated
Yellow fever	Live-attenuated	Yellow fever virus, 17D-204 strain	Contraindicated
Typhoid fever	Live-attenuated	Live-attenuated <i>Salmonella typhi</i> , Ty21a strain	Contraindicated
	Simple polysaccharide	<i>Salmonella typhi</i> , PSC Vi	Allowed
Poliomyelitis	Inactivated	Inactivated poliovirus serotypes 1, 2, and 3	Allowed
Influenza	Fractional	Inactivated influenza virus (split virion)	Recommended
	Subunit	Influenza surface antigens H and N	
Influenza A (H1N1)	Subunit	Influenza surface antigens	Allowed
Haemophilus influenzae B	Conjugate	Polyribosylribitol phosphate-tetanus toxoid conjugate	Allowed
COVID-19 (SARS-CoV-2)	Adenovirus (AstraZeneca)	non-replicating recombinant adenoviral vector containing the S protein gene	Use of one of the available vaccines is recommended
	mRNA (Pfizer/BioNTech and Moderna)	S protein-encoding mRNA	Use of one of the available vaccines is recommended
	Recombinant	Purified S protein	Use of one of the available vaccines is recommended
Hepatitis A	Inactivated	Inactivated hepatitis A virus	Allowed
	Virosome-based	Inactivated hepatitis A virus	
Hepatitis B	Recombinant	Recombinant hepatitis B surface antigen	Recommended
Herpes zoster	Recombinant	Recombinant varicella zoster virus glycoprotein E	Recommended in patients classified as high risk, with advanced age and/or on tsDMARDs
	Live-attenuated	Live-attenuated virus herpes zoster	Not recommended

Human papillomavirus (HPV)	Recombinant	L1 proteins of the HPV	Allowed
Meningococcal serogroup C	Conjugate	De-O-acetylated meningococcal C polysaccharide-tetanus toxoid conjugate	Allowed
Pneumococcus	Simple polysaccharide	23-valent pneumococcal polysaccharide	Recommended
	Conjugate	Pneumococcal saccharide-CRM197 conjugate	
	Conjugate	Pneumococcal polysaccharide Protein D conjugate	
Diphtheria	Toxoid	Adult diphtheria toxoid	Allowed
Tetanus	Toxoid	Tetanus toxoid	Allowed
Pertussis (whooping cough)	Toxoid	Pertussis toxoid	Allowed

#### 10.4. Pregnancy and breastfeeding

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 period<sup>357-359</sup>. Disease activity at the start of pregnancy increases the likelihood that the disease remains active during the entire period and seems to increase the risk of flares during the puerperium<sup>360</sup>. Active RA is associated<sup>361</sup> with an increased risk of preeclampsia, caesarean section and low infant birth weight<sup>361-364</sup>; nonetheless, most pregnancies proceed without complications, and the rate of miscarriage does not seem to increase<sup>365</sup>. Regarding planning for pregnancy, experts agree that efforts should be made to achieve remission (or if not, the lowest possible disease activity) with non-teratogenic drugs, at least 6 to 12 months before conception, and women should be monitored in a multidisciplinary high-risk pregnancy clinic<sup>366, 367</sup>. In the case of mothers who are anti-Ro or anti-La positive, there is a greater risk of neonatal lupus<sup>368</sup>. EULAR has recently updated its recommendations on the use of antirheumatic drugs preconception, as well as during pregnancy and breastfeeding<sup>369</sup>, and the conclusions are summarised in Tables 11 to 13; for detailed information, please consult the original publication.

### Treatment for women 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 early weeks or last trimester of pregnancy, and as these drugs are associated with premature closure of the ductus arteriosus, those with short half-lives (such as ibuprofen or ketoprofen) are preferred. Data on COX-2 inhibitors are more limited; therefore, they are not recommended. Regarding glucocorticoids, it is possible to use non-fluorinated glucocorticoids such as prednisone and prednisolone at low or moderate doses<sup>370</sup>.
- csDMARDs such as MTX, LEF, and MMF, and JAK inhibitors are contraindicated during pregnancy, given known potential teratogenic effects or a lack of reliable data supporting their use; however, it is safe to use SSZ or HCQ<sup>367, 370</sup>.

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 is expressed from the end of the second trimester, this increasing through the third trimester. CZP is a pegylated TNF inhibitor, which differs from other TNF inhibitors in that it lacks an Fc region. This region plays a key role in placental transfer by binding to neonatal Fc receptor, and since CZP does not have this region, it does not cross the placenta<sup>371</sup>.

It has also been suggested that the lack of the Fc region hinders binding with RF, and hence, the formation of large immune complexes in patients with high titres, something which may occur when full therapeutic antibodies are used in these patients. Such immune complexes would have the effect of decreasing drug concentrations, impairing clinical efficacy and drug survival, although these findings need to be confirmed in clinical trials<sup>372</sup>.

No TNF inhibitors have been shown to lead to obstetric complications or teratogenicity in animal models using doses hundreds of times higher than those recommended in humans; however, no controlled human studies have been conducted, and therefore, these drugs are in US FDA Pregnancy Category B. Several studies in patients with inflammatory bowel disease treated with TNF inhibitors 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)<sup>373, 374</sup>. Hence, TNF inhibitors can be considered safe during pregnancy,

but there is a lack of data regarding 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<sup>36</sup>.

The EMA's Committee for Medicinal Products for Human Use has approved the use of ADA under these circumstances; however, given uncertainty about the safety of placental transfer of TNF inhibitors for the foetus, in terms of infections or vaccine response, the panel recommends using CZP instead (see Table 11 in Appendix 6).

RTX is able to cross the placental barrier in the second and third trimesters and produce a transient decrease in B lymphocytes in newborns, increasing the risk of infection.

There are insufficient data on ANA, ABA and TCZ<sup>375</sup>. For this reason, experts suggest these drugs be discontinued as soon as pregnancy is confirmed, if not withdrawn beforehand<sup>367</sup>. JAK inhibitors are contraindicated during pregnancy.

#### **Treatment for men seeking fatherhood**

Active disease may alter fertility in men as well as in women, and hence, control of disease activity is a key factor in achieving safe conception<sup>376</sup>. SSZ may cause a reversible decrease in sperm count, and hence, this effect should be borne in mind in men receiving this drug. On the other hand, it is considered safe during pregnancy and breastfeeding, and therefore, can be continued in men seeking fatherhood, but if there are difficulties achieving conception, sperm quality should be tested<sup>377</sup>.

#### **Treatment for women during breastfeeding**

Experts conclude that breastfeeding is not contraindicated in patients with RA, and that, if treatment is required during this period (which is not unusual as patients often relapse during the puerperium), only drugs compatible with breastfeeding should be used. Evidence on pharmacological safety during breastfeeding is scarce. Based on expert opinion, the drugs that are incompatible with breastfeeding include: JAK inhibitors, cyclophosphamide, LEF, and MMF. On the other hand, NSAIDs (particularly ibuprofen), glucocorticoids, AZA, SSZ and antimalarial drugs may be administered in this period. In the case of glucocorticoids, if the dose is above 40 mg/day, mothers should try to wait at least 4 hours after taking the drug before breastfeeding. In the case of TNF inhibitors, it is concluded that they are 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 µg/mL (<1% of the expected plasma concentration for a therapeutic dose)<sup>378</sup>. JAK

inhibitors are contraindicated during breastfeeding as there are no data demonstrating that they are safe.

The tables in Appendix 6 summarise the EULAR recommendations on the use of antirheumatic drugs in men seeking fatherhood, as well as in women during pregnancy and breastfeeding.

## 11. Treatment adherence

**Clinical question 17** (valid)

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

**Clinical question 18** (valid)

In patients with RA, what is the efficacy of nurse-led educational intervention programmes?

### Recommendations

**Recommendation 26:** In patients with RA, treatment adherence should be monitored, especially in women, as well as individuals with advanced age or multimorbidity (Good clinical practice)<sup>v</sup>.

**Recommendation 27:** To improve treatment adherence, patient education programmes should be run and relationships of trust fostered between patients and doctors (Good clinical practice)<sup>v</sup>.

<sup>v</sup> Recommendation related to a question in the previous GUIPCAR guideline considered still valid.

The GDG considers that numerous highly complex factors influence treatment adherence but that the GUIPCAR 2019 recommendations remain fully valid. In relation to this, results from the ADHIERA study instigated by SER were published in 2022. The study explored adherence-related factors in Spain, and found that the provision of information and shared decision-making concerning treatment are the most important factors<sup>379</sup>.

## 12. The role of nursing

### Recommendations

**Recommendation 28:** Specific individual or group-based educational programmes delivered by nursing staff should be part of the routine follow-up for patients with RA (Good clinical practice)<sup>v</sup>.

**Recommendation 29:** Continuity should be ensured in the delivery of specific nurse-led education programmes (Good clinical practice)<sup>v</sup>.

<sup>v</sup>Recommendation related to a question in the previous GUIPCAR guideline considered still valid.

The GDG considers that the role of rheumatology nurse specialists and nurse-led clinics is becoming increasingly important. These recommendations have not been modified because nurses are involved in ever more aspects of the care of patients with rheumatic disease.

### 13. General advice on patient management

The management of RA should take into account individual patient characteristics (Good clinical practice).

Treatment should be started as early as possible; hence, prompt diagnosis is essential. It is also crucial to avoid delays in changing treatment when a patient does not respond well to a given therapy or experiences a flare-up (Good clinical practice).

Before starting a treatment, patients should be adequately informed about the pharmacological properties of the medication, treatment duration, and expected benefits, as well as potential adverse effects, taking their preferences into account (Good clinical practice).

Before prescribing bDMARDs or tsDMARDs, the following should be considered: age, previous treatment, patient preferences, tolerance, the risk of adverse events, the possibility of pregnancy, and the cost-effectiveness ratio (Good clinical practice).

In the treatment of RA, it is essential to take into account the assessment and treatment of related comorbidities (Good clinical practice).

Patients and/or their families should be instructed in joint self-care and in self-management of bDMARD and tsDMARD therapy (Good clinical practice).

## 14. Review of other chapters in GUIPCAR 2019

### Disease burden of RA in Spain

The working group considers that the content of the “Disease burden of RA in Spain” chapter in GUIPCAR 2019 remains valid<sup>7</sup>.

### Other treatments

The working group considers that the content of the “Other treatments” section in GUIPCAR 2019 remains valid<sup>7</sup>.

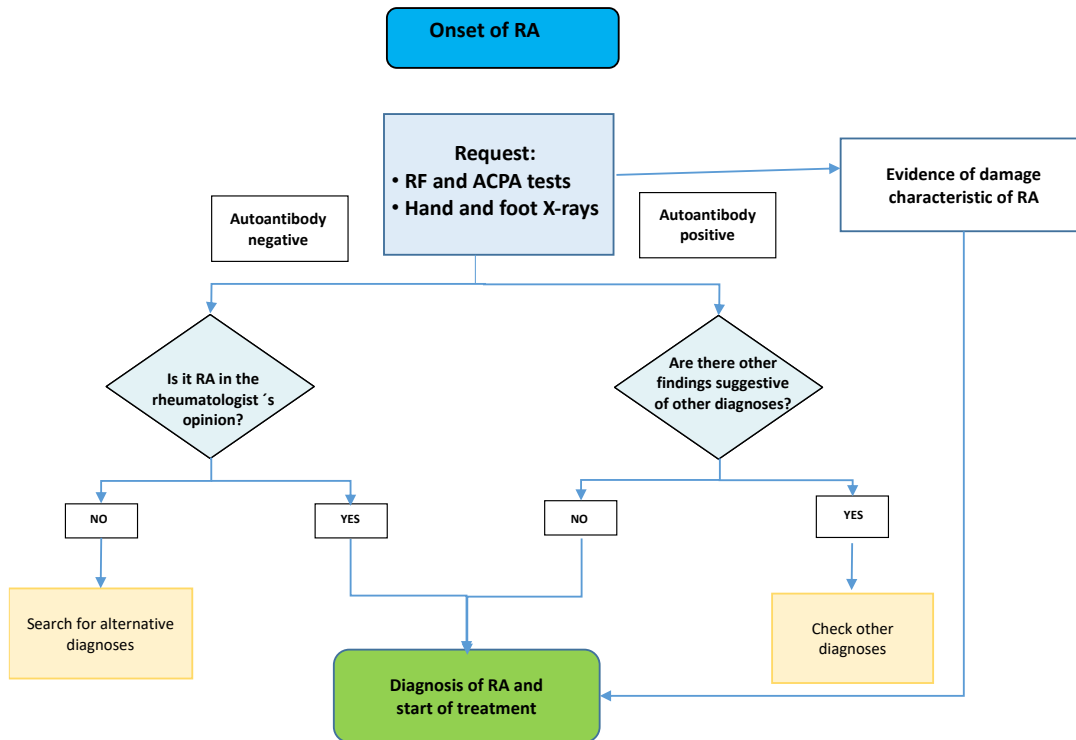
### The patient perspective

The working group considers that the content of “The patient perspective” chapter in GUIPCAR 2019 remains valid<sup>7</sup>.

## 15. Diagnostic and therapeutic strategies

### Algorithm 1

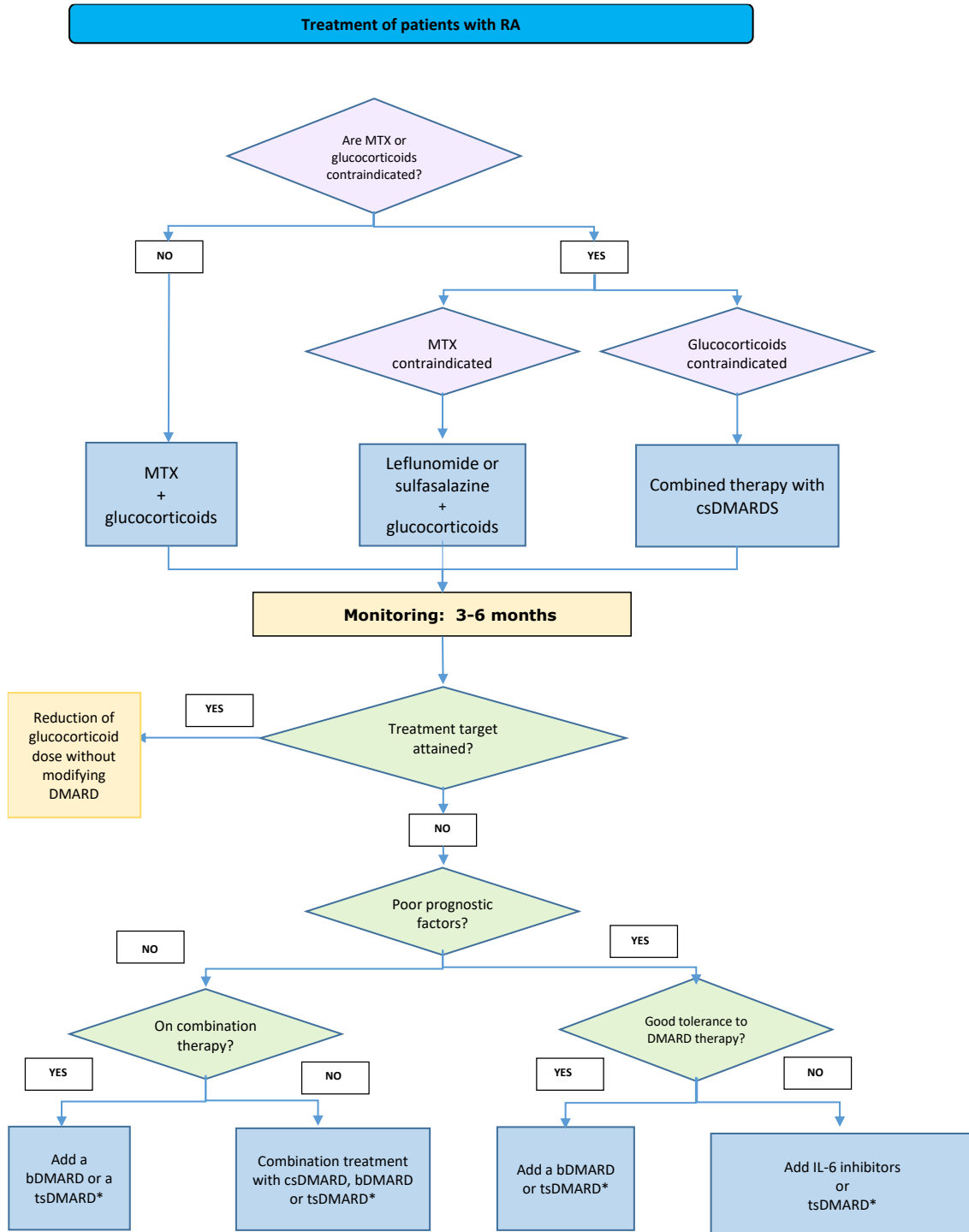
#### Algorithm for diagnosing RA



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

Algorithm 2

Algorithm for treating RA



bDMARD: biological disease-modifying anti-rheumatic drug; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; DMARD: disease-modifying anti-rheumatic drug; MTX: methotrexate; RA: rheumatoid arthritis; tsDMARD: targeted synthetic disease-modifying anti-rheumatic drug.

Regarding the use of tsDMARDs, take into account the AEMP recommendations for managing the associated risk, as outlined in this guideline.

## 16. Dissemination and implementation

### **Dissemination strategy**

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

- Announcement of the completion and availability of the guideline through the members' newsletter on the SER website
- Publication of the guideline in electronic format on this website
- Dissemination of the guideline to health professionals through social media: Twitter, LinkedIn and Facebook
- Presentation of the guideline to the various scientific societies involved
- Promotion of the informational material developed for patients at all presentations of the guideline, to encourage its distribution to all clinicians and, in turn, to patients with this health problem
- Publication of the guideline in scientific journals
- Targeted and effective distribution of the guideline to all groups of health professionals involved (rheumatologists, cardiologists, pulmonologists, general practitioners, and rheumatology nurse specialists) to facilitate dissemination
- Evaluation of the effectiveness of the guideline implementation, with the establishment of decision support systems, and integration of the recommendations and selected indicators into primary care computer systems
- Presentation of the guideline at scientific events (conferences, seminars and meetings).

### **Proposal of indicators**

The AGREE II manual highlights the importance of developing 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 regularly, allow the monitoring of disease progression. The team responsible for assessing the impact of the CPG and the care provided to patients should select an appropriate source of data and time frame for each indicator (Table 10).

**Table 10. Proposed indicators**

Area	Type of indicator	Name of the indicator	Threshold 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 RA referred from primary care within the first 3 months after the onset of symptoms	50%	1
Treatment	Process	Percentage of patients who initiate background MTX in combination with glucocorticoids	90%	2
Treatment	Process	Percentage of patients treated using a T2T strategy	70%	2
Treatment	Process	Percentage of patients who receive appropriate risk management before starting bDMARDs or tsDMARDs	100%	1,2
Treatment	Process	Percentage of patients who start bDMARDs or tsDMARDs after optimisation of MTX or other csDMARDs	90%	2
Treatment	Process	Percentage of patients who start biological therapy with TNF inhibitors in combination with a csDMARD	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
Treatment	Process	Percentage of patients who undergo risk assessment before starting tsDMARD therapy	100%	2
Treatment	Process	Percentage of patients on long-term glucocorticoid therapy who undergo osteoporosis risk assessment	100%	2

Treatment	Process	Percentage of patients who have their bDMARD or tsDMARD therapy adjusted after sustained attainment of the treatment target	90%	2
Treatment	Process	Percentage of patients who receive nurse-led training on the disease, recommendations, self-care and treatment adherence	100%	2

## 17. 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 according to patients' specific disease characteristics
- 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, and especially prognosis, to be able to provide the most appropriate treatment based on disease characteristics and potential severity
- High-quality studies that demonstrate the efficacy and cost-effectiveness of initiating bDMARDs or tsDMARDs with the goal of providing intensive therapy and then being able to discontinue it for long periods of time
- Further research to identify measures for assessing the disease that effectively combine key outcomes for patients and doctors and are more accurate than current tools, reflecting the reality of the disease and less influenced by confounders such as subjective states or comorbidities
- More high-quality RCTs comparing bDMARDs with tsDMARDs in different clinical scenarios, such as patients with early RA, those who have an inadequate response to csDMARD therapy or those who are resistant to bDMARDs or tsDMARDs
- Studies to assess the efficacy of bDMARD or tsDMARD monotherapy in all clinical scenarios
- Further research to identify the indications and protocols for treatment tapering (dose reduction or spacing) once patients have achieved the therapeutic target
- Well-designed long-term studies on the indication and treatment of choice for certain comorbidities associated with RA, such as depression, cardiovascular disease and lung disease
- RCTs dedicated to assessing the efficacy of csDMARDs (MTX and LEF), immunosuppressants (MMF, AZA and CP) and bDMARDs in the treatment of RA-associated ILD, given the low quality of the evidence available addressing this question and the need for data on which to base more robust evidence-based recommendations
- Head-to-head studies of approved treatments to establish whether certain types of patients are at higher risk of cardiovascular and thromboembolic events associated with the drugs used

- RCTs that assess the development of cancer, ideally as the primary outcome, to be able to establish the risk of cancer associated with the use of bDMARDs and tsDMARDs in RA. As an RCT of this design has already been undertaken for TOF (namely, ORAL Surveillance), similar studies will likely be conducted for other JAK inhibitors. Regarding bDMARDs, as no specific alert has emerged concerning the development of cancer during the 25 years of experience in the use of TNF inhibitors, it is unlikely that new RCTs will be conducted on this type of DMARD with cancer as the primary outcome. Nonetheless, more observational studies are needed with non-TNF-inhibitor biologics for which there are currently insufficient data to evaluate the risk of cancer.
- Studies including samples of the general population with similar comorbidities to those commonly seen in patients attending rheumatology clinics for comparison.
- High-quality studies to identify nurse-led health education programmes that are applicable in our setting and may help to achieve good outcomes in patients with RA.

## APPENDICES

### Appendix 1. Quality of evidence and strength of recommendation

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system

#### GRADE approach to rating the quality of evidence

Quality	Study design	Factors that can reduce the quality of the evidence*	Factors that can increase the quality of the evidence**
High ⊕⊕⊕⊕	RCT	<ul style="list-style-type: none"> <li>• <b>Limitations in study quality (design):</b> Serious (-1) Very large (-2)</li> <li>• <b>Inconsistency:</b> Serious (-1) Very large (-2)</li> <li>• <b>Indirectness of evidence:</b> Serious (-1) Very large (-2)</li> <li>• <b>Imprecision:</b> Serious (-1) Very large (-2)</li> <li>• <b>High likelihood of publication bias:</b> (-1)</li> </ul>	<p><b>Association:</b></p> <ul style="list-style-type: none"> <li>• Scientific evidence of a strong association (RR&gt;2 or &lt;0.5 based on observational studies with no plausible confounders) (+1)</li> <li>• Scientific evidence of a very strong association (RR&gt;5 or &lt;0.2 based on studies with a low risk of bias) (+2)</li> </ul> <p><b>Dose-response gradient</b> (+1)</p> <p><b>Possible confounders:</b> All plausible confounding would reduce the demonstrated effect (+1)</p>
Moderate ⊕⊕⊕⊖	--		
Low ⊕⊕⊖⊖	Observational studies		
Very low ⊕⊖⊖⊖	Studies with other designs		
<p>* In the case of RCTs, the rating of the quality of the scientific evidence may decrease</p> <p>** In the case of observational studies, the rating of the quality of the evidence may increase</p>			

#### Implications of the strength of recommendations in the GRADE system

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

		that you (the doctor) must help each patient make the decision that is most consistent with their values and preferences.	
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**Recommendations for good clinical practice\***

Good clinical practice	Practice recommended based on the group's clinical experience and by consensus among members
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\*On some occasions, the GDG identified important practical issues it wanted to highlight but related to which there was unlikely to be any supporting evidence. In general, these issues concern aspects of treatment considered good clinical practice and which are not commonly questioned. Such issues have been evaluated as matters of good clinical practice.

Appendix 2. Extract of the SER-SEPAR recommendations for the management of rheumatoid arthritis-related interstitial lung disease

**Incidence and prevalence of diffuse interstitial lung disease (ILD) in rheumatoid arthritis (RA)**

<b>Clinical question:</b> What is the incidence and prevalence of rheumatoid arthritis-related interstitial lung disease (RA-ILD) in patients with RA?	<b>Strength of the recommendation<sup>1</sup></b>
<b>Recommendation 1:</b> Based on its incidence and prevalence, it is recommended that the possibility of interstitial lung disease should always be considered in the initial assessment and follow-up of patients with RA.	<i>Good clinical practice</i>

**Important risk factors for the onset and progression of diffuse ILD**

<b>Clinical question: 2.</b> In patients with RA, what are the risk factors for the onset of ILD?	<b>Strength of the recommendation<sup>1</sup></b>
<b>Recommendation 2:</b> Patients with RA should be systematically screened for interstitial lung disease in cases with respiratory symptoms or if “Velcro-like” crackles are heard.	<i>Good clinical practice</i>
<b>Recommendation 3:</b> In cases without respiratory symptoms and with normal auscultation, the need for screening should be assessed individually according to the number of risk factors* for onset of this complication, regardless of the time since onset of RA.  <i>* The main risk factors for the development of interstitial lung disease, easily identifiable in the clinic, are male sex, advanced age, late disease onset, duration of RA, history of smoking, sustained moderate, or high disease activity, and rheumatoid factor and anti-citrullinated protein/peptide antibody positivity.</i>	<i>Good clinical practice</i>
<b>Recommendation 4:</b> The presence of interstitial lung disease should always be considered when deciding on treatment, given the potential risk of pneumonitis described with some of the drugs commonly used in RA.	<i>Good clinical practice</i>

<p><b>Recommendation 5:</b> In patients with RA, none of the investigational serum biomarkers tested so far has been shown to have better predictive value for the onset of interstitial lung disease than anti-citrullinated protein/peptide antibodies. Based on the current evidence, the drafting group does not recommend the use of other serum biomarkers in routine clinical practice.</p>	<p>GRADE D</p>
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**Prognostic factors for the progression of ILD and death**

<p><b>Clinical question:</b> What are the prognostic factors for mortality and progression of lung disease in patients with RA-ILD?</p>	<p><b>Strength of the recommendation<sup>1</sup></b></p>
<p><b>Recommendation 6:</b> In patients with RA and interstitial lung disease, it is recommended that the presence of prognostic factors associated with progression** and mortality*** be considered when planning follow-up (frequency of check-ups) and treatment strategy</p> <p><i>**The main predictors of progression of interstitial lung disease are the radiological pattern of usual interstitial pneumonia, elevated anti-citrullinated protein/peptide antibody titres, degree of baseline DLCO impairment, a <math>\geq 10\%</math> decrease (percentage of estimated theoretical value) in FVC during follow-up, extensive lung involvement on chest HRCT, and elevated serum levels of interleukin-6 and Krebs von den Lungen-6 glycoprotein.</i></p> <p><i>***The main prognostic factors associated with increased mortality are advanced age at diagnosis of ILD, male sex, duration of RA, moderate or high disease activity, the usual radiological pattern of interstitial pneumonia, low baseline FVC and/or DLCO, a decrease in FVC <math>&gt; 10\%</math> or DLCO <math>&gt; 15\%</math> during follow-up, extensive lung involvement on chest HRCT, Gender, Age, Physiology index and Composite Physiologic Index scores, and elevated serum levels of Krebs von den Lungen-6 glycoprotein.</i></p>	<p>GRADO B</p>

**Pharmacological treatment**

<p><b>Clinical question: 4.</b> In patients with RA-ILD, which is the safest bDMARD or tsDMARD?</p>	<p><b>Strength of the recommendation<sup>1</sup></b></p>
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In patients with RA and RA-ILD, which drugs have been shown to be effective for the treatment of the lung disease?	
<b>Recommendation 7:</b> For the treatment of patients with RA-ILD, multidisciplinary therapeutic management is recommended.	<i>Good clinical practice</i>
<b>Recommendation 8:</b> If interstitial lung disease is present at RA debut, an individualised assessment for the use of MTX is recommended, as there is a risk of drug-induced acute pneumonitis, albeit low.	<i>GRADE A</i>
<b>Recommendation 8.1:</b> In these cases, the drafting group considers that the best strategy to minimise risks is to use another conventional synthetic DMARD whenever possible.	<i>Good clinical practice</i>
<b>Recommendation 9:</b> In patients with RA, when ILD is diagnosed or worsens during the first year of MTX treatment, MTX should be temporarily discontinued until it is clear whether or not there is a causal relationship.	<i>Good clinical practice</i>
<b>Recommendation 10:</b> In patients with RA on MTX for more than 1 year who are diagnosed with ILD, the drug can be maintained as there is no evidence to justify discontinuation.	<i>GRADO D</i>
<b>Recommendation 11:</b> In patients with RA-ILD who are not of Asian descent, LEF can be considered a safe drug.	<i>Good clinical practice</i>
<b>Recommendation 12:</b> In patients with RA and ILD requiring biological therapy, abatacept or rituximab should be used interchangeably as the safest options.	<i>GRADE D</i>
<b>Recommendation 13:</b> In patients with RA and ILD, in cases of contraindication or inadequate response to abatacept and rituximab, the use of an IL-6 inhibitor or a tsDMARD can be considered.	<i>GRADE D</i>
<b>Recommendation 14:</b> In patients with RA being treated with anti-TNF and stable ILD, there is inconclusive evidence to recommend discontinuation if the drug has achieved good control of joint symptoms.	<i>Good clinical practice</i>
<b>Recommendation 15:</b> In patients with RA-ILD with an inflammatory radiological pattern (nonspecific interstitial pneumonia, organising pneumonia, lymphoid interstitial pneumonia, etc.) in whom	<i>Good clinical practice</i>

glucocorticoids are considered necessary, their use is always recommended at the lowest dose and for the shortest possible time.	
<b>Recommendation 16:</b> The drafting group considers that the available evidence is insufficient to issue a conclusive recommendation on the use of immunosuppressants in the treatment of RA-ILD.	<i>GRADE D</i>
If it is decided to use them, the drafting group suggests the use of mycophenolate because of its better safety profile.	<i>Good clinical practice</i>
<b>Recommendation 17:</b> Although evidence of efficacy of biologic DMARDs in the treatment of RA-ILD is scarce, real-world data suggest that both abatacept and rituximab could be useful in stabilising or improving lung function, particularly in patients with a non-fibrotic radiological pattern.	<i>GRADE D</i>
<b>Recommendation 18:</b> In the subgroup of patients with RA-ILD with a progressive fibrosing phenotype, the use of NTB is recommended, while maintaining background RA treatment.	<i>GRADE B</i>

<sup>1</sup>Strength of the recommendation: recommendations graded according to the modified Scottish Intercollegiate Guidelines Network (SIGN) system<sup>380</sup>

DLCO: diffusing capacity of the lungs for carbon monoxide; DMARD: disease-modifying antirheumatic drug; FVC: forced vital capacity; IL-6: interleukin 6; HRCT: high-resolution computed tomography.

## Appendix 3. Glossary and abbreviations

### Glossary

**Burden of disease:** an indicator that measures the loss of health due to the fatal and non-fatal consequences of a disease (mortality and morbidity) in a population. It is measured in disability-adjusted life years (DALYs).

**Efficacy:** the extent to which an intervention is beneficial under ideal conditions.

**Open trial:** 1. Clinical trial in which the researcher knows details about the intervention given to the participant, also called an open-label trial. 2. Clinical trial with an open sequential design.

**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.

**Randomised clinical trial:** an experimental study in which participants are assigned randomly (at random) to one of two (or more) groups: one (the experimental group) receives the treatment under study and the other/others (the comparison or control group/groups) receive the conventional treatment (or sometimes placebo). Both groups are monitored to assess any potential differences in outcomes. In this way, the efficacy of the treatment of interest is assessed.

**Case-control study:** a study that identifies people with a disease (cases), e.g., lung cancer, and compares them with a group of people without the disease (controls). The relationship between one or various disease-related factors (e.g., smoking) is assessed by comparing the rate of exposure to these or other factors between cases and controls.

**Cohort study:** a study that involves following up one or more cohorts of individuals with different levels of exposure to a risk factor and assessing whether they develop the disease or condition of interest.

**Primary study:** the type of research that collects original data. Primary studies are different from reviews or syntheses, which are based on data from individual primary studies. They also differ from systematic reviews, which summarise the results of a set of primary studies.

**Cross-sectional descriptive study:** a study that describes the rate of an event or exposure at a specific time (single measurement). Also called a prevalence study, it makes it possible 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).

**Indirect evidence:** information is described as indirect in situations when no direct comparisons are made between the interventions of interest, or there are major differences between the studies available and the population, interventions or outcomes of interest.

**Discussion group:** a qualitative research technique used for investigating attitudes, opinions, appraisals or perceptions among a group of individuals regarding something or someone.

**Clinical practice guideline:** a set of recommendations based on a systematic review of the evidence and the assessment of the risks and benefits of the options available, seeking to optimise the healthcare provided to patients.

**Heterogeneity:** In the context of meta-analysis, heterogeneity refers to the variability or differences in the estimated effect between studies. It is important to distinguish between “statistical heterogeneity”, that is, differences in the stated effect, and “clinical heterogeneity”, that is, differences between studies in the key characteristics of participants, interventions, or outcome measures. Statistical tests for heterogeneity are used to assess whether the variability in results observed across studies is larger than would be expected by chance alone.

**Confidence interval:** the range within which the real size of the effect (never known exactly) is likely to fall, with a pre-set level of confidence. Commonly, researchers speak of a “95% confidence interval”, which means that the true value would lie in this interval in 95% of the cases measured. Note: confidence intervals reflect uncertainty due to random errors, but not systematic errors (bias).

**Qualitative research:** a concept that covers a wide range of theoretical, methodological and technical approaches and is characterised by studying phenomena in their natural context, attempting to make sense of, or interpret, them based on the meanings people attach to them. To this end, it uses the types of empirical material (interviews, observations, texts, etc.) that may best describe both routine and problematic situations, and what they mean in the lives of individuals.

**MEDLINE/PubMed:** PubMed is a search engine that accesses citations and abstracts of biomedical literature in the MEDLINE database maintained by the US National Library of Medicine.

**Meta-analysis:** a statistical approach that makes it possible to combine the results of different studies (diagnostic test studies, clinical trials, cohort studies, etc.) to assess heterogeneity and obtain overall results. This term is also used to refer to systematic reviews that include meta-analysis.

**Morbidity:** the state of having an illness or medical problems associated with a treatment or the amount of illness (incidence or prevalence) in a given population.

**Mortality:** the rate or proportion of people in a given population that die from a given disease in a given period of time.

**National Institute for Health and Care Excellence (NICE):** a public body in the United Kingdom that is independent of the National Health Service (NHS), whose role is to provide clinicians, public health and social care practitioners with access to the best available scientific evidence, in the form of clinical guidelines and advice concerning public health and healthcare technologies.

**Odds ratio (OR):** a measure of the strength of association between two variables, e.g., an exposure and an outcome, and hence, serves as an indicator of the efficacy or effectiveness of a treatment. If the OR is 1, the effect of the treatment is not different from that observed in the control group. If it is above (or below) 1, the effect of treatment is higher (or lower) than that observed in the control group. It should be noted that the effect being measured may be undesirable (e.g., death or disability) or desirable (e.g., smoking cessation).

**Placebo:** an inactive substance or procedure administered to a participant to compare its effects with those of the intervention of interest. It is used in clinical trials to blind participants to the

treatment they have been assigned. Ideally, to preserve blinding, the placebo and the intervention should be indistinguishable.

**Prevalence:** the rate or proportion of people in a given population who have a given condition or finding at a given time.

**Systematic review:** a review of the evidence on a given topic in the form of a summary of studies addressing a specific question, created using systematic methods for identifying, critically appraising and synthesising information in the scientific literature. It may or may not include a meta-analysis.

**Case series:** a type of study that analyses a group of patients with a given disease or outcome.

**Scottish Intercollegiate Guidelines Network (SIGN):** A Scottish network of multidisciplinary groups that develop clinical practice guidelines containing recommendations based on the best available scientific evidence, as well as documents concerning the methods used to develop the guidelines.

## Abbreviations

ABA: abatacept

ACPA: anti-citrullinated protein antibody

ACR: American College of Rheumatology

ADA: adalimumab

AEMPS: Spanish Agency of Medicines and Medical Devices

ALAT: Latin American Thorax Society

ANA: anakinra

ATS: American Thoracic Society

BAR: baricitinib

bDMARD: biological disease-modifying antirheumatic drug

BT: biological therapy

CDAI: Clinical Disease Activity Index

CI: confidence interval

CIMT: carotid intima–media thickness

CPG: clinical practice guideline

CRP: C-reactive protein

csDMARD: conventional synthetic disease-modifying antirheumatic drug

CT: computed tomography

CZP: certolizumab pegol

DAS28: 28-joint Disease Activity Score

DLCO: diffusing capacity of the lungs for carbon monoxide

DMARD: disease-modifying antirheumatic drug

EMA: European Medicines Agency

EPISER: study on the prevalence of rheumatic diseases in adults in Spain

ERS: European Respiratory Society

ESR: erythrocyte sedimentation rate

EtD: Evidence to Decision

ETN: etanercept

EULAR: European Alliance of Associations for Rheumatology

FDA: Food and Drug Administration

FER: Foundation of the Spanish Society of Rheumatology

FVC: forced vital capacity  
GC: glucocorticoid  
GGO: ground-glass opacity  
GDG: guideline development group  
GM-CSF: granulocyte–macrophage colony-stimulating factor  
GOL: golimumab  
GRADE: Grading of Recommendations Assessment, Development, and Evaluation  
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  
HR: hazard ratio  
HRCT: high-resolution computed tomography  
IFX: infliximab  
ILD: interstitial lung disease  
IRR: incidence rate ratio  
JAK: Janus kinase  
LEF: leflunomide  
MD: mean difference  
MRI: magnetic resonance imaging  
mTSS: modified Total Sharp Score  
MTX: methotrexate  
NSAID: nonsteroidal anti-inflammatory drug  
NSIP: non-specific interstitial pneumonia  
NTB: nintedanib  
OR: odds ratio  
PFT: pulmonary function test  
PICO: Patient, Intervention, Comparison and Outcome  
PFN: pirfenidone

PROM: patient-reported outcome measure  
RA: rheumatoid arthritis  
RCT: randomised controlled trial  
RF: rheumatoid factor  
RR: relative risk  
RTX: rituximab  
SDAI: Simplified Disease Activity Index  
SEPAR: Spanish Society of Pulmonology and Thoracic Surgery  
SER: Spanish Society of Rheumatology  
SF-36: 36-item Short Form Health Survey  
SIGN: Scottish Intercollegiate Guidelines Network  
SORCOM: Rheumatology Society of the Madrid Region  
SR: systematic review  
SSZ: sulfasalazine  
T2T: treat-to-target  
TCZ: tocilizumab  
TNF: tumour necrosis factor  
TOF: tofacitinib  
tsDMARD: targeted synthetic disease-modifying antirheumatic drug  
UIP: usual interstitial pneumonia  
WHO: World Health Organization

## Appendix 4. From evidence to decision

### EtD Question 1. Initial pharmacological treatment

#### **In DMARD-naïve patients with RA, what is the effect of treatment with bDMARDs or tsDMARDs, compared to csDMARDs?**

Patient: Adult patients ( $\geq 18$  years) diagnosed with RA (2010 ACR/EULAR criteria) not previously treated with a DMARD.

Intervention: Pharmacological treatments with bDMARDs: TNF inhibitors (IFX, ETN, ATA, CZP, or GOL); IL-6R inhibitors (TCZ, or SAR); RTX, ABA; JAK inhibitors (BAR, TOF, UPA, or FIL).

Comparison: csDMARDs (MTX and/or LEF and/or SSZ and/or antimalarials, with or without glucocorticoids).

Outcomes: Efficacy based on disease activity: DAS28, CDAI, SDAI, ACR20/50/70/90 response, remission according to any of its definitions or EULAR response; efficacy based on structural damage: radiographs (Sharp, van der Heijde/Larsen scores), MRI; improvement in activity, functional capacity or quality of life (patient-reported outcome measures): SF-36, HAQ, etc.; major adverse events: death, cancer, etc.

### From the evidence to the recommendations: Initial pharmacological treatment

#### **a) Is this problem a priority?**

- Judgement: Yes

#### **bDMARDs**

##### *TNF inhibitors*

#### TNF inhibitor monotherapy vs conventional therapy (MTX)

#### **b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible

#### **Research-based evidence:**

The review identified four RCTs<sup>108-111</sup> assessing the efficacy of TNF inhibitor monotherapy compared to MTX for treating patients with RA. The following table summarises the overall results by outcome:

Outcome	Study event rates (%)		Effect		Quality and importance of the outcome (GRADE)
	csDMARDs	TNF inhibitor monotherapy	Relative effect (95% CI)	The difference in risk compared to TNF inhibitor monotherapy	
<b>ACR20</b>					
1,274 (3 RCTs)	364/634 (57.4%)	365/640 (57.0%)	<b>RR 1.00</b> (0.91 to 1.10)	<b>0 fewer per 1,000</b> (from 52 fewer to 57 more)	⊕○○○ Very low <sup>a,b,c</sup>
<b>ACR50</b>					
850 (2 RCTs)	158/417 (37.9%)	153/433 (35.3%)	<b>RR 0.93</b> (0.78 to 1.11)	<b>27 fewer per 1,000</b> (from 83 fewer to 42 more)	⊕○○○ Very low <sup>a,c,d</sup>
<b>ACR70</b>					
850 (2 RCTs)	97/417 (23.3%)	99/433 (22.9%)	<b>RR 0.97</b> (0.76 to 1.24)	<b>7 fewer per 1,000</b> (from 56 fewer to 56 more)	⊕⊕○○ Low <sup>a,c</sup>
<b>28-item Disease Activity Score &lt; 2.6</b>					
850 (2 RCTs)	109/417 (26.1%)	109/433 (25.2%)	<b>RR 0.96</b> (0.77 to 1.21)	<b>10 fewer per 1,000</b> (from 60 fewer to 55 more)	⊕⊕○○ Low <sup>a,c</sup>
<b>No radiographic progression (modified Total Sharp Score &lt; 0.5)</b>					
1,083 (3 RCTs)	233/542 (43.0%)	306/541 (56.6%)	<b>RR 1.33</b> (1.18 to 1.49)	<b>142 more per 1,000</b> (from 77 more to 211 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>Health Assessment Questionnaire (decrease of ≥ 0.22 points)</b>					
531 (1 RCT)	162/257 (63.0%)	159/274 (58.0%)	<b>RR 0.92</b> (0.80 to 1.06)	<b>50 fewer per 1,000</b> (from 126 fewer to 38 more)	⊕⊕○○ Low <sup>a,c</sup>
<b>Adverse events</b>					
850 (2 RCTs)	361/417 (86.6%)	369/433 (85.2%)	<b>RR 0.98</b> (0.89 to 1.08)	<b>17 fewer per 1,000</b> (from 95 fewer to 69 more)	⊕⊕○○ Low <sup>a,c</sup>
<b>Serious adverse events</b>					
447 (2 RCTs)	15/228 (6.6%)	12/219 (5.5%)	<b>RR 0.83</b> (0.40 to 1.73)	<b>11 fewer per 1,000</b> (from 39 fewer to 48 more)	⊕⊕○○ Low <sup>a,c</sup>

**Abbreviations**

ACR20, ACR50 and ACR70: 20%, 50% and 70% improvement respectively, as measured by American College of Rheumatology criteria; CI: confidence interval; csDMARD: conventional synthetic disease-modifying drug; RCT: randomised controlled trial; RR: relative risk; TNF: tumour necrosis factor

**Explanations**

- High risk of bias
- $I^2 = 61\%$ . The estimates from the studies are contradictory, indicating that risk may increase or decrease.
- Imprecision: wide 95% CIs which include both higher and lower risk scenarios
- $I^2 = 45\%$ . The estimates from the studies are contradictory, indicating that risk may increase or decrease.

**c) What is the overall certainty of the evidence regarding the effects?**

- **Judgement:** Low/very low

The quality of the evidence was rated as low or very low due to the high risk of bias and due to imprecision associated with wide 95% CIs and the study estimates including both higher and lower risk scenarios.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

Weighing this balance, there is insufficient evidence to draw definitive conclusions on the potential additional benefit of TNF inhibitor monotherapy compared to MTX.

TNF inhibitors + csDMARDs vs conventional therapy (MTX)**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** moderate

**Research-based evidence:**

The review identified 13 RCTs evaluating the efficacy of TNF inhibitors combined with a csDMARD (MTX), compared to MTX monotherapy, in treating patients with RA<sup>73, 110-118</sup>. The following table summarises the overall results by outcome:

Outcomes	Study event rates (%)		Relative effect (95% CI)	Difference in risk compared to TNF inhibitor monotherapy	Quality and importance of the outcome (GRADE)
	csDMARD	TNF inhibitor + csDMARD			
<b>ACR20</b>					
4,749 (13 RCTs)	1193/2023 (59.0%)	1890/2726 (69.3%)	<b>RR 1.19</b> (1.14 to 1.24)	<b>112 more per 1,000</b> (from 83 more to 142 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>ACR50</b>					
4,749 (13 RCTs)	829/2,023 (41.0%)	1,520/2,726 (55.8%)	<b>RR 1.36</b> (1.27 to 1.44)	<b>148 more per 1,000</b> (from 111 more to 180 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>ACR70</b>					
4,749 (13 RCTs)	534/2,023 (26.4%)	1,149/2,726 (42.1%)	<b>RR 1.57</b> (1.44 to 1.70)	<b>150 more per 1,000</b> (from 116 more to 185 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>28-item Disease Activity Score &lt; 2.6</b>					
4,796 (13 RCTs)	522/2,120 (24.6%)	1,024/2,676 (38.3%)	<b>RR 1.66</b> (1.52 to 1.81)	<b>163 more per 1,000</b> (from 128 more to 199 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>Clinical Disease Activity Index</b>					
583 (2 RCTs)	115/291 (39.5%)	160/292 (54.8%)	<b>RR 1.39</b> (1.16 to 1.65)	<b>154 more per 1,000</b> (from 63 more to 257 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>Simplified Disease Activity Index</b>					
1,931 (4 RCTs)	215/965 (22.3%)	353/966 (36.5%)	<b>RR 1.64</b> (1.43 to 1.87)	<b>143 more per 1,000</b> (from 96 more to 194 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>Good EULAR response</b>					
648 (3 RCTs)	208/323 (64.4%)	245/325 (75.4%)	<b>RR 1.17</b> (1.06 to 1.30)	<b>109 more per 1,000</b> (from 39 more to 193 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>Radiographic progression (modified Total Sharp Score)</b>					
1,395 (4 RCTs)	335/633 (52.9%)	564/762 (74.0%)	<b>RR 1.36</b> (1.13 to 1.63)	<b>191 more per 1,000</b> (from 69 more to 333 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>Quality of life (Health Assessment Questionnaire)</b>					
1,196 (2 RCTs)	346/555 (62.3%)	466/641 (72.7%)	<b>RR 1.17</b> (1.08 to 1.26)	<b>106 more per 1,000</b> (from 50 more to 162 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>Adverse events</b>					
3,118 (8 RCTs)	1,124/1,415 (79.4%)	1,400/1,703 (82.2%)	<b>RR 1.04</b> (1.00 to 1.07)	<b>32 more per 1,000</b> (from 0 fewer to 56 more)	⊕⊕○○ Low <sup>a,b</sup>

Serious adverse events					
3,945 (11 RCTs)	187/1,711 (10.9%)	208/2,234 (9.3%)	<b>RR 1.09</b> (0.90 to 1.32)	<b>10 more per 1,000</b> (from 11 fewer to 35 more)	⊕⊕○○ Low <sup>a,c</sup>
<p><b>Abbreviations</b> ACR20, ACR50 and ACR70: 20%, 50% and 70% improvement respectively as measured by American College of Rheumatology criteria; CI: confidence interval; csDMARDs: conventional synthetic disease-modifying drug; EULAR: European Alliance of Associations for Rheumatology; HAQ: Health Assessment Questionnaire; RCT: randomised controlled trial; RR: relative risk; TNF: tumour necrosis factor</p> <p><b>Explanations</b> a. High risk of bias b. Imprecision: wide 95% CIs that include scenarios with no difference in effect and scenarios with higher risk. c. Imprecision: wide 95% CIs that include both higher and lower risk scenarios.</p>					

**c) What is the overall certainty of the evidence regarding the effects?**

- **Judgement:** Moderate/low

The quality of the evidence was rated as moderate for efficacy outcomes and low for adverse effect outcomes, due to either a high risk of bias or imprecision associated with wide 95% CIs that included both higher and lower risk scenarios.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence favours TNF inhibitors combined with MTX, but is insufficient to draw definitive conclusions regarding the additional benefit of this combination over MTX monotherapy.

***IL-6R inhibitors***

IL-6R inhibitor monotherapy vs. conventional therapy (MTX)

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** moderate

**Research-based evidence:**

The review identified two RCTs (FUNCTION<sup>119, 120</sup> and U-ACT-EARLY<sup>121</sup>), included in two SRs<sup>122, 123</sup>, assessing the efficacy of IL-6R inhibitors compared to MTX monotherapy in treating patients with RA. The following table summarises the overall results by outcome:

Outcomes	Study event rates (%)		Effect		Quality and importance of the outcome (GRADE)
	csDMARDs	IL-6R inhibitor monotherapy	Relative effect (95% CI)	Difference in risk	
<b>ACR20</b>					
790 (2 RCTs)	250/395 (63.3%)	282/395 (71.4%)	<b>RR 1.13</b> (1.02 to 1.24)	<b>82 more per 1,000</b> (from 13 more to 152 more)	⊕⊕⊕⊕ High
<b>ACR50</b>					
790 (2 RCTs)	160/395 (40.5%)	199/395 (50.4%)	<b>RR 1.24</b> (1.07 to 1.45)	<b>97 more per 1,000</b> (from 28 more to 182 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>ACR70</b>					
790 (2 RCTs)	89/395 (22.5%)	126/395 (31.9%)	<b>RR 1.41</b> (1.12 to 1.78)	<b>92 more per 1,000</b> (from 27 more to 176 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>28-item Disease Activity Score &lt; 2.6</b>					
579 (1 RCT)	43/287 (15.0%)	113/292 (38.7%)	<b>RR 2.58</b> (1.89 to 3.53)	<b>237 more per 1,000</b> (from 133 more to 379 more)	⊕⊕⊕○ Moderate <sup>b</sup>
<b>Good EULAR response</b>					
211 (1 RCT)	50/108 (46.3%)	84/103 (81.6%)	<b>RR 1.76</b> (1.4 to 2.20)	<b>352 more per 1,000</b> (from 190 more to 556 more)	⊕⊕⊕○ Moderate <sup>b</sup>
<b>modified Total Sharp Score</b>					
579 (1 RCT)	287	292	-	<b>MD 0.88 smaller</b> (1.53 smaller to 0.23 larger)*	⊕⊕⊕○ Moderate <sup>c</sup>
<b>Health Assessment Questionnaire (decrease of ≥ 0.22 points)</b>					
211 (1 RCT)	55/108 (50.9%)	68/103 (66.0%)	<b>RR 1.30</b> (1.03 to 1.63)	<b>153 more per 1,000</b> (from 15 more to 321 more)	⊕⊕⊕⊕ High
<b>Explanations</b>					
a. $I^2 = 84\%$ . The CIs from the studies include different scenarios, one of which involves a possibility of decreased risk.					
b. Imprecision: fewer than 300 events per arm; optimal information size not met.					
c. The 95% CI was estimated based on the authors' assumptions about the measure of dispersion (standard deviation), applied equally to both groups.					
* The relevance of the differences found should be assessed in light of the minimal important difference as defined by experts.					
<b>Outcomes</b>	<b>Study event rates (%)</b>		<b>Effect</b>		

	csDMARDs	IL-6R inhibitor + csDMARDs	Relative risk (95% CI)	Difference in risk	Quality and importance of the outcome (GRADE)
<b>ACR20</b>					
791 (2 RCTs)	250/395 (63.3%)	295/396 (74.5%)	<b>RR 1.18</b> (1.07 to 1.29)	<b>114 more per 1,000</b> (from 44 more to 184 more)	⊕⊕⊕⊕ High
<b>ACR50</b>					
791 (2 RCTs)	160/395 (40.5%)	232/396 (58.6%)	<b>RR 1.45</b> (1.25 to 1.67)	<b>182 more per 1,000</b> (from 101 more to 271 more)	⊕⊕⊕⊕ High
<b>ACR70</b>					
791 (2 RCTs)	89/395 (22.5%)	158/396 (39.9%)	<b>RR 1.77</b> (1.42 to 2.20)	<b>173 more per 1,000</b> (from 95 more to 270 more)	⊕⊕⊕⊕ High
<b>DAS 28 &lt; 2.6</b>					
577 (1 RCT)	43/287 (15.0%)	130/290 (44.8%)	<b>RR 2.99</b> (2.21 to 4.10)	<b>298 more per 1,000</b> (from 181 more to 464 more)	⊕⊕⊕⊕ High
<b>Good EULAR response</b>					
214 (1 RCT)	50/108 (46.3%)	93/106 (87.7%)	<b>RR 1.90</b> (1.53 to 2.40)	<b>417 more per 1,000</b> (from 245 more to 648 more)	⊕⊕⊕⊕ High
<b>modified Total Sharp Score</b>					
577 (1 RCT)	287	290	-	<b>MD 1.06 smaller</b> (1.71 smaller to 0.41 smaller)*	⊕⊕⊕○ Moderate <sup>a</sup>
<b>Health Assessment Questionnaire (decrease of ≥ 0.22 points)</b>					
214 (1 RCT)	55/108 (50.9%)	67/106 (63.2%)	<b>RR 1.24</b> (0.98 to 1.57)	<b>122 more per 1,000</b> (from 10 more to 290 more)	⊕⊕⊕○ Moderate <sup>b</sup>
<p><i>Explanations</i></p> <p>a. The 95% CI was estimated based on the authors' assumptions regarding the measure of dispersion (standard deviation), applied equally to both groups.</p> <p>b. Imprecision: wide 95% CIs that included both higher and lower risk scenarios.</p> <p>* The relevance of the differences found should be considered in light of the minimal clinically important difference as defined by experts.</p>					

**c) What is the overall certainty of the evidence regarding the effects?**

- **Judgement:** High/Moderate

The quality of the evidence was rated as high or moderate depending on the outcome considered, due to the risk of bias, inconsistency (because the studies' CIs included different scenarios), or imprecision (because the optimal information size was not met).

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence favours IL-6R inhibitors alone or combined with MTX, but is insufficient to draw definitive conclusions regarding the advantages in clinical practice of these treatments over MTX monotherapy.

**Abatacept**

Abatacept combined with csDMARDs vs. csDMARD monotherapy

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** moderate

**Research-based evidence:**

Two RCTs have been identified<sup>124, 125</sup>, one of which was included in an SR<sup>126</sup>, assessing the effect of treatment with ABA plus MTX compared to MTX monotherapy for patients with RA. The following table summarises the overall results by outcome.

Outcomes	Study event rates (%)		Effect		Quality and importance of the outcome (GRADE)
	MTX	ABA + MTX	Relative effect (95% CI)	Difference in risk	
<b>ACR20</b>					
752 (1 RCT)	185/301 (61.5%)	340/451 (75.4%)	<b>RR 1.23</b> (1.11 to 1.36)	<b>141 more per 1,000</b> (from 68 more to 221 more)	⊕⊕⊕⊕ High <sup>a</sup>
<b>ACR50</b>					

1,261 (2 RCTs)	148/554 (26.7%)	308/707 (43.6%)	<b>RR 1.63</b> (1.39 to 1.92)	<b>168 more per 1,000</b> (from 104 more to 246 more)	⊕⊕⊕⊕ High
Remission as measured by DAS 28-CRP					
1,261 (2 RCTs)	135/554 (24.4%)	281/707 (39.7%)	<b>RR 1.63</b> (1.37 to 1.94)	<b>154 more per 1,000</b> (from 90 more to 229 more)	⊕⊕⊕⊕ High
Remission as measured by Simplified Disease Activity Index					
752 (1 RCT)	40/301 (13.3%)	100/451 (22.2%)	<b>RR 1.67</b> (1.19 to 2.34)	<b>89 more per 1,000</b> (from 25 more to 178 more)	⊕⊕⊕⊕ High <sup>a</sup>
Radiological progression as measured by TS (Sharp Score)					
509 (1 RCT)	133/253 (52.6%)	156/256 (60.9%)	<b>RR 1.16</b> (1.00 to 1.35)	<b>84 more per 1,000</b> (from 0 fewer to 184 more)	⊕⊕⊕⊕ High <sup>a</sup>
Radiological progression as measured by the modified Total Sharp Score					
752 (1 RCT)	301	451	-	<b>MD 2 smaller</b> (2.73 smaller to 1.27 smaller)	⊕⊕⊕⊕ High <sup>a</sup>
Improvement in Health Assessment Questionnaire-Disability Index [dichotomous variable]					
1,211 (2 RCTs)	360/504 (71.4%)	515/707 (72.8%)	<b>RR 1.12</b> (1.03 to 1.20)	<b>86 more per 1,000</b> (from 21 more to 143 more)	⊕⊕⊕⊕ High
Improvement in Health Assessment Questionnaire-Disability Index [dichotomous variable]					
509 (1 RCT)	253	256	-	<b>MD 0.2 smaller</b> (0.21 smaller to 0.19 smaller)	⊕⊕⊕○ Moderate <sup>b</sup>
Improvement in QoL as measured by SF-36 Physical Component Summary					
509 (1 RCT)	253	256	-	<b>MD 2.5 larger</b> (2.39 larger to 2.61 larger)	⊕⊕⊕⊕ High <sup>a</sup>
Improvement in QoL as measured by SF-36 Mental Component Summary					
509 (1 RCT)	253	256	-	<b>MD 1.81 larger</b> (1.7 larger to 1.92 larger)	⊕⊕⊕⊕ High <sup>a</sup>
Serious adverse events					
1,261 (2 RCTs)	28/554 (5.1%)	50/707 (7.1%)	<b>RR 1.48</b> (0.93 to 2.34)	<b>24 more per 1,000</b> (from 4 fewer to 68 more)	⊕⊕○○ Low <sup>c</sup>
<p><i>Explanations</i></p> <p>a. Not applicable</p> <p>b. Downgraded due to wide 95% CIs.</p> <p>c. The small number of events contributes to wide confidence intervals, reflecting uncertainty in the estimate (95% CIs compatible with benefit, no effect and harm).</p>					

**c) What is the overall certainty of the evidence on the effects?**

- **Judgement:** High/Moderate

The quality of the evidence was rated as high for the majority of the outcomes; however, the certainty was downgraded for some due to imprecision, associated with wide 95% CIs that reflect uncertainty in the estimate.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence favours ABA combined with MTX, but is insufficient to draw definitive conclusions regarding the advantages in clinical practice of this treatment over MTX monotherapy.

**JAK inhibitors**

JAK inhibitors vs conventional therapy (MTX)

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** Moderate

**Research-based evidence:**

The review identified 11 RCTs<sup>127-138</sup>, 7 of which are included in SRs<sup>122, 139-141</sup>, evaluating the safety and effectiveness of JAK inhibitors compared to MTX in patients with RA. The following table summarises the overall results by outcome.

Outcomes	Study event rates (%)		Effect		
	csDMARD	JAK inhibitors	Relative effect (95% CI)	Difference in risk	
<b>ACR20 (monotherapy)</b>					
2,282 (5 RCTs) <sup>1,2,3,4,5</sup>	708/1,163 (60.9%)	815/1,119 (72.8%)	<b>RR 1.27</b> (1.13 to 1.42)	<b>164 more per 1,000</b> (from 79 more to 256 more)	⊕⊕⊕⊕ High <sup>a</sup>
<b>ACR20 (combination therapy)</b>					
904 (2 RCTs) <sup>1,5</sup>	312/453 (68.9%)	366/451 (81.2%)	<b>RR 1.23</b> (1.01 to 1.51)	<b>158 more per 1,000</b> (from 7 more to 351 more)	⊕⊕⊕⊕ High
<b>ACR50 (monotherapy)</b>					
704	117/351	208/353	<b>RR 1.77</b>	<b>257 more per 1,000</b>	⊕⊕⊕⊕

(2 RCTs) <sup>1,4</sup>	(33.3%)	(58.9%)	(1.49 to 2.10)	(from 163 more to 367 more)	High
<b>ACR50 (combination therapy)</b>					
72 (1 RCT) <sup>1</sup>	13/37 (35.1%)	23/35 (65.7%)	<b>RR 1.87</b> (1.14 to 3.08)	<b>306 more per 1,000</b> (from 49 more to 731 more)	⊕⊕⊕○ Moderate <sup>b</sup>
<b>ACR70 (monotherapy)</b>					
704 (2 RCTs) <sup>1,4</sup>	69/351 (19.7%)	155/353 (43.9%)	<b>RR 2.01</b> (1.24 to 3.27)	<b>199 more per 1,000</b> (from 47 more to 446 more)	⊕⊕⊕○ Moderate <sup>c</sup>
<b>ACR70 (combination therapy)</b>					
72 (1 RCT) <sup>1</sup>	9/37 (24.3%)	10/35 (28.6%)	<b>RR 1.17</b> (0.54 to 2.54)	<b>41 more per 1,000</b> (from 112 fewer to 375 more)	⊕⊕○○ Low <sup>b</sup>
<b>Remission as measured by DAS28-CRP; score &lt; 2.6 [monotherapy]</b>					
1,699 (4 RCTs) <sup>1,3,4,5</sup>	236/977 (24.2%)	318/722 (44.0%)	<b>RR 1.85</b> (1.36 to 2.51)	<b>205 more per 1,000</b> (from 87 more to 365 more)	⊕⊕⊕⊕ High <sup>a</sup>
<b>Remission as measured by DAS28-CRP; score &lt; 2.6 [combination therapy]</b>					
496 (2 RCTs) <sup>1,3</sup>	55/247 (22.3%)	147/249 (59.0%)	<b>RR 2.64</b> (2.05 to 3.39)	<b>365 more per 1,000</b> (from 234 more to 532 more)	⊕⊕⊕⊕ High
<b>Remission as measured by DAS28-ESR; score &lt; 2.6 [monotherapy]</b>					
952 (2 RCTs) <sup>2,3</sup>	56/396 (14.1%)	124/556 (22.3%)	<b>RR 1.66</b> (0.88 to 3.15)	<b>93 more per 1,000</b> (from 17 fewer to 304 more)	⊕⊕○○ Low <sup>c,d</sup>
<b>Remission as measured by Clinical Disease Activity Index [monotherapy]; score ≤ 2.8</b>					
631 (1 RCT) <sup>4</sup>	35/314 (11.1%)	89/317 (28.1%)	<b>RR 2.52</b> (1.76 to 3.61)	<b>169 more per 1,000</b> (from 85 more to 291 more)	⊕⊕⊕⊕ High
<b>Remission as measured by Clinical Disease Activity Index [monotherapy]; score ≤ 10</b>					
229 (2 RCTs) <sup>6,7</sup>	41/107 (38.3%)	60/122 (49.2%)	<b>RR 1.25</b> (0.85 to 1.83)	<b>96 more per 1,000</b> (from 57 fewer to 318 more)	⊕⊕○○ Low <sup>b</sup>
<b>Remission as measured by Simplified Disease Activity Index; score ≤ 3.3 [monotherapy]</b>					
1,000 (2 RCTs) <sup>4,8</sup>	95/524 (18.1%)	143/476 (30.0%)	<b>RR 1.82</b> (0.61 to 5.38)	<b>149 more per 1,000</b> (from 71 fewer to 794 more)	⊕○○○ Very low <sup>b,d</sup>
<b>Remission measured by Simplified Disease Activity Index; score ≤ 11 [monotherapy]</b>					
469 (2 RCTs) <sup>6,8v</sup>	120/261 (46.0%)	116/208 (55.8%)	<b>RR 1.24</b> (1.04 to 1.48)	<b>110 more per 1,000</b> (from 18 more to 221 more)	⊕⊕⊕⊕ High
<b>Disease activity as measured by DAS28-CRP; score ≤ 3.2 [monotherapy]</b>					

542 (3 RCTs) <sup>1,3,6</sup>	105/298 (35.2%)	119/244 (48.8%)	<b>RR 1.41</b> (1.16 to 1.72)	<b>144 more per 1,000</b> (from 56 more to 254 more)	⊕⊕⊕⊕ High <sup>a</sup>
<b>Disease activity as measured by DAS28-CRP; score ≤ 3.2 [combination therapy]</b>					
496 (2 RCTs) <sup>1,3</sup>	87/247 (35.2%)	125/249 (50.2%)	<b>RR 1.86</b> (0.79 to 4.42)	<b>303 more per 1,000</b> (from 74 fewer to 1,000 more)	⊕○○○ Very low <sup>b,d</sup>
<b>Radiological progression as measured by the van der Heijde method [monotherapy]</b>					
73 (1 RCT) <sup>1</sup>	37	36		<b>MD 1.51 smaller</b> (1.75 smaller to 1.27 smaller)	⊕⊕⊕⊕ High <sup>e</sup>
<b>Radiological progression as measured by the van der Heijde method [monotherapy] dichotomous variable</b>					
704 (2 RCTs) <sup>1,9</sup>	264/351 (75.2%)	287/353 (81.3%)	<b>RR 1.07</b> (0.99 to 1.15)	<b>53 more per 1,000</b> (from 8 fewer to 113 more)	⊕⊕○○ High <sup>f</sup>
<b>Radiological progression as measured by the van der Heijde method [combination therapy]</b>					
71 (1 RCT) <sup>1</sup>	37	34		<b>MD 0.51 smaller</b> (0.75 smaller to 0.27 smaller)	⊕⊕⊕⊕ High
<b>Radiological progression as measured by the van der Heijde method [Combination therapy] dichotomous variable</b>					
71 (1 RCT) <sup>1</sup>	17/37 (45.9%)	22/34 (64.7%)	<b>RR 1.41</b> (0.92 to 2.16)	<b>188 more per 1,000</b> (from 37 fewer to 533 more)	⊕⊕⊕○ Moderate <sup>e,f</sup>
<b>Radiological progression as measured by erosion [monotherapy]</b>					
1,000 (2 RCTs) <sup>3,4</sup>	524	476		<b>MD 0.28 smaller</b> (0.42 smaller to 0.15 smaller)	⊕⊕⊕⊕ High
<b>Radiological progression as measured by joint space narrowing [monotherapy]</b>					
1,000 (2 RCTs) <sup>3,4</sup>	524	476		<b>MD 0.1 smaller</b> (0.36 smaller to 0.17 more)	⊕⊕⊕○ Moderate <sup>f</sup>
<b>Radiological progression as measured by the modified Total Sharp Score</b>					
631 (1 RCT) <sup>4</sup>	314	317		<b>MD 0.53 smaller</b> (0.86 smaller to 0.2 smaller)	⊕⊕⊕⊕ High <sup>e</sup>
<b>Improvement in HAQ-DI; score ≥0.22 [monotherapy]</b>					
1692 (5 RCTs) <sup>1,3,4,6,10</sup>	412/768 (53.6%)	593/924 (64.2%)	<b>RR 1.23</b> (1.01 to 1.49)	<b>123 more per 1,000</b> (from 5 more to 263 more)	⊕⊕○○ Low <sup>a,f</sup>
<b>Improvement in HAQ-DI score ≥0.22 [combination therapy]</b>					

496 (2 RCT) <sup>1,3</sup>	147/247 (59.5%)	180/249 (72.3%)	<b>RR 1.17</b> (0.94 to 1.44)	<b>101 more per 1,000</b> (from 36 fewer to 262 more)	⊕⊕⊕○ Moderate <sup>b</sup>
<b>Improvement in HAQ-DI [monotherapy] continuous variable</b>					
1,000 (2 RCT) <sup>4,11</sup>	524	476		<b>MD 0.27 smaller</b> (0.34 smaller to 0.21 smaller)	⊕⊕⊕⊕ High
<b>Improvement as measured by SF-36 Physical Component Summary [monotherapy] continuous variable</b>					
1,150 (2 RCT) <sup>10,12</sup>	470	680		<b>MD 4.48 larger</b> (3.49 larger to 5.47 larger)	⊕⊕⊕⊕ High
<b>Improvement as measured by SF-36 Mental Component Summary [monotherapy] continuous variable</b>					
1,147 (2 RCT) <sup>10,13</sup>	470	677		<b>MD 2.04 larger</b> (1.91 more to 2.16 more)	⊕⊕⊕⊕ High
<b>Improvement as measured by SF-36 Physical Component Summary</b>					
369 (1 RCT) <sup>11</sup>	101/210 (48.1%)	103/159 (64.8%)	<b>RR 1.35</b> (1.12 to 1.61)	<b>168 more per 1,000</b> (from 58 more to 293 more)	⊕⊕⊕⊕ High
<b>Improvement as measured by Functional Assessment of Chronic Illness Therapy – Fatigue scale [monotherapy] continuous variable</b>					
1,519 (3 RCTs) <sup>4,10,11</sup>	680	839		<b>MD 2.26 larger</b> (2.17 larger to 2.35 larger)	⊕⊕⊕⊕ High
<b>Improvement as measured by Functional Assessment of Chronic Illness Therapy – Fatigue scale [monotherapy]</b>					
888 (2 RCTs) <sup>10,11</sup>	168/366 (45.9%)	282/522 (54.0%)	<b>RR 1.25</b> (1.08 to 1.43)	<b>115 more per 1,000</b> (from 37 more to 197 more)	⊕⊕⊕○ Moderate <sup>g</sup>
<b>Serious adverse events [monotherapy]</b>					
1,073 (3 RCTs)	35/561 (6.2%)	27/512 (5.3%)	<b>RR 0.90</b> (0.55 to 1.48)	<b>6 fewer per 1,000</b> (from 28 fewer to 30 more)	⊕⊕○○ Low <sup>b,f</sup>
<b>Serious adverse events [combination therapy]</b>					
498 (2 RCTs)	22/247 (8.9%)	19/251 (7.6%)	<b>RR 0.85</b> (0.47 to 1.53)	<b>13 fewer per 1,000</b> (from 47 fewer to 47 more)	⊕⊕○○ Low <sup>b,f</sup>

**Abbreviations**

ACR20, ACR50 and ACR70: 20%, 50% and 70% improvement respectively as measured by American College of Rheumatology criteria, respectively; CI: confidence interval; csDMARD: conventional synthetic disease-modifying drug; DAS28-ESR or DAS28-CRP: 28-item Disease Activity Score calculated with erythrocyte sedimentation rate or C-reactive protein, respectively; HAQ-DI: Health Assessment Questionnaire Disability Index; JAK: Janus kinase; RCT: randomised controlled trial; RR: relative risk; SF\_36: 36-item Short Form Health Survey; TNF: tumour necrosis factor

**Explanations**

- a. Despite substantial heterogeneity ( $I^2$ ), the quality was not downgraded for inconsistency since studies consistently indicated the same direction of effects, except for one in which the 95% CI crossed the line of no effect, but which included very few events.
- b. The small number of events contributes to wide confidence intervals, reflecting uncertainty in the estimate (95% CIs compatible with benefit, no effect, and harm).
- c. The estimate is based on a small number of events (fewer than 300), which is reflected in the very wide confidence interval.
- d. The certainty is downgraded by one level due to substantial heterogeneity.
- e. Not applicable
- f. 95% CI was wide, including the possibility of no effect (RR = 1.0), which suggests imprecision.
- g. Downgraded due to wide 95% CIs.

**c) What is the overall certainty of the evidence regarding the effects?**

- **Judgement:** High/moderate/low

The quality of the evidence was rated as high for some outcomes; however, in other cases, it was downgraded to moderate or low, either due to imprecision, associated with small event numbers and subsequent wide CIs and therefore the possibility of no effect, indicating uncertainty in the estimate, or due to inconsistency from substantial heterogeneity.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence favours JAK inhibitors alone and combined with MTX, but is insufficient to draw definitive conclusions regarding the advantages in clinical practice of these treatments over MTX monotherapy.

## EtD Question 2. Treatment after an inadequate response to a first bDMARD

**In patients with RA who have an inadequate response to a first TNF inhibitor, what is the effect of a second TNF inhibitor, a non-TNF-inhibitor bDMARD or a tsDMARD?**

Patients: Adults ( $\geq 18$  years old) diagnosed with RA (2010 ACR/EULAR criteria), who have failed to respond adequately to first-line biological therapy with TNF inhibitors.

Intervention: Pharmacological treatment with bDMARDs: TNF inhibitors (IFX, ETN, ADA, CZP, or GOL).

Comparison: Pharmacological treatments with bDMARDs (RTX, ABA, TCZ, SAR); or JAK inhibitors (BAR, TOF, UPA, FIL).

Outcomes: Efficacy based on disease activity: DAS28, CDAI, SDAI, ACR20/50/70/90 response, remission according to any of its definitions or EULAR response; efficacy based on structural damage: radiographs (Sharp, van der Heijde or Larsen scores), MRI; improvement in activity, functional capacity or quality of life (patient-reported outcome measures): SF-36, HAQ, etc.; major adverse events: death, cancer, etc.

From the evidence to the recommendations: Treatment after an inadequate response to a first bDMARD

### a) Is this problem a priority?

- Judgement: Yes

### Efficacy in controlling disease activity

#### b) What is the magnitude of the expected desirable effects?

- **Judgement:** small

### Research-based evidence

The review identified two clinical trials<sup>145, 146</sup> and one prospective cohort study<sup>147</sup> assessing the efficacy of a second TNF inhibitor in controlling disease activity compared to other biologics in patients with RA after discontinuation of a first TNF inhibitor for lack of effectiveness. The following table summarises the overall results by outcome:

Outcomes	Number of patients		Effect		Quality and importance of the outcome (GRADE)
	A second TNF inhibitor	Non-TNF-inhibitor bDMARD	Relative risk (95% CI)	Absolute (95% CI)	
<b>Good to moderate EULAR response at 6 months</b>					
(2 RCTs)	102/187 (54.5%)	141/227 (62.1%)	<b>RR 0.97<sup>1</sup></b> (0.57 to 1.63)	<b>19 fewer per 1,000</b> (from 267 fewer to 391 more)	⊕⊕⊕○ Moderate <sup>a</sup> critical
<b>Good to moderate EULAR response at 12 months</b>					
(1 RCT)	57/134 (42.5%)	78/131 (59.5%)	<b>RR 0.71<sup>2</sup></b> (0.56 to 0.91)	<b>173 fewer per 1,000</b> (from 333 fewer to 95 more)	⊕⊕⊕○ Moderate <sup>a</sup> critical
<b>Good to moderate EULAR response at 24 months</b>					
(1 Observational study)	37/75 (49.3%)	37/48 (77.1%)	<b>RR 0.64</b> (0.49 to 0.84)	<b>278 fewer per 1,000</b> (from 393 fewer to 123 fewer)	⊕⊕○○ Low important
<b>Low disease activity according to DAS28 at 6 months</b>					
(2 RCTs)	43/181 (23.8%)	69/220 (31.4%)	<b>RR 0.65</b> (0.48 to 0.89)	<b>110 fewer per 1,000</b> (from 163 fewer to 34 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>Low disease activity according to DAS28 at 12 months</b>					
(1 RCT)	31/133 (23.3%)	53/130 (40.8%)	<b>RR 0.57</b> (0.39 to 0.83)	<b>175 fewer per 1,000</b> (from 269 fewer to 12 fewer)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>Remission according to DAS28 at 6 months</b>					
(2 RCTs)	30/181 (16.6%)	45/221 (20.4%)	<b>RR 0.72</b> (0.48 to 1.09)	<b>57 fewer per 1,000</b> (from 106 fewer to 18 more)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>Remission according to DAS28 at 12 months</b>					
(1 RCT)	18/133 (13.5%)	35/130 (26.9%)	<b>RR 0.50</b> (0.30 to 0.84)	<b>135 fewer per 1,000</b> (from 197 fewer to 16 fewer)	⊕⊕⊕○ Moderate <sup>a</sup>
<b>Additional data from observational studies</b>					
<sup>1</sup>	45/77 (58.4%)	33/50 (66.0%)	<b>RR 0.89</b> (0.67 to 1.16)	<b>73 fewer per 1,000</b> (from 218 fewer to 106 more)	⊕⊕○○ Low <sup>b</sup>
<sup>2</sup>	43/74 (58.1%)	33/49 (67.3%)	<b>RR 0.86</b> (0.66 to 1.14)	<b>94 fewer per 1,000</b> (from 229 fewer to 94 more)	⊕⊕○○ Low <sup>b</sup>
<b>Abbreviations</b> CI: confidence interval; bDMARDs: biological disease-modifying drug; DAS28: 28-item Disease Activity Score; RCT: randomised controlled trial; RR: relative risk; TNF: tumour necrosis factor					
<b>Explanations</b>					

1. Study by Brown et al. (2018): study terminated early. Desired sample size not attained.
- a. Quality downgraded due to imprecision associated with 95% CIs crossing either the line of no effect or the threshold of clinical significance.
- b. Evidence from uncontrolled observational studies. Considered to be at high risk of bias by default.

## Efficacy as assessed by patient-reported outcome measures

### TNF inhibitors vs non-TNF-inhibitor bDMARD

The review identified one RCT<sup>146</sup> assessing the efficacy of a second TNF inhibitor in improving quality of life in patients with RA who have an inadequate response to a first TNF inhibitor. The following table summarises the overall results by outcome:

Outcomes	Number of patients		Effect		Quality and importance of the outcome (GRADE)
	A second TNF inhibitor	Non-TNF-inhibitor bDMARD	Relative effect (95% CI)	Absolute (95% CI)	
Health Assessment Questionnaire at 6 months					
(1 RCT)	No information	No information	Not estimable	<b>4 more per 100</b> (from 7 fewer to 15 more) <sup>c</sup>	⊕⊕⊕○ Moderate <sup>a</sup>
Health Assessment Questionnaire at 12 months					
(1 RCT)	No information	No information	Not estimable	<b>2 more per 100</b> (from 13 fewer to 9 more) <sup>c</sup>	⊕⊕⊕○ Moderate <sup>a</sup>
a. The authors do not provide mean values for each treatment group, rather only the differences in means, with corresponding CIs.					

### TNF inhibitors vs abatacept

The review identified one RCT<sup>145</sup> assessing the efficacy of ABA in improving quality of life in patients with RA who have an inadequate response to a first TNF inhibitor. The following table summarises the overall results by outcome.

Outcome	Number of patients		Effect		Quality and importance of the outcome (GRADE)
	Abatacept	TNF inhibitor bDMARD	Relative effect (95% CI)	Absolute (95% CI)	
Reduction in EQ-5D					

(1 RCT)	41	41	-	mean <b>0.11 lower</b> (0.24 lower to 0.02 higher)	⊕⊕⊕○ Moderate <sup>a</sup>
Mean EQ-5D score					
(1 RCT)	41	41	-	mean <b>0.02 higher.</b> (0.1 lower to 0.14 higher)	⊕⊕⊕○ Moderate <sup>a</sup>
a. Study terminated early. Desired sample size not attained.					

### TNF inhibitors vs rituximab

The review identified one RCT<sup>145</sup> that assessed the efficacy of RTX in improving quality of life in patients with RA who have an inadequate response to a first TNF inhibitor. The following table summarises the overall results by outcome.

Outcomes	Number of patients		Effect		Quality and importance of the outcome (GRADE)
	Rituximab	Non-TNF-inhibitor bDMARD	Relative risk (95% CI)	Absolute (95% CI)	
Reduction in EQ-5D					
(1 RCT)	41	40	-	mean <b>0.02 lower</b> (0.17 lower to 0.13 higher.)	⊕⊕⊕○ Moderate <sup>a</sup>
Mean EQ-5D score					
(1 RCT)	41	40	-	mean <b>0.09 higher</b> (0.1 lower to 0.14 higher)	⊕⊕⊕○ Moderate <sup>a</sup>
a. Study terminated early. Desired sample size not attained.					

### **Safety** (major adverse events)

#### TNF inhibitors vs non-TNF-inhibitor bDMARDs

The review identified two RCT<sup>145, 146</sup> and two observational studies<sup>147, 148</sup> assessing the adverse effects of a second TNF inhibitor for treating patients with RA who have an inadequate response to a first TNF inhibitor. The following table summarises the overall results by outcome:

Outcomes	Number of patients		Effect		Quality and importance of the outcome (GRADE)
	A second TNF inhibitor bDMARD	Non-TNF-inhibitor bDMARD	Relative effect (95% CI)	Absolute (95% CI)	
<b>Adverse effects</b>					
(1 observational study)	6/77 (7.8%)	7/50 (14.0%)	<b>RR 0.56</b> (0.20 to 1.56)	<b>62 fewer per 1,000</b> (from 112 fewer to 78 more)	⊕⊕○○ Low <sup>a</sup>
<b>Adverse effects with discontinuation</b>					
(1 RCT)	4/41 (9.8%)	6/81 (7.4%)	<b>RR 1.32<sup>1</sup></b> (0.39 to 4.40)	<b>2 fewer per 1,000</b> (from 32 fewer to 47 more)	⊕⊕⊕○ Moderate <sup>b</sup>
<b>Serious infections</b>					
(2 RCTs)	10/187 (5.3%)	9/227 (4.0%)	<b>RR 1.27</b> (0.52 to 3.12)	<b>11 more per 1,000</b> (from 19 fewer to 84 more)	⊕⊕⊕○ Moderate <sup>b</sup>
<b>Death</b>					
(2 RCTs)	1/187 (0.5%)	3/227 (1.3%)	<b>RR 0.67</b> (0.10 to 4.50)	<b>4 fewer per 1,000</b> (from 12 fewer to 46 more)	⊕⊕⊕○ Moderate <sup>b</sup>
<b>Results from observational studies</b>					
<sup>1</sup>	14/77 (18.2%)	1/50 (2.0%)	<b>RR 9.09</b> (1.23 to 66.99)	<b>162 more per 1,000</b> (from 5 more to 1,000 more)	⊕⊕○○ Low <sup>a</sup>
<b>Explanations</b>					
<p>1. Study by Brown et al. (2018): study terminated early. Desired sample size not attained.</p> <p>a. Evidence from uncontrolled observational studies. Considered to be at high risk of bias by default</p> <p>b. The quality was downgraded by one level due to imprecision associated with the 95% CIs crossing the line of no effect or the threshold of clinical significance</p>					

• **Other considerations:**

Other studies were identified that explore this question further<sup>149-155</sup>. In general, despite certain limitations, the results of these studies are in line with those of studies included in the SR conducted to answer this question.

**c) What is the overall certainty of the evidence regarding the effects?**

- **Judgement:** Moderate/low

The quality of the evidence was rated as low to moderate depending on the outcome considered, due to imprecision associated with the 95% CI crossing the line of no effect or the threshold of clinical significance. In addition, the quality of the evidence is limited by certain methodological issues, including early termination in the case of one of the clinical trials, the open-label nature of the research and the potential effect of TCZ on disease activity indices in the other, and the fact that the other two sources are cohort studies.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

After weighing the benefits and risks, the low quality of the evidence and the methodological limitations of the studies mean that it is not possible to establish whether there are differences in terms of efficacy and safety between a second TNF inhibitor and a non-TNF-inhibitor biologic or a JAK inhibitor in patients in whom previous TNF inhibitor therapy is discontinued for inadequate response.

### EtD Question 3. Interstitial lung disease

**In patients with RA and ILD, which drugs have been shown to be efficacious/effective/safe for the treatment of the lung disease?**

Patients: Adults ( $\geq 18$  years old) diagnosed with ILD and RA (2010 ACR/EULAR criteria)

Intervention: Pharmacological treatment with glucocorticoids (prednisone or methylprednisolone), bDMARDs (RTX, ABA, TCZ or SAR), JAK inhibitors (BAR, TOF, UPA or FIL), antifibrotics (PFN or NTB) or other immunosuppressants (MMF, AZA, tacrolimus, ciclosporin, cyclophosphamide, MTX, or LEF),

Comparison: Any prior intervention or placebo

Outcomes: Survival/death; progression of radiological lesions or pulmonary function test results: FVC, DLCO, Six-Minute Walk Test, or the Gender, Age, Physiology index; improvement in activity, impact, functional capacity, or quality of life (patient-reported outcome measures: SF-36, HAQ-DI, St. George’s Respiratory Questionnaire, King’s Brief Interstitial Lung Disease, etc.)

From the evidence to the recommendations: Interstitial lung disease

**a) Is this problem a priority?**

- Judgement: Yes

**bDMARDs**

*IL-6R inhibitors*

Tocilizumab

**b) What is the magnitude of the expected desirable effects?**

- Judgement: small

**Research-based evidence:**

This review identified one multicentre retrospective observational study<sup>182</sup>, included in an SR<sup>189</sup>, assessing the efficacy and safety of TCZ in treating lung disease in 28 patients with RA-ILD. The following table summarises the results by outcome:

Outcomes	Number of patients tocilizumab	Mean difference in effect 95% CI	Quality and importance of the outcome (GRADE)
<b>FVC</b>			
(1 observational study)	25	3.00 (-7.89 to 13.89) FVC remained stable in 14/25 patients (56%)	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>DLCO (%)</b>			
(1 observational study)	25	1.50 (-9.83 to 12.83) DLCO remained stable in 14/25 patients (56%)	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>No progression on HRCT</b>			
(1 observational study)	25	0.929 (0.765 to 0.991) No progression on HRCT. p<0.001	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>Explanations:</b>			
a) No control group. Not controlled for possible confounders.			
b) CI crossed the line of no effect. Small sample size.			

- **Other considerations:**

The review identified a study of 55 patients with RA-ILD in which TCZ also did not accelerate ILD progression, KL-6 levels decreasing significantly at 6 months<sup>183</sup>. Another study assessed the impact of SAR therapy, showing stability on lung CT in 85.7% of patients. Levels of KL-6 remained stable or improved in the majority of patients, and no serious adverse events were recorded<sup>184</sup>.

### Abatacept

#### **b) What is the magnitude of the expected desirable effects?**

- **Judgement:** small

#### **Research-based evidence:**

The review identified two observational studies assessing the efficacy and safety of ABA in treating RA-ILD<sup>185, 186</sup>. The following table summarises the overall results by outcome:

Outcomes	Usual interstitial pneumonia	Non-specific interstitial pneumonia	Change from baseline to 12 months	Mean change from baseline to end of follow-up	Quality and importance of the outcome (GRADE)
<b>FVC</b>					
<u>FVC improvement</u> (1 study, n=190)	15%	15%			⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<u>FVC stabilisation</u> (1 study, n=190)	67%	63%			
<u>FVC &lt; 80% (%)</u> (1 study, n=57)			22 (43.1%) p=0.690	27 (47.3%); p=0.202	
<u>FVC ≥ 80% (%)</u> (1 study, n=57)			29 (56.8%); p=0.690	30 (52.6%); p=0.202	
<u>Estimated FVC, mean (SD)</u> (1 study, n=57)			76.3 (16.1); p=0.990	75.7 (14.4); p=0.883	
<b>DLCO</b>					
<b>DLCO improvement</b> (1 study, n=190)	13%	17%			⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>DLCO stabilisation</b> (1 study, n=190)	81%	80%			
<b>Predicted DLCO %, mean (SD)</b> (1 study, n=57)			60.6 (16); p=0.340	59.7 (15.7); p=0.133	

Outcomes	Usual interstitial pneumonia	Non-specific interstitial pneumonia	Change from baseline to 12 months	Mean change from baseline to end of follow-up	Quality and importance of the outcome (GRADE)
<b>HRCT</b>					
HRCT stabilisation (1 study, n=190)	52 (59.6%)	48 (52.1%)			⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
HRCT stabilisation (1 study, n=57)			35 (68.6%)	39 (68.4%)	
HRCT improvement (1 study, n=57)			10 (19.6%)	13 (22.8%)	
HRCT progression (1 study, n=57)			10 (19.6%)	13 (22.8%)	
<b>Infections</b>					
(1 study, n=190)	8	7			⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
(1 study, n=57)			25 (43.9%)		
<b>Death</b>					
(1 study, n=190)	3	0			⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
(1 study, n=57)			3 (5.2%)		
<b>Explanations:</b>					
a) No control group. Not controlled for possible confounders.					
b) CI crossed the line of no effect. Small sample size.					

The review also identified an SR and meta-analysis<sup>189</sup> assessing the efficacy of biologics (ABA; RTX, TCZ), JAK inhibitors, and TNF inhibitors in patients with RA-ILD, as monotherapy or in combination with csDMARDs or immunosuppressants. The following table shows the overall results of the studies that included ABA, distributed by outcome.

Outcomes	Number of patients abatacept	Mean difference in effect (95% CI)	Quality and importance of the outcome (GRADE)
<b>FVC</b>			

(3 studies)	243	0.37 (-2.29 to 3.03)	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>DLCO (%)</b>			
(3 studies)	221	-0.65 (-3.58 to 2.28)	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>No progression on HRCT</b>			
(3 studies)	-	0.804 (0.747 to 0.856) No progression on HRCT. P<0.001	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>Death due to disease progression</b>			
(1 study)	-	0.008 (0.001 to 0.027) Death due to disease progression. P<0.001	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>Explanations:</b> a) No control group. Not controlled for possible confounders b) CI that crosses the line of no effect. Small sample size			

- **Other considerations:**

The SR<sup>189</sup> included one study<sup>187</sup> assessing the efficacy of ABA in patients with RA-ILD. After 1 year of treatment, Shoda et al.<sup>187</sup> observed significant improvement in RA disease activity indices, as well as a reduction in ground-glass opacities in patients with UIP-like and non-UIP-like patterns. Further, in the UIP-like group, there was a reduction in total fibrosis score, while FVC remained stable.

#### *Rituximab*

##### **b) What is the magnitude of the expected desirable effects?**

- **Judgement:** small

#### **Research-based evidence**

The review identified an SR and meta-analysis based on 15 studies, including 314 patients<sup>188</sup>. It also identified an SR that conducted the same analysis based on eight studies<sup>189</sup>. The following table summarises the results by outcome.

Outcomes	Number of patients rituximab	Mean difference in effect (95% CI)	Quality and importance of the outcome (GRADE)
<b>FVC</b>			
(3 studies)	-	7.43 (1.14 to 13.72) p=0.02	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup>
(7 studies)	121	-4.62 (-8.90 to -0.33) FVC remained stable in 14/25 patients (56%)	Critical
<b>DLCO (%)</b>			
(3 studies)	55	6.39 (-1.66 to 14.43) p=0.12	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup>
(5 studies included in sensitivity analysis)	77	0.01 (-4.16 to 4.17) p=0.79	Critical
<b>Stabilisation or improvement of RA-ILD (proportion of patients)</b>			
(4 studies)	-	0.85 (0.62 to 0.99) P<0.001	
<b>No progression on HRCT</b>			
(5 studies)	-	0.661 (0.542 to 0.773) No progression on HRCT. p<0.001	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>Explanations:</b> a) No control group. Not controlled for possible confounders b) CI that crosses the line of no effect. Small sample size			

- **Other considerations:**

Boppana et al. conducted a sensitivity analysis on the effects of RTX considering only studies that reported data on patients with RA-ILD separately<sup>188</sup>. Two outcomes were analysed: the percentage of patients in whom lung function stabilised or improved and mean change in FVC, data that have been included in the table. In the meta-analysis of Yuan et al., the sensitivity analysis was only performed for mean change in DLCO<sup>189</sup>.

### JAK inhibitors

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** small

**Research-based evidence**

The review identified 1 observational study assessing the efficacy and safety of JAK inhibitors in 43 patients with RA-ILD<sup>193</sup>. The following table summarises the overall results by outcome:

Outcomes	Number of patients JAK inhibitors	Mean difference in effect (95% CI)	Quality and importance of the outcome (GRADE)
<b>FVC</b>			
(1 study)	43	(FVC data only available for 28 of 43 patients) FVC was stable in 22 (78.57%) patients, improved in 3 (10.71%), and worsened in 3 (10.71%). Mean difference from baseline: 3.39% ±11.18; p=0.12	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>DLCO (%)</b>			
(1 study)	43	(DLCO data only available for 25 of 43 patients) DLCO was stable in 18 (72%) patients, improved in 2 (8%) and worsened in 5 (20%). Mean difference from baseline (reduction): 3.44% ±7.18; p=0.02	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>HRCT</b>			
(1 study)	43	(HRCT data available for all patients) HRCT was stable in 37 (86.05%) patients, improved in 2 (4.65%) and worsened in 4 (9.30%). Mean difference from baseline: 3.39%±11.18; p=0.12	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>Explanations:</b> a) Retrospective study. No control group. b) The results are presented only with p-values; no CIs are reported. Small sample size			

Tofacitinib

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** small

**Research-based evidence**

The review identified 1 observational study assessing the efficacy and safety of TOF in 47 patients with RA-ILD, compared to 387 patients with RA not diagnosed with ILD<sup>191</sup>. The following table summarises the overall results by outcome:

Outcomes	Number of patients		Improvement in effect (%)	Quality and importance of the outcome (GRADE)
	RA-ILD	RA but not ILD		
<b>FVC</b>				
(1 study)	47	387	(FVC% and FEV1% data available for 22 patients before the treatment and 18 patients before and after the treatment)  Pre- and post-treatment FVC% respectively: 79.83% and 82.78%, P=0.014  Pre- and post-treatment FEV1% respectively: 82.11% and 82.84%, P=0.079	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>Safety</b>				
(1 study)	47	387	Infections: 25 % Worsening respiratory function: 10%	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>Explanations:</b> a) Retrospective study. No control group b) The results are presented only with p-values; no CIs are reported. Small sample size.				

### JAK inhibitors vs. abatacept

#### **b) What is the magnitude of the expected desirable effects?**

- **Judgement:** small

#### **Research-based evidence:**

The review identified three observational studies assessing the efficacy and safety of JAK inhibitors compared to ABA in treating lung disease in patients with RA-ILD. The studies included 75, 30 and 61 patients followed up for 18, 12 and 24 months, respectively<sup>196,194,192</sup>. The following table summarises the overall results by outcome:

Outcomes	Number of patients		Effect Mean and standard deviation	Absolute effect	Quality and importance of the outcome (GRADE)
	JAK inhibitors	Abatacept			

<b>FVC</b>					
(1 study)	31	44	Pre ABA*: 82.29±4.86 Post ABA*: 81.24±11.97; p=0.59  Pre JAK inhibitors*: 81.18±5.07 Post JAK inhibitors *: 79.59±14.02; p=0.55	-	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>DLCO</b>					
(1 study)	31	44	Pre ABA*: 58.69±8.24 Post ABA*: 61.26±11.23; p=0.22  Pre JAK inhibitors *: 59.72±8.56 Post JAK inhibitors *: 62.75±11.84; p=0.28	-	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>HRCT</b>					
(1 study)	31	44	Extent of fibrosis (%) Pre ABA*: 19.41±5.89 Post ABA*: 18.94±6.06; p=0.71  Pre JAK inhibitors *: 18.54±6.31 Post JAK inhibitors *: 17.52±6.35; p=0.53	Extent of fibrosis > 20%: Lower in ABA group: -0.043 (-142.2 lower to 355.1 higher)	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
(1 study)	11	19	ILD progression in 2 (10.5%) patients treated with ABA vs. 2 (18.2%) patients treated with JAK inhibitors; p=0.611	Lower risk of ILD progression with ABA vs JAK inhibitors: 0.077 (-164.7 lower to 463.9 higher)	
(1 study)	21	21	-After JAK inhibitor therapy: - GGO score improved. Data available for only 8 patients, p=0.03 - Fibrosis score did not change. Data available for only 8 patients, p=0.82  After ABA therapy: - GGO score did not change. Data available for only 7 patients, p=0.87 - Fibrosis score did not change. Data available for only 7 patients, p=0.78	-	
<b>All adverse events</b>					
(1 study)	5 (23.8%)	4 (19%)		Fewer events in the ABA group -0.048 (-116.4 fewer to 574.7 more)	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
<b>Infections</b>					
(1 study)	2 (9.5%)	0		-0.095 (not available)	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical

\* mean  $\pm$  standard deviation

**Explanations:**

- a) Retrospective study. No control group. Not controlled for possible confounders. No tests performed to assess the significance of between-group differences in patient baseline characteristics.
- b) The results are presented only with p-values; no CIs are reported. Small sample size.

JAK inhibitors vs. rituximab

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** small

**Research-based evidence**

The review identified one observational study assessing the safety of JAK inhibitors compared to RTX<sup>190</sup>. It compared 28 patients receiving JAK inhibitors with 19 receiving RTX. The following table summarises the overall results by outcome:

Outcomes	Number of patients		Relative effect (95% CI)	Absolute effect (95% CI)	Quality and importance of the outcome (GRADE)
	JAK inhibitors	RTX			
<b>Survival</b>					
(1 study)	26	17	Not adjusted HR: 1.38 (0.36 to 5.28); p=0.64	JAK inhibitors vs. RTX: 0.034 fewer per 1,000 (-123.2 fewer to 222.9 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Mortality</b>					
(1 study)	2	2	RR: 0.68 (0.10 to 4.41) Reduction in RR: 0.321 (-3.41 to 0.90)	JAK inhibitors vs. RTX: 0.034 fewer per 1,000 (-94.3 fewer to 358.8 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Explanations:</b>					
<ul style="list-style-type: none"> <li>a) Retrospective study. No control group. Not controlled for possible confounders. No tests performed to assess the significance of between-group differences in patient baseline characteristics.</li> <li>b) CI crossed the line of no effect. Small sample size</li> </ul>					

- **Other considerations:**

Three other studies assessed the risk of incident ILD in patients with RA receiving JAK inhibitors. In one study on TOF<sup>197</sup> and another on BAR<sup>198</sup>, the incidence rates did not exceed those estimated for the general population with RA. In another study, based on more than 28,000 people with RA<sup>190</sup>, TOF was associated with a lower incidence of ILD. After adjusting for covariates, the risk of ILD was 69% lower in patients treated with TOF than those treated with RTX.

Another meta-analysis suggested that JAK inhibitors lead to a modest but significant improvement in PFT results, specifically in FVC and DLCO. Additionally, improvements were seen on pulmonary CT in at least 11% of patients<sup>200</sup>.

**c) What is the overall certainty of the evidence on the effects?**

- **Judgement:** low/very low

The quality of the evidence was rated as low or very low for the observational studies without a comparator, the majority not controlling for possible confounding factors and having small sample sizes.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence indicates that ABA, RTX, IL-6R inhibitors and JAK inhibitors are safe for controlling RA-ILD.

**Antifibrotics**

*Nintedanib, pirfenidone*

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** small

**Research-based evidence**

The review identified one SR<sup>381</sup> assessing the efficacy and safety of antifibrotics in patients with RA-ILD based on two observational studies<sup>201,203</sup>. Another observational study was identified

that included 74 patients (40 patients treated with NTB and 34 with PFN)<sup>204</sup>. The following table summarises the results by outcome:

Outcome	Number of patients		Relative effect (95% CI)	Absolute effect (95% CI)	Quality and importance of the outcome (GRADE)
	Nintedanib	Pirfenidone			
<b>Patients with a FVC reduction <math>\geq 10\%</math></b>					
(2 studies)	5/42	5/63	Nintedanib: OR: 0.29 (0.09 to 0.88)  Pirfenidone: OR: 0.65 (0.20 to 2.18)	Nintedanib: 627 fewer per 1,000 (from 272 fewer to 20 more)  Pirfenidone: 37 fewer per 1,000 (from 90 fewer to 120 more)	⊕⊕⊕⊖ MODERATE Critical
<b>Slowing of FVC decline</b>					
(1 study)	27/40	22/34	-	28 more per 1,000 (from 161 fewer to 290 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Mortality (all causes)</b>					
(2 studies)	7/42	2/63	Nintedanib: RR: 0.87 (0.36 to 2.13)  Pirfenidone: RR: 0.63 (0.11 to 3.67)	Nintedanib: 25 fewer per 1,000 (from 123 fewer to 217 more) Pirfenidone: 18 fewer per 1,000 (from 45 fewer to 133 more)	⊕⊕⊕⊖ MODERATE Critical
<b>Risk of lung transplant or death (overall)</b>					
(1 study)	-	-	Nintedanib HR: 1.03 (0.46 to 2.29)  Pirfenidone HR: 1.0 (NI)	-	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Serious adverse events</b>					
(2 studies)	26/42	10/63	Nintedanib: RR: 1.00 (0.72 to 1.39)  Pirfenidone: RR: 1.21 (0.51 to 2.86)	Nintedanib: 2 more per 1,000 (from 170 fewer to 242 more)  Pirfenidone: 28 more per 1,000 (from 65 fewer to 248 more)	⊕⊕⊕⊖ MODERATE Critical

(1 study)	11/13	8/11	-	119 more per 1,000 (between 177 fewer to 573 more)
<p><b>Explanations:</b></p> <p>a) Retrospective study. No control group. Not controlled for possible confounders. No tests performed to assess the significance of between-group differences in patient baseline characteristics.</p> <p>b) The CI crosses the line of no effect: Small sample size</p>				

- **Other considerations:**

The 2023 ACR and CHEST guidelines conditionally recommend PFN as a second-line therapeutic option in patients with progressive RA-ILD who do not respond to first-line treatment<sup>381</sup>.

Other observational studies have provided complementary data on the efficacy and safety of antifibrotics in clinical practice. Real-world studies have shown stabilisation and even improvements in this parameter<sup>197, 206</sup>. Another study<sup>207</sup> reported stabilisation of lung function at 6 months, with non-significant improvement in FVC, whereas another study<sup>381</sup> described an initial stabilisation of FVC at 6 months, followed by a modest improvement at 1 year, while there was a non-significant reduction in DLCO. Similarly, it has been reported that the antifibrotic treatment stopped FVC decline, while there was a slight downward trend in DLCO<sup>208</sup>. All four studies found that the FVC changes were similar with NTB and PFN.

These observational studies confirm the safety of antifibrotics combined with glucocorticoids, csDMARDs/immunosuppressants (LEF, MTX or MMF), as well as biologics, mainly ABA and RTX, or JAK inhibitors.

Finally, two studies suggest that switching to PFN may be a feasible alternative in patients with intolerance to NTB, although evidence is from only 19 cases, and in 13 (68.4%) of these cases, the second antifibrotic treatment was continued successfully<sup>202, 204</sup>.

**c) What is the overall certainty of the evidence on the effects?**

- **Judgement:** Moderate/very low

The quality of the evidence was rated as moderate for the outcome variables assessed in RCTs and very low for those based on observational studies with no comparator group and small sample sizes, and in which the analysis is not controlled for possible confounders.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence indicates that NTB is efficacious for treating RA-ILD, in that it shows a significant reduction in the annual rate of FVC decline. In the case of PFN, the results suggest it may be a suitable alternative in patients intolerant to NTB.

**Other immunosuppressants**

*Leflunomide*

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible

**Research-based evidence:**

The review identified 1 multicentre prospective observational study assessing the effectiveness and safety of LEF in relation to RA-ILD progression based on 26 patients<sup>209</sup>. The following table summarises the overall results by outcome:

Outcomes	Number of patients		Relative effect (95% CI)	Absolute effect (95% CI)	Quality and importance of the outcome (GRADE)
	LEF	No LEF			
<b>FVC ≥70% and DLCO ≥60%</b>					
(1 study)	11/16	33/48	Adjusted HR: 1.17 (0.58 to 2.35), p= 0.007	<0.001 more per 1,000 (-218 fewer to 319.3 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>FVC &lt;70% or DLCO &lt;60%</b>					
(1 study)	5/16	15/48	Adjusted HR: 8.42 (2.61 to 27.15), p= 0.007	<0.001 more per 1,000 (-177.5 fewer to 410.8 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Extent of ILD involvement on HRCT &lt;10%</b>					

(1 study)	8/16	24/48	Adjusted HR: 1.66 (0.70 to 3.93), p= 0.616	<0.001 more per 1,000 (-216 fewer to 380.4 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Extent of ILD involvement on HRCT 10–30%</b>					
(1 study)	6/16	13/48	Adjusted HR: 2.51 (0.90 to 6.98), p= 0.616	0.104 fewer per 1,000 (-99.7 fewer to 551 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Extent of ILD involvement on HRCT &gt; 30%</b>					
(1 study)	2/16	11/48	Adjusted HR: 9.05 (1.06 to 77.46), p= 0.616	0.104 more per 1,000 (-198.2 fewer to 276 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Fibrosis score &lt; 12 on HRCT</b>					
(1 study)	8/16	26/48	Adjusted HR: 1.60 (0.69 to 3.71), p= 0.338	0.042 more per 1,000 (-255 fewer to 329 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Fibrosis score ≥12 on HRCT</b>					
(1 study)	8/16	22/48	Adjusted HR: 3.15 (1.31 to 7.57), p= 0.338	0.042 fewer per 1,000 (-178 fewer to 433.3 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Abbreviations</b>					
DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; ILD: interstitial lung disease; LEF: leflunomide; HR: hazard ratio; HRCT: high-resolution computed tomography. HR adjusted for age, sex and 28-item Disease Activity Score calculated with erythrocyte sedimentation rate ILD was considered to have progressed if patients met ≥1 of the following criteria: FVC decline ≥10%, DLCO decline ≥15%, and/or death due to ILD and/or pneumonia					
<b>Explanations:</b>					
a) Retrospective study. No control group. Not controlled for possible confounders. No tests performed to assess the significance of between-group differences in patient baseline characteristics. b) The CI crossed the line of no effect or was very wide. Small sample size.					

## MTX

### b) What is the magnitude of the expected desirable effects?

- **Judgement:** negligible

### Research-based evidence:

The same study assessed the effectiveness and safety of MTX in relation to ILD progression<sup>209</sup>.

The following table summarises the overall results by outcome.

Outcomes	Number of patients		Relative effect (95% CI)	Absolute effect (95% CI)	Quality and importance of the outcome (GRADE)
	MTX	No MTX			
<b>ILD progression (%)</b>					
(1 study)	27/61 (44.3%)	37/82 (45.1%)	Non-adjusted HR: 0.84 (0.51 to 1.39) Adjusted HR: 1.06 (0.59 to 1.89)	0.009 fewer per 1,000 (from -145.2 fewer to 189.1 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<p><b>Abbreviations</b> ILD: interstitial lung disease; MTX: methotrexate; HR: hazard ratio. ILD was considered to have progressed if patients met ≥1 of the following criteria: FVC decline ≥10%, DLCO decline ≥15%, and/or death due to ILD and/or pneumonia</p> <p><b>Explanations:</b> a) Retrospective study. No control group. Not controlled for possible confounders. No tests performed to assess the significance of between-group differences in patient baseline characteristics. b) CI that crosses the line of no effect. Small sample size.</p>					

### Tacrolimus

#### b) What is the magnitude of the expected desirable effects?

- **Judgement:** negligible

#### Research-based evidence:

The same study assessed the effectiveness and safety of tacrolimus in relation to ILD progression<sup>209</sup>. The following table summarises the overall results by outcome:

Outcomes	Number of patients		Relative effect (95% CI)	Absolute effect (95% CI)	Quality and importance of the outcome (GRADE)
	Tacrolimus	No tacrolimus			
<b>ILD progression (%)</b>					
(1 study)	22/56 (39.3%)	42/87 (48.3%)	Non-adjusted HR: 0.66 (0.39 to 1.12) Adjusted HR: 0.94 (0.52 a 1.72)	<0.001 fewer 1,000 (from -144 fewer to 229.8 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical

**Abbreviations**

ILD: interstitial lung disease; HR: hazard ratio.

ILD was considered to have progressed if patients met  $\geq 1$  of the following criteria: FVC decline  $\geq 10\%$ , DLCO decline  $\geq 15\%$ , and/or death due to ILD and/or pneumonia

**Explanations:**

a) Retrospective study. No control group. Not controlled for possible confounders. No tests were performed to assess the significance of between-group differences in patient baseline characteristics.

b) CI crossed the line of no effect. Small sample size.

- **Other considerations:**

The 2023 ACR/CHEST guidelines also prefer the use of MMF as the immunosuppressant of choice<sup>205</sup>. Nonetheless, there are not yet any data from RCTs supporting its use in RA-ILD, and the evidence available remains scarce. One study described functional and radiological improvements in a series of three patients<sup>210</sup>. Another study reported greater all-cause and respiratory mortality in patients treated with CZP or AZA than those treated with MMF<sup>211</sup>. Lastly, a study comparing AZA and MMF in patients with fibrosing connective tissue disease-related ILD, including 15 with RA-ILD, found that lung function remained stable over time in both groups<sup>212</sup>.

**c) What is the overall certainty of the evidence on the effects?**

- **Judgement:** Very low

The quality of the evidence was rated as very low for observational studies without a comparator, most of which did not control for confounding factors and had small sample sizes.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

Please consult the previously published recommendations on ILD developed by the SER research unit, available in Appendix 2 of this guideline and on the SER website.

## EtD Question 4. Cardiovascular comorbidity

### In patients with RA, what is the risk of cardiovascular events and thromboembolic disease associated with bDMARDs and tsDMARDs?

Patient: adults ( $\geq 18$  years old) diagnosed with RA (2010 ACR/EULAR criteria)

Intervention: pharmacological treatments with bDMARDs: TNF inhibitors (IFX, ETN, ADA, CZP, GOL); IL-6R inhibitors (TCZ, SAR); RTX; ABA; tsDMARDs (JAK inhibitors): TOF, BAR, UPA, or FIL.

Comparison: csDMARDs; bDMARDs; JAK inhibitors.

Outcomes: MACE (onset of cardiovascular events): acute MI, stroke, heart failure, unstable angina with or without the need for coronary revascularisation; thromboembolism including pulmonary embolism; venous or arterial thrombosis; cardiovascular mortality; hospitalisation due to heart failure; coronary revascularisation.

### From the evidence to the recommendations: Cardiovascular comorbidity

#### a) Is this problem a priority?

- Judgement: Yes

#### bDMARDs

#### bDMARDs vs csDMARDs

#### b) What is the magnitude of the expected desirable effects?

- Judgement: negligible

#### Research-based evidence:

The review identified three SRs assessing the safety of bDMARDs in patients with RA<sup>264-266</sup>. The following table summarises the overall results by outcome:

Outcomes	Study event rates (%)		Effect		Quality and importance of the outcome (GRADE)
	With csDMARDs	With bDMARDs	Relative effect (95% CI)	Difference in risk	
<b>MACE</b>					
(5 non-randomised studies; n= 59,804)	1,583/25,254 (6.3%)	1,060/34,550 (3.1%)	<b>RR 0.97</b> (0.66 to 1.44)	<b>2 fewer per 1,000</b> (from 21 fewer to 28 more)	⊕⊕⊕⊕ VERY LOW <sup>a,b,c,d</sup> Critical

Outcomes	Study event rates (%)		Effect		Quality and importance of the outcome (GRADE)
	With csDMARDs	With bDMARDs	Relative effect (95% CI)	Difference in risk	
<b>Myocardial infarction</b>					
(7 non-randomised studies, 11 RCTs; n= 76,034)	243/26,524 (0.9%)	395/49,510 (0.8%)	<b>OR 0.74</b> (0.63 to 0.87)	<b>2 fewer per 1,000</b> (from 3 fewer to 1 more)	⊕⊕⊕⊖ LOW <sup>a,d,e</sup> Critical
<b>Stroke</b>					
(4 non-randomised studies; n= 56,732)	266/21,183 (1.3%)	391/35,549 (1.1%)	<b>OR 0.90</b> (0.73 to 1.11)	<b>1 fewer per 1,000</b> (from 3 fewer to 1 more)	⊕⊕⊕⊖ VERY LOW <sup>a,c,d</sup> Critical
<b>Congestive heart failure</b>					
(7 non-randomised studies, 7 RCTs; n= 57,313)	679/28,688 (2.4%)	406/28,625 (1.4%)	<b>OR 0.83</b> (0.73 to 0.95)	<b>4 fewer per 1,000</b> (from 6 fewer to 1 fewer)	⊕⊕⊕⊖ LOW <sup>a,f</sup> Critical
<b>Thromboembolism/Pulmonary embolism</b>					
(1 non-randomised study; n= 130,502)	316/92,509 (0.3%)	165/37,993 (0.4%)	<b>HR 1.10</b> (0.91 to 1.34)	<b>0 fewer per 1,000</b> (from 0 fewer to 1 more)	⊕⊕⊕⊖ VERY LOW <sup>a,c</sup> Critical
<b>Deep vein thrombosis</b>					
(1 non-randomised study; n= 130,502)	509/92,509 (0.6%)	263/37,993 (0.7%)	<b>HR 1.13</b> (0.97 to 1.32)	<b>1 more per 1,000</b> (from 0 fewer to 2 more)	⊕⊕⊕⊖ VERY LOW <sup>a,c</sup> Critical
<b>Cardiovascular mortality</b>					
(4 non-randomised studies, 7 RCTs; n= 22,997)	42/9,636 (0.4%)	30/13,361 (0.2%)	<b>OR 0.60</b> (0.38 to 0.96)	<b>2 fewer per 1,000</b> (from 3 fewer to 0 fewer)	⊕⊕⊕⊖ MODERATE/LOW <sup>a</sup> Critical
<p><b>Abbreviations</b> bDMARDs: biological disease-modifying drug; csDMARDs: conventional synthetic disease-modifying drug; HR: hazard ratio; OR: odds ratio; RCT: randomised controlled trial.</p> <p><b>Explanations</b> a. High risk of bias: the body of the evidence comes from non-randomised studies. b. Heterogeneity among studies, with conflicting estimates in the visual analysis and an <math>I^2 = 96\%</math> c. Imprecision: wide 95% CIs that include values compatible with benefit, no effect and harm d. Possible publication bias: asymmetry in the funnel plot.</p>					

Outcomes	Study event rates (%)		Effect		Quality and importance of the outcome (GRADE)
	With csDMARDs	With bDMARDs	Relative effect (95% CI)	Difference in risk	
e. Heterogeneity among studies. No overlap of the CIs from some studies in the visual analysis, with an $I^2 = 31\%$ .					
f. Heterogeneity among studies. No overlap of the CIs from some studies in the visual analysis, with an $I^2 = 41\%$ .					

### TNF inhibitors vs. other bDMARDs

The review identified one SR<sup>266</sup> assessing the safety of TNF inhibitors compared to TCZ in patients with RA based on one non-randomised study<sup>271</sup>. The following table summarises the results by outcome:

Outcomes	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With other bDMARDs	With TNF inhibitors	Relative effect (95% CI)	Difference in risk	
<b>Major adverse cardiac events</b>					
(1 non-randomised study; n= 48,018)	104/8,045 (1.3%)	600/39,973 (1.5%)	<b>HR 1.27</b> (1.02 to 1.59)	<b>3 more per 1,000</b> (from 0 fewer to 8 more)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<b>Acute myocardial infarction</b>					
(1 non-randomised study; n= 48,186)	56/8,073 (0.7%)	308/40,113 (0.8%)	<b>HR 1.20</b> (0.88 to 1.62)	<b>1 fewer per 1,000</b> (from 1 fewer to 4 more)	⊕⊕⊕⊖ VERY LOW <sup>a,b</sup> Critical
<b>Stroke</b>					
(1 non-randomised study; n= 48,256)	50/8,083 (0.6%)	275/40,173 (0.7%)	<b>HR 1.25</b> (0.90 to 1.73)	<b>2 more per 1,000</b> (from 1 fewer to 4 more)	⊕⊕⊕⊖ VERY LOW <sup>a,b</sup> Critical
<b>Abbreviations</b> bDMARDs: biological disease-modifying drug; CI: confidence interval; HR: hazard ratio; TNF: tumour necrosis factor.					
<b>Explanations</b> a. High risk of bias: the body of evidence comes from non-randomised studies. b. Imprecision: wide 95% CIs that include values compatible with benefit, no effect and harm					

- **Other considerations:**

German (RABBIT) and French national registries and large studies based on databases from American insurance companies (STAR-RA) have not shown differences in the development of cardiovascular and thromboembolic events between csDMARDs and bDMARDs<sup>267-269</sup>.

**c) What is the overall certainty of the evidence on the effects?**

**Judgement:** Low/very low

The quality of the evidence was rated as low or very low, given that the body of evidence comes mainly from non-randomised studies, also due to imprecision, associated with the 95% CIs crossing the line of no effect or threshold of clinical significance, heterogeneity among studies and potential publication bias.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence indicates that bDMARDs are as safe as csDMARDs.

IL-6R inhibitors

*Tocilizumab vs. etanercept*

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible.

**Research-based evidence:**

The review identified one SR<sup>266</sup> assessing the safety of TCZ compared to ETN in patients with RA based on one RCT<sup>246</sup>. The following table summarises the results by outcome:

Outcomes	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With etanercept	With tocilizumab	Relative effect (95% CI)	Difference in risk	
<b>Major adverse cardiac events</b>					
(1 RCT, n= 3,080)	78/1,542 (5.1%)	81/1,538 (5.3%)	<b>HR 1.05</b> (0.77 to 1.43)	<b>2 more per 1,000</b> (from 11 fewer to 21 more)	⊕⊕⊕⊖ MODERATE <sup>a,b</sup> Critical
<p><b>Abbreviations:</b> CI: confidence interval; HR: hazard ratio.</p> <p><b>Explanations</b></p> <p>a. High risk of bias: participants and healthcare providers not blinded to the assigned intervention.</p> <p>b. Imprecision: wide 95% CIs that include values compatible with benefit, no effect and harm.</p>					

*Tocilizumab vs. TNF inhibitors*

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible

**Research-based evidence:**

The review identified one SR<sup>270</sup> assessing the safety of TCZ compared to TNF inhibitors in patients with RA based on two non-randomised studies<sup>272,273</sup>. The following table summarises the results by outcome:

Outcomes	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With TNF inhibitors	With TCZ	Relative effect (95% CI)	Difference in risk	
<b>Major adverse cardiac events</b>					
(2 non-randomised studies, n= 29,780)	132/19,896 (0.7%)	30/9,884 (0.3%)	<b>OR 0.59</b> (0.34 to 1.00)	<b>3 fewer per 1,000</b> (from 4 fewer to 0 fewer)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Stroke</b>					
(2 non-randomised studies, n= 29,780)	Not reported	Not reported	<b>OR 0.98</b> (0.59 to 1.61)	<b>0 fewer per 1,000</b> (from 3 fewer to 4 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
Explanations a. High risk of bias: body of the evidence comes from non-randomised studies b. Imprecision: wide 95% CIs that include values compatible with benefit, no effect and harm.					

- **Other considerations:**

The results of a study analysing data from the Swedish registry of patients with RA were similar in that the risk of thromboembolic events was not higher in patients receiving IL-6R inhibitors (TCZ or SAR) than in those receiving other bDMARDs<sup>274</sup>.

**c) What is the overall certainty of the evidence regarding the effects?**

- **Judgement:** moderate/very low

The quality of the evidence was rated as moderate in the case of the ENTRACTE study, an RCT whose primary objective was to assess safety, and very low in the case of non-randomised studies. All the studies have imprecision bias, with wide 95% CIs and a small number of events.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence indicates that TCZ is as at least as safe as TNF inhibitors, in relation to the risk of cardiovascular/thromboembolic events.

Rituximab

*Rituximab vs tocilizumab*

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible

**Research-based evidence**

The review identified one SR<sup>266</sup> assessing the safety of RTX compared to TCZ in patients with RA based on two non-randomised studies<sup>271, 275</sup>. The following table summarises the results by outcome:

Outcome	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With TCZ	With RTX	Relative effect (95% CI)	Difference in risk	
<b>Major adverse cardiac events</b>					
(1 non-randomised study, n= 14,382)	104/8,045 (1.3%)	105/6,337 (1.7%)	<b>HR 1.16</b> (0.89 to 1.53)	<b>2 more per 1,000</b> (from 1 fewer to 7 more)	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
(1 non-randomised study, n= 1,207)	7/761 (0.9%)	11/446 (2.5%)	<b>HR 2.44</b> (1.39 to 4.35)		⊕⊕⊕⊕ <u>MODERATE/LOW</u> <sup>a,b</sup> Critical
<b>Acute myocardial infarction</b>					
(1 non-randomised study, n= 16,716)	56/8073 (0.7%)	52/8,643 (0.6%)	<b>HR 1.05</b> (0.72 to 1.54)	<b>0 fewer per 1,000</b> (from 2 fewer to 4 more)	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical

Outcome	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With TCZ	With RTX	Relative effect (95% CI)	Difference in risk	
(1 non-randomised, n= 1,207)	1/761 (0.1%)	3/446 (0.7%)	<b>HR 8.33</b> (1.79 to 50.00)		⊕⊕⊕⊖ MODERATE/LOW <sup>a,b</sup> Critical
<b>Stroke</b>					
(1 non-randomised study, n= 14,457)	50/8,083 (0.6%)	47/6,374 (0.7%)	<b>HR 1.10</b> (0.74 to 1.63)	<b>1 more per 1,000</b> (from 2 fewer to 4 more)	⊕⊕⊕⊖ VERY LOW <sup>a,b</sup> Critical
(1 non-randomised study, n= 1,207)	5/761 (0.7%)	6/446 (1.3%)	<b>HR 1.85</b> (0.89 to 3.85)		⊕⊕⊕⊖ LOW <sup>a,b,c</sup> Critical
<b>Congestive heart failure</b>					
(1 non-randomised study, n= 1,207)	3/761 (0.4%)	3/446 (0.7%)	<b>HR 2.08</b> (0.76 to 5.56)		⊕⊕⊕⊖ LOW <sup>a,b,c</sup> Critical
<b>Cardiovascular mortality</b>					
(1 non-randomised study, n= 1,207)	1/761 (0.1%)	1/446 (0.3%)	<b>HR 1.35</b> (0.31 to 5.88)		⊕⊕⊕⊖ LOW <sup>a,b,c</sup> Critical
Explanations a. High risk of bias: the body of the evidence comes from non-randomised studies. b. Imprecision: wide 95% CIs that include values compatible with benefit, no effect and harm. c. Indirect evidence: patients included were required to have been exposed to TNF inhibitors.					

### c) What is the overall certainty of the evidence on the effects?

- **Judgement:** moderate/low/very low

The quality of the evidence was rated as moderate or low for some outcome variables, and very low for others, given that the body of evidence comes from non-randomised studies and also due to imprecision, associated with wide 95% CIs. Further, it should be noted that some of the patients had been exposed to TNF inhibitors previously, and hence, the effects observed may have been influenced by these earlier treatments.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence indicates no significant difference between RTX and TCZ in relation to the risk of cardiovascular/thromboembolic events.

Abatacept

*Abatacept vs. TNF inhibitors*

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible

**Research-based evidence:**

The review identified three SR<sup>264, 270</sup> assessing the safety of ABA compared to TNF inhibitors in patients with RA based on non-randomised studies (two<sup>276, 277</sup>, three<sup>278-280</sup> and one<sup>271</sup>, respectively). The following table summarises the results by outcome:

Outcomes	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With TNF inhibitors	With ABA	Relative effect (95% CI)	Difference in risk	
<b>Major adverse cardiac events</b>					
(5 non-randomised studies, n= 87189)	1424/59,313 (2.4%)	578/27,876 (2.1%)	<b>OR 0.98</b> (0.88 to 1.09)	<b>0 fewer per 1,000</b> (from 3 fewer to 2 more)	⊕⊕⊕⊕ VERY LOW <sup>a,b,c</sup> Critical
<b>Stroke</b>					
(1 non-randomised study, n> 31,000)	Not reported	Not reported	<b>OR 1.08</b> (0.85 to 1.34)	<b>5 more per 1,000</b> (from 10 fewer to 21 more)	⊕⊕⊕⊕ VERY LOW <sup>a,b</sup> Critical
Explanations a. High risk of bias: the body of evidence comes from non-randomised studies b. Imprecision: wide 95% CIs that include values compatible with benefit, no effect and harm. c. Heterogeneity among the studies, with contradictory estimates in the visual analysis and an I <sup>2</sup> = 89%.					

*Abatacept vs. tocilizumab*

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible

### Research-based evidence:

The review identified one SR<sup>266</sup> assessing the safety of ABA compared to TCZ in patients with RA based on a non-randomised study<sup>271</sup>. The following table summarises the results by outcome:

Outcomes	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With TCZ	With ABA	Relative effect (95% CI)	Difference in risk	
<b>Major adverse cardiac events</b>					
(1 non-randomised study, n= 19,348)	95/7,369 (1.3%)	164/11,979 (1.4%)	<b>HR 1.01</b> (0.79 to 1.28)	<b>0 fewer per 1,000</b> (from 3 fewer to 4 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>AMI</b>					
(1 non-randomised study, n= 19,348)	51/7,369 (0.7%)	87/11,979 (0.7%)	<b>HR 1.01</b> (0.73 to 1.40)	<b>0 fewer per 1,000</b> (from 2 fewer to 3 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Stroke</b>					
(1 non-randomised study, n= 19,348)	46/7,369 (0.6%)	77/11,979 (0.6%)	<b>HR 0.99</b> (0.70 to 1.40)	<b>0 fewer per 1,000</b> (from 2 fewer to 2 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b,c</sup> Critical
Explanations a. High risk of bias: the body of evidence comes from non-randomised studies b. Imprecision: wide 95% CIs that include values compatible with benefit, no effect and harm.					

### c) What is the overall certainty of the evidence regarding the effects?

- **Judgement:** Very low

The quality of the evidence was rated as very low, given that it comes from non-randomised studies, the heterogeneity of studies and imprecision associated with wide 95% CIs even in the case of studies including a large number of patients (comparisons of ABA with TNF inhibitors or TCZ).

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the Table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence indicates that the level of risk is not higher in patients treated with ABA than in those treated with TNF inhibitors, TCZ or RTX.

**JAK inhibitors**

JAK inhibitors vs TNF inhibitors

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible

The review identified one SR<sup>281</sup> assessing the safety of JAK inhibitors compared to TNF inhibitors in patients with RA based on four RCTs<sup>142, 282-284</sup>. The following table summarises the overall results by outcome:

Outcomes	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With TNF inhibitors	With JAK inhibitors	Relative risk (95% CI)	Difference in risk	
<b>Major adverse cardiac events</b>					
(4 RCTs, n= 7229)	46/2,307 (2.0%)	113/4,922 (2.3%)	<b>OR 1.20</b> (0.82 to 1.76)	<b>4 more per 1,000</b> (from 4 fewer to 15 more)	⊕⊕⊖⊖ LOW <sup>a,b</sup> Critical
Explanations a. High risk of bias: the study with the greatest weight was open label (not blinded) b. Imprecision: wide 95% CIs that include values compatible with benefit, no effect and harm.					

*Tofacitinib vs. bDMARDs*

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible

**Research-based evidence:**

The review identified one SR<sup>266</sup> assessing the safety of TOF compared to bDMARDs in patients with RA based on one non-randomised study<sup>285</sup>. The following table summarises the overall results by outcome:

Outcomes	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With bDMARDs	With TOF	Relative effect (95% CI)	Difference in risk	
<b>Major adverse cardiac events</b>					
(1 non-randomised study, n= 10,357)	108/8,358 (1.3%)	19/1,999 (1.0%)	<b>HR 0.61</b> (0.34 to 1.06)	<b>5 fewer per 1,000</b> (from 9 fewer to one more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
Explanations a. High risk of bias: the study with the greatest weight in the meta-analysis was open label (not blinded) b. Imprecision: Wide 95% CIs that include values compatible with benefit, no effect and harm.					

### Tofacitinib vs. TNF inhibitors

#### b) What is the magnitude of the expected desirable effects?

- **Judgement:** negligible

#### Research-based evidence:

The review identified one SR<sup>266</sup> assessing the safety of TOF compared to bDMARDs in patients with RA based on one non-randomised study<sup>328</sup>. The following table summarises the overall results by outcome:

Outcome	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With TNF inhibitors	With TOF	Relative effect (95% CI)	Difference in risk	
<b>AMI</b>					
(1 non-randomised study, n= 101,993)	561/89,411 (0.6%)	88/12,582 (0.7%)	<b>HR 1.04</b> (0.82 to 1.33)	<b>0 fewer per 1,000</b> (from 1 fewer to 2 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Stroke</b>					
(1 non-randomised study, n= 101,993)	307/89,411 (0.3%)	44/12,582 (0.3%)	<b>HR 0.93</b> (0.66 to 1.31)	<b>0 fewer per 1,000</b> (from 1 fewer to 1 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Congestive heart failure</b>					
(1 non-randomised study,	354/89,411 (0.4%)	58/12,582 (0.5%)	<b>HR 1.07</b> (0.79 to 1.46)	<b>0 fewer per 1,000</b> (from 1 fewer to 2 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical

Outcome	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With TNF inhibitors	With TOF	Relative effect (95% CI)	Difference in risk	
n= 101,993)					
<b>Pulmonary embolism</b>					
(1 non-randomised study, n= 87,653)	365/80,879 (0.5%)	29/6,774 (0.4%)	<b>HR 1.13</b> (0.77 to 1.65)	<b>1 more per 1,000</b> (from 1 fewer to 3 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
<b>Coronary revascularisation</b>					
(1 non-randomised study, n= 101,993)	453/89,411 (0.5%)	59/12,582 (0.5%)	<b>HR 1.04</b> (0.78 to 1.40)	<b>0 fewer per 1,000</b> (from 1 fewer to 2 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Important
Explanations a. High risk of bias: the body of evidence comes mainly from non-randomised studies b. Imprecision: wide 95% CIs that include values compatible with benefit, no effect and harm.					

### *Tofacitinib vs. adalimumab*

#### **b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible

#### **Research-based evidence:**

The review identified one SR<sup>266</sup> assessing the safety of TOF compared to ADA in patients with RA based on one RCT<sup>142</sup>. The following table summarises the overall results by outcome:

Outcomes	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With ADA	With TOF	Relative effect (95% CI)	Difference in risk	
<b>Pulmonary embolism</b>					
TOF 5 mg (1 RCT, n= 2,906)	3/1451 (0.2%)	9/1,455 (0.6%)	<b>HR 2.93</b> (0.79 to 10.83)	<b>4 more per 1,000</b> (from 0 fewer to 20 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
TOF 10 mg (1 RCT, n= 2,907)	3/1,451 (0.2%)	24/1,456 (1.6%)	<b>HR 8.26</b> (2.49 to 27.43)	<b>15 more per 1,000</b> (from 3 more to 53 more)	⊕⊕⊕⊖ Moderate <sup>a</sup> Critical
<b>Cardiovascular mortality</b>					

Outcomes	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With ADA	With TOF	Relative effect (95% CI)	Difference in risk	
TOF 5 mg (1 RCT) (n= 2906)	10/1,451 (0.7%)	13/1,455 (0.9%)	<b>OR 1.30</b> (0.57 to 2.95)	<b>2 more per 1,000</b> (from 3 fewer to 13 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical
TOF 10 mg (1 RCT) (n= 2907)	10/1,451 (0.7%)	20/1,456 (1.4%)	<b>OR 2.00</b> (0.94 to 4.24)	<b>7 more per 1,000</b> (from 0 fewer to 22 more)	⊕⊖⊖⊖ VERY LOW <sup>a,b</sup> Critical

**Explanations**  
a. High risk of bias: participants and healthcare providers not blinded to the intervention assigned  
b. Imprecision: wide 95% CIs that include scenarios with decreased risk and scenarios with increased risk. Downgraded by two levels due to imprecision, given the small number of events on which estimates were based.

### Baricitinib vs. TNF inhibitors

#### b) What is the magnitude of the expected desirable effects?

- **Judgement:** negligible

#### Research-based evidence:

The review identified a meta-analysis of data on patients from 14 databases (registries) using propensity score matching to evaluate the safety of BAR compared to TNF inhibitors in patients with RA<sup>287</sup>. The following table summarises the overall results by outcome:

Outcome	Study event rate (%)		Effect		Quality and importance of the outcome (GRADE)
	With BAR	With TNF inhibitors	Relative effect (95% CI)	Difference in risk	
<b>Venous thromboembolism</b>					
Non-randomised observational study (propensity score matching)	Exposure: 5,879.34 person-years, number of events ≈ 65	Exposure: 6,511.60 person-years, number of events ≈ 52	<b>IRR 1.51</b> (1.10 to 2.08)		⊕⊕⊖⊖ LOW <sup>a</sup> Critical
<b>Major adverse cardiac events</b>					
Non-randomised observational study (propensity score matching)	Exposure: 5,872.72 person-years, number of events ≈ 62	Exposure: 6,513.82 person-years, number of events ≈ 56	<b>IRR 1.54</b> (0.93 to 2.54)		⊕⊕⊖⊖ LOW <sup>a</sup> Critical

Serious infections					
Non-randomised observational study (propensity score matching)	Exposure: 5,936.89 person-years, number of events ≈ 200	Exposure: 6,632.86 person-years, number of events ≈ 167	<b>IRR 1.36</b> (0.86 to 2.13)		⊕⊕⊖⊖ LOW <sup>a</sup> Critical
<b>Abbreviations</b> BAR: baricitinib; IRR: incidence rate ratio; TNF: tumour necrosis factor					
<b>Explanation</b> a. Pooled analysis of databases using propensity score matching for the main risk factors					

- **Other considerations:**

Along similar lines, evaluations of populations from various national registries have yielded mixed results. Data from the Swedish and German registries have not shown a higher cardiovascular or thromboembolic risk in patients with RA treated with csDMARDs than in those treated with TNF inhibitors, whereas data from the French registry indicated a numerically - though not significantly- higher risk in patients treated with JAK inhibitors<sup>267, 291, 293</sup>.

**c) What is the overall certainty of the evidence regarding the effects?**

- **Judgement:** low/very low

The quality of the evidence was rated as low or very low, due to imprecision associated with wide 95% CIs and because the occurrence of cardiovascular events was not the primary endpoint of many of these RCTs.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence indicates that the risk of developing pulmonary embolism is higher in patients treated with BAR than in those treated with TNF inhibitors (ADA or ETN).

## EtD Question 5. Cancer

**In patients with RA, what is the risk of new or recurrent cancer (melanoma or nonmelanoma skin cancer, solid tumours or haematological cancer) with bDMARD and tsDMARD therapy?**

Patient: Adults ( $\geq 18$  years old) diagnosed with RA (2010 ACR/EULAR criteria).

Intervention: Pharmacological treatments with bDMARDs (IFX, ETN, ADA, CZP, GOL); IL-6R inhibitors (TCZ, SAR); RTX; ABA; tsDMARDs (JAK inhibitors): TOF, BAR, UPA, or FIL.

Comparison: csDMARDs; bDMARDs; JAK inhibitors.

Outcomes: new cancer; cancer recurrence; death.

From evidence to recommendations: cancer

### a) Is this problem a priority?

- Judgement: Yes

### bDMARDs

*TNF inhibitors*

### b) What is the magnitude of the expected desirable effects?

- Judgement: negligible

### Research-based evidence:

The review identified 19 observational studies<sup>299-314</sup>, corresponding to large cohort studies (mostly based on registries), assessing the risk of different types of cancer in patients with RA treated with TNF inhibitors compared to that in those treated with csDMARDs. The following table summarises the results by outcome:

Outcomes	Number of patients		Effect	Quality and importance of the outcome (GRADE)
	With TNF inhibitors	With csDMARDs	Relative effect (95% CI)	
<b>All types of cancer</b>				
(11 observational studies)	Huss 2022: 33,609	Huss 2022: 58,233	Huss 2022: <b>adjusted HR</b> 1.0 (0.9 to 1.0)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
	Seror 2022: 16,333	Seror 2022: 16,333	Seror 2022: <b>adjusted HR</b> 1.03 (0.88 to 1.21)	
	Jung 2019: 2,337	Jung 2019: 43,086		

	<p>Wadström 2017: 1<sup>st</sup> TNF inhibitor 10,782; 2<sup>nd</sup> TNF inhibitor 4,347</p> <p>Aaltonen 2015: 3,094</p> <p>Morgan 2014: 3,529</p> <p>Solomon 2014: 3,761</p> <p>Haynes 2013: 19,750</p> <p>Carmona 2011: 2,531</p> <p>Strangfeld 2010: 3,346</p> <p>Asking 2009: 6,366</p>	<p>Wadström 2017: 46,610</p> <p>Aaltonen 2015: 1,400</p> <p>Morgan 2014: 2,864</p> <p>Solomon 2014: 1,566</p> <p>Haynes 2013: 9,805</p> <p>Carmona 2011: 789</p> <p>Strangfeld 2010: 1,174</p> <p>Asking 2009: 61,160</p>	<p>Jung 2019: <b>adjusted HR</b> 0.913 (0.679 to 1.227)</p> <p>Wadström 2017: 1<sup>st</sup> TNF inhibitor: <b>adjusted HR</b> 0.93 (0.85 to 1.01); 2<sup>nd</sup> TNF inhibitor: <b>adjusted HR</b> 0.89 (0.7 to 1.04)</p> <p>Aaltonen 2015: TNF inhibitor <b>adjusted HR</b> 1.2 (0.6 to 2.2); ADA <b>adjusted HR</b> 1.1 (0.5 to 2.2); ETN <b>adjusted HR</b> 1.3 (0.7 to 2.6); IFX <b>adjusted HR</b> 1.2 (0.4 to 3.1)</p> <p>Morgan 2014: ETN <b>adjusted HR</b> 0.8 (0.7 to 1.0)</p> <p>Solomon 2014: <b>adjusted HR</b> 0.3 (0.1 to 0.6)</p> <p>Haynes 2013: <b>adjusted HR</b> 0.8 (0.6 to 1.1)</p> <p>Carmona 2011: <b>adjusted HR</b> 0.5 (0.1 to 2.5)</p> <p>Strangfeld 2010: <b>adjusted HR</b> 0.7 (0.4 to 1.1)</p> <p>Asking 2009: <b>adjusted HR</b> vs MTX 1.0 (0.8 to 1.2); <b>adjusted HR</b> vs csDMARD combinations 1.0 (0.7 to 1.4)</p>	
<b>Solid cancer</b>				
(2 observational studies)	<p>Mercer 2015: 11,767</p> <p>Solomon 2014: 3,761</p>	<p>Mercer 2015: 3,249</p> <p>Solomon 2014: 1,566</p>	<p><u>Mercer 2015</u>: <b>adjusted HR</b> vs csDMARD: TNF inhibitor: 0.8 (0.6 to 1.1) ADA: 0.8 (0.6 to 1.1) ETN: 0.9 (0.7 to 1.2) IFX: 0.8 (0.6 to 1.1)</p> <p><u>Solomon 2014</u>: <b>adjusted HR</b> vs MTX: 0.2 (0.1 to 0.6)</p>	<p>⊕⊕⊕⊖ LOW<sup>a</sup> Critical</p>
<b>Nonmelanoma skin cancer</b>				
(6 observational studies)	<p><u>Wadström 2017</u>: 1<sup>st</sup> TNF inhibitor 10,782; 2<sup>nd</sup> TNF inhibitor 4,347</p> <p><u>Solomon 2014</u>: 3,761</p> <p><u>Haynes 2013</u>: 19,750</p> <p><u>Mercer 2012</u>: 11,881</p> <p><u>Amari 2011</u>: 18,396</p>	<p><u>Wadström 2017</u>: 46,610</p> <p><u>Solomon 2014</u>: 1,566</p> <p><u>Haynes 2013</u>: 9,805</p> <p><u>Mercer 2012</u>: 3,629</p> <p><u>Amari 2011</u>: 4,088</p>	<p><u>Wadström 2017</u>: <b>adjusted HR</b> 1<sup>st</sup> TNF inhibitor 0.86 (0.54 to 1.39); <b>adjusted HR</b> 2<sup>nd</sup> TNF inhibitor 1.09 (0.84 to 1.42).</p> <p><u>Solomon 2014</u>: <b>adjusted HR</b> vs MTX 0.4 (0.1 to 1.2)</p> <p><u>Haynes 2013</u>: <b>adjusted HR</b> 0.8 (0.5 to 1.4)</p> <p><u>Mercer 2012</u>: Basal cell carcinoma <b>adjusted HR</b> 1.0 (0.5 to 1.7) Squamous cell carcinoma <b>adjusted HR</b> 1.2 (0.4 to 3.8)</p> <p><u>Amari 2011</u>: <b>adjusted HR</b> 1.4 (1.2 to 1.6)</p> <p><u>Meta-analysis Wang 2020</u>: <b>RR</b> 1.28 (1.19 to 1.38)</p>	<p>⊕⊕⊕⊖ LOW<sup>a</sup> Critical</p>
<b>Melanoma</b>				

(3 observational studies)	<u>Mercer 2017</u> : 28,304  <u>Wadström 2017</u> : 1 <sup>st</sup> TNF inhibitor 10,782; 2 <sup>nd</sup> TNF inhibitor 4,347  <u>Raaschou 2013</u> : 10878	<u>Mercer 2017</u> : 68,411  <u>Wadström 2017</u> : 46,610  <u>Raaschou 2013</u> : 42,198	<u>Mercer 2017</u> : <b>HR vs csDMARD 1.14 (0.8 to 1.6)</b>  <u>Wadström 2017</u> : <b>adjusted HR vs csDMARD:</b> 1 <sup>st</sup> TNF inhibitor 0.84 (0.60 to 1.18); 2 <sup>nd</sup> TNF inhibitor 0.94 (0.53 to 1.66).  <u>Raaschou 2013</u> : <b>adjusted HR vs csDMARD 1.5 (1.0 to 2.2)</b>	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<b>Lymphoma</b>				
(4 observational studies)	<u>Jung 2019</u> : 2,337  <u>Mercer 2017</u> : TNF inhibitor 11,931 ADA 4,288 ETN 4,144 IFX 3,499  <u>Haynes 2013</u> : 19,750  <u>Askling 2009</u> : 6,366	<u>Jung 2019</u> : 43,086  <u>Mercer 2017</u> : 3,367  <u>Haynes 2013</u> : 9,805  <u>Askling 2009</u> : 61,160	<u>Jung 2019</u> : 0 cases with TNF inhibitor vs 80.53 with csDMARDs per 100,000 patient-years  <u>Mercer 2017</u> : TNF inhibitor <b>adjusted HR 1.00 (0.56 to 1.80)</b> ADA <b>adjusted HR 1.00 (0.49 to 2.03)</b> ETN <b>adjusted HR 1.02 (0.45 to 2.33)</b> IFX <b>adjusted HR 0.91 (0.39 to 2.13)</b>  <u>Haynes 2013</u> : <b>adjusted HR 0.8 (0.3 to 2.1)</b>  <u>Askling 2009</u> : <b>adjusted HR 1.4 (0.8 to 2.1)</b>	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<b>Cervical cancer</b>				
(1 observational study)	Wadström 2016: 9,629	Wadström 2016: 34,984	Wadström 2016: <b>adjusted HR 1.36 (0.59 to 3.13)</b>	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<p><b>Abbreviations</b>            ADA: adalimumab; CI: confidence interval; csDMARD: conventional synthetic disease-modifying drug; ETN: etanercept; HR: hazard ratio; IFX: infliximab; MTX: methotrexate; RCT: randomised controlled trial; RR: relative risk; TNF: tumour necrosis factor</p> <p>1. In the majority of the studies, there are no differences. Only in the study by Solomon 2014, cancer risk was lower with TNF inhibitors.            2. Some studies found a clear association. A meta-analysis published in 2020 (Wang) supports this finding.</p> <p><b>Explanations</b>            a. Evidence from uncontrolled observational studies. Considered to be at high risk of bias by default.</p>				

- **Other considerations:**

The review also identified an SR<sup>317</sup> on the risk of NMSC in patients with RA treated with TNF inhibitors. It was concluded that TNF inhibitor therapy in patients with RA does increase the risk of NMSC.

**c) What is the overall certainty of the evidence regarding the effects?**

- **Judgement:** Low

The quality of the evidence was rated as low, given that it was from non-randomised studies that have an inherently high risk of bias.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence indicates that treatment with TNF inhibitors may increase the risk of NMSC compared to treatment with csDMARDs.

Abatacept

*Abatacept vs. bDMARDs/tsDMARDs*

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** small/moderate

**Research-based evidence:**

The review identified seven studies<sup>306, 318-323</sup> assessing the incidence of cancer in patients with RA treated with ABA compared to those treated with other bDMARDs or tsDMARDs. The following table summarises the results by outcome:

Outcomes	Number of patients		Effect	Quality and importance of the outcome (GRADE)
	With abatacept	With other bDMARDs or tsDMARDs	Relative effect (95% CI)	
<b>All types of cancer</b>				
(7 observational studies)	<p><u>Simon 2024:</u> ARTIS: 2,434 BC: 637 FORWARD: 1,496</p> <p>Westerman 2024: 1,016 De Germy 2020: 15,846</p> <p>Montastruc 2019: 4,328 Ozen 2019: 1,496</p> <p><u>Simon 2019:</u> MarketScan: 17,517</p>	<p><u>Simon 2024:</u> ARTIS: 22,439 BC: 4,456 FORWARD: 3,490</p> <p>Westerman 2024: 7,458 TNF inhibitor De Germy 2020: 290,568 (253,915 TNF inhibitor; 53,687 non-TNF inhibitor) Montastruc 2019: 59,860 Ozen 2019: 3,490</p> <p><u>Simon 2019:</u> MarketScan: 32,277</p>	<p><u>Simon 2024:</u> RR 1.0 (0.8 to 1.3) ARTIS: RR 1.0 (0.7 to 1.3) BC: RR 1.0 (0.4 to 2.6) FORWARD: RR 1.2 (0.6 to 2.3)</p> <p>Westerman 2024: <b>adjusted HR</b> 1.1 (0.78 to 1.50)</p> <p>De Germy 2020: <b>adjusted HR</b> 1.13; HR 0.98 (0.91 to 1.05)</p> <p>Montastruc 2019: <b>adjusted HR</b> 1.39; HR 1.17 (1.06 to 1.30)</p> <p>Ozen 2019; <b>adjusted HR</b> 2.32 (0.84 to 6.44); HR 1.89 (0.93 to 3.84)</p> <p><u>Simon 2019:</u></p>	<p>⊕⊕⊕⊖ LOW<sup>a</sup> Critical</p>

	PharMetrics: 12,120 Optum: 3,354  Wadström 2017: 2,021	PharMetrics: 21,145 Optum: 5,604  Wadström 2017: 10,782 TNF inhibitor	MarketScan: <b>adjusted HR</b> 1.02 (0.91 to 1.15) PharMetrics: <b>adjusted HR</b> 1.41 (0.99 to 1.31) Optum: <b>adjusted HR</b> 1.23 (0.90 to 1.67)  Wadström 2017: <b>adjusted HR</b> 1.10 (0.82 to 1.48)	
<b>Nonmelanoma skin cancer</b>				
(3 observational studies)	Montastruc 2019: 4,328 (182 events)  Ozen 2019: 1,496  Wadström 2017: 2,016 (17 events)	Montastruc 2019: 59,860 (1,798 events)  Ozen 2019: 3,490  Wadström 2017: 15,093 (71 events)	Montastruc 2019: <b>adjusted HR</b> 1.45 (1.03 to 1.39)  Ozen 2019: <b>adjusted HR</b> 1.10 (0.57 to 2.11)  Wadström 2017: <b>adjusted HR</b> vs TNF inhibitor: 2.12 (1.14 to 3.95)	⊕⊕⊕⊕ VERY LOW <sup>a</sup> Critical
<b>Melanoma</b>				
(2 observational studies)	De Gernay 2020: 15,846 (52 events) Montastruc2019: 4,328	De Gernay 2020: 290,568 (567 events) Montastruc2019: 59,860	De Gernay 2020: <b>adjusted HR</b> 1.56 (1.17 to 2.08)  Montastruc 2019: <b>adjusted HR</b> 0.86 (0.38 to 1.59)	⊕⊕⊕⊕ VERY LOW <sup>a</sup> Critical
<b>Lymphoma and other haematological cancers</b>				
(2 observational studies)	De Gernay 2020: 15,846  <u>Simon 2019:</u> MarketScan 17,517 PharMetrics 12,120 Optum 3,354	De Gernay 2020: 290,568  <u>Simon 2019:</u> MarketScan 32,277 PharMetrics 21,145 Optum 5,604	De Gernay 2020: 0.76 (0.60 to 0.97)  Simon 2019: <b>adjusted HR</b> 1.27 (0.94 to 1.72), based on 3 databases. - MarketScan: <b>adjusted HR</b> 1.21 (0.79 to 1.85) - PharMetrics: <b>adjusted HR</b> 1.32 (0.84 to 2.09) - Optum: <b>adjusted HR</b> 1.43 (0.39 to 5.22)	⊕⊕⊕⊕ VERY LOW <sup>a</sup> Critical
<p><b>Abbreviations</b> CI: confidence interval; bDMARD: biological disease-modifying drug; tsDMARD: targeted synthetic disease-modifying drug; HR: hazard ratio; RR: relative risk; TNF: tumour necrosis factor</p> <p>1. Westerman et al. only compare with TNF inhibitors and exclude NMSC. 2. Wadström et al. reported a higher risk of NMSC with very high HRs while the other studies did not find differences. 3. De Gernay et al. found significant differences but Montastruc et al. did not. 4. The studies of De Gernay and Simon yielded conflicting results (indicating lower and higher rates of lymphoma, respectively), but none of the differences reached significance.</p> <p><b>Explanations</b> a. Evidence is from uncontrolled observational studies. Considered to be at high risk of bias by default.</p>				

### Abatacept vs. csDMARDs

The review identified seven studies assessing the incidence of cancer in patients with RA treated with ABA compared to csDMARDs<sup>304, 306, 309, 310, 320, 322, 323</sup>.

Outcomes	Number of patients		Effect	Quality and importance of the outcome (GRADE)
	With abatacept	With csDMARDs	Relative effect (95% CI)	
<b>All types of cancer</b>				
(5 observational studies)	<u>Simon 2024:</u> ARTIS: 2,434 BC: 637 RABBIT: 615  Westerman 2024: 1,016  Huss 2022: 3,558  Wadström 2017: 2,021  Solomon 2014: 408	<u>Simon 2024:</u> ARTIS: 67,762 BC: 1,274 RABBIT: 3,199  Westerman 2024: 11,361  Huss 2022: 58,233  Wadström 2017: 46,610  Solomon 2014: 904	<u>Simon 2024:</u> RR 1.1 (0.8 to 1.5) BC: RR 1.3 (0.5 to 3.3) FORWARD: RR 0.8 (0.2 to 3.4) RABBIT: RR 1.1 (0.8 to 1.6)  Westerman 2024: <b>adjusted HR</b> 1.08 (0.79 to 1.51)  Huss 2022: <b>adjusted HR</b> 1.2 (1.0 to 1.4)  Wadström 2017: <b>adjusted HR</b> 0.88 (0.68 to 1.14) Wadström 2017: <b>adjusted HR</b> 1.10 (0.82 to 1.48)  Solomon 2014: <b>adjusted HR</b> 1.6 (0.4 to 6.0)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<b>Nonmelanoma skin cancer</b>				
(3 observational studies)	Ozen 2019: 1,496  Wadström 2017: 2,021  Solomon 2014:408	Ozen 2019: 1,520  Wadström 2017: 46,610  Solomon 2014: 904	Ozen 2019: <b>adjusted HR</b> 1.05 (0.22 to 4.98)  <u>Wadström 2017:</u> <b>adjusted HR</b> vs csDMARD: 2.15 (1.31 to 3.52) <b>adjusted HR</b> vs the general population: 4.56 (2.76 to 7.52)  Solomon 2014: <b>adjusted HR</b> vs MTX 15.3 (2.1 to 114.0)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<b>Melanoma</b>				
(2 observational studies)	De Germy 2020: 15846	Wadström 2017: 46610  Mercer 2017: vs general population	Wadström 2017: <b>Adjusted HR</b> vs csDMARD: 12.39 (0.90 to 6.33) <b>Adjusted HR</b> vs general population: 1.63 (0.76 to 3.49)  Mercer 2017: <b>Adjusted HR</b> (vs general population) 1.6 (0 to 12,704)	⊕⊖⊖⊖ VERY LOW <sup>a</sup> Critical
<b>Abbreviations</b> CI: confidence interval; csDMARD: conventional synthetic disease-modifying drug; HR: hazard ratio; MTX: methotrexate; RR: relative risk				
<b>Explanations</b> - Westerman et al. only compared with TNF inhibitors and excluded NMSC. - The studies by Ozen (2019) and Solomon (2014) obtained very wide CIs. - Wadström et al. obtained wide CIs.				
a. Evidence from uncontrolled observational studies. Considered to be at high risk of bias by default.				

c) What is the overall certainty of the evidence regarding the effects?

- **Judgement:** Low

The quality of the evidence was rated as low, given that it was from non-randomised studies that have an inherently high risk of bias.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence indicates that treatment with ABA may increase the risk of NMSC both compared to treatment with either other bDMARDs or csDMARDs, and to a lesser extent, the risk of melanoma compared to that with other bDMARDs.

*IL-6R inhibitors*

Tocilizumab

*Tocilizumab vs. TNF inhibitors*

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible

**Research-based evidence:**

The review identified two studies<sup>306, 324</sup> assessing the development of cancer in patients with RA treated with TCZ compared to TNF inhibitors. The following table summarises the results by outcome:

Outcomes	Number of patients		Effects	Quality and importance of the outcome (GRADE)
	With tocilizumab	With TNF inhibitor	Relative effect (95% CI)	
<b>All types of cancer</b>				
(3 observational studies)	<u>Kim 2019:</u> Medicare: 4,360 IMS: 3,828 MarketScan: 4,644 Combined dataset: 12,832  Wadström 2017: 1,798	<u>Kim 2019:</u> Medicare: 8,450 IMS: 8,449 MarketScan: 9,828 Combined dataset: 26,727  Wadström 2017: 10,782	<u>Kim 2019:</u> three databases: Medicare: <b>adjusted HR</b> 1.05 (0.81 to 1.37) IMS: <b>adjusted HR</b> 0.80 (0.52 to 1.24) MarketScan: <b>adjusted HR</b> 0.97 (0.64 to 1.47) Combined dataset: <b>adjusted HR</b> 0.98 (0.80 to 1.19)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical

	Westermann 2024: 1,457	Westermann 2024: 7,458	Wadström 2017: <b>adjusted HR</b> 1.12 (0.81 to 1.54)  Westermann 2024: <b>adjusted HR</b> 1.01 (0.78 to 1.29)	
<b>NMSC</b>				
(1 observational study)	Wadström 2017: 1,798	Wadström 2017: 4,347	Wadström 2017: <b>adjusted HR</b> 1.04 (0.39 to 2.80)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<b>Melanoma</b>				
(1 observational study)	<u>Kim 2019</u> : Medicare: 4,360 IMS: 3,828 MarketScan: 4,644 Combined dataset: 12,832	<u>Kim 2019</u> : Medicare: 8,450 IMS: 8,449 MarketScan: 9,828 Combined dataset: 26,727	<u>Kim 2019</u> : Three databases: Combined dataset: <b>adjusted HR</b> 0.71 (0.36 to 1.40)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<b>Lymphoma</b>				
(1 observational study)	<u>Kim 2019</u> : Medicare: 4,360 IMS: 3,828 MarketScan: 4,644 Combined dataset: 12,832	<u>Kim 2019</u> : Medicare: 8,450 IMS: 8,449 MarketScan: 9,828 Combined dataset: 26,727	<u>Kim 2019</u> : Three databases: Combined dataset: <b>adjusted HR</b> 1.31 (0.60 to 2.88)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<b>Abbreviations</b> CI: confidence interval; HR: hazard ratio; TNF: tumour necrosis factor				
<b>Explanations</b> a. Evidence based on uncontrolled observational studies. Considered to be at high risk of bias by default.				

### *Tocilizumab vs. csDMARDs*

The review found two studies assessing the development of cancer in patients with RA treated with TCZ compared to traditional non-biological DMARDs<sup>306, 309</sup>. The following table summarises the results by outcome:

Outcomes	Number of patients		Effect	Quality and importance of the outcome (GRADE)
	With tocilizumab	With csDMARDs	Relative effect (95% CI)	
<b>All types of cancer</b>				
(3 observational studies)	Huss 2022: 2,895  Wadström 2017: 1,798  Westermann 2024: 1,457	Huss 2022: 58,223  Wadström 2017: 46,610  Westermann 2024: 11,361	Huss 2022: <b>adjusted HR</b> 1.0 (0.8 to 1.2)  Wadström 2017: <b>adjusted HR</b> 1.12 (0.81 to 1.54)  Westermann 2024: <b>adjusted HR</b> 1.00 (0.76 to 1.32)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
Nonmelanoma skin cancer				

(1 observational study)	Wadström 2017: 1,798	Wadström 2017: 46,610	<u>Wadström 2017</u> : <b>adjusted HR</b> 0.93 (0.39 to 2.21)	⊕⊖⊖⊖ VERY LOW <sup>a</sup> Critical
<p><b>Abbreviations</b> CI: confidence interval; csDMARD: conventional synthetic disease-modifying drug; HR: hazard ratio</p> <p><b>Explanations</b> - Wide CIs in the only study: Wadström 2017 a. Evidence based on uncontrolled observational studies. Considered to be at high risk of bias by default.</p>				

**c) What is the overall certainty of the evidence regarding the effects?**

- **Judgement:** Low/very low

The quality of the evidence was rated as low or very low given that it was based on uncontrolled observational studies.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence below.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence indicates that TCZ does not increase the risk of developing cancer of any type in patients with RA.

Rituximab

*Rituximab vs. TNF inhibitors*

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible

**Research-based evidence:**

The review identified a single study assessing the risk of cancer in patients treated with RTX compared to TNF inhibitors<sup>323</sup>. The following table summarises the results by outcome:

Outcomes	Number of patients		Effect	Quality and importance of the outcome (GRADE)
	With rituximab	With TNF inhibitors	Relative effect (95% CI)	
All types of cancer				

(1 observational study)	Westermann 2024: 690	Westermann 2024: 7458	Westermann 2024: <b>adjusted HR</b> 0.70 (0.46 to 1.03)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<b>Abbreviations</b> CI: confidence interval; HR: hazard ratio; TNF: tumour necrosis factor				
<b>Explanations</b> a. Evidence based on uncontrolled observational studies. Considered to be at high risk of bias by default.				

### *Rituximab vs. csDMARDs*

The review identified three studies comparing the risk of cancer in patients treated with RTX and csDMARDs<sup>299, 306, 323</sup>. The following table summarises the results by outcome:

Outcomes	Number of patients		Effect	Quality and importance of the outcome (GRADE)
	With rituximab	With csDMARDs	Relative effect (95% CI)	
<b>All types of cancer</b>				
(3 observational studies)	Westermann 2024: 690	Westermann 2024: 11,361	Westermann 2024: <b>adjusted HR</b> 0.70 (0.47 to 1.02)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
	Wadström 2017: 3,119	Wadström 2017: 42,365	Wadström 2017: <b>adjusted HR</b> 0.86 (0.73 to 1.03)	
	Aaltonen 2015: 438	Aaltonen 2015: 1,400	Aaltonen 2015: <b>adjusted HR</b> 1.2 (0.49 to 3.2)	
<b>Abbreviations</b> CI: confidence interval; csDMARDs: conventional synthetic disease-modifying drug; HR: hazard ratio				
<b>Explanations</b> a. Evidence based on uncontrolled observational studies. Considered to be at high risk of bias by default.				

- **Other considerations:**

The review also identified three observational studies that assessed all bDMARDs as a single group, without differentiating between mechanisms of action, which means that their results are of very little relevance to clinical practice. One study compared cancer risk in patients with RA who started their first biologic and patients who stayed on csDMARDs<sup>314</sup>. Another study<sup>324</sup> assessed whether the incidence of cervical cancer was higher in patients treated with bDMARDs than those treated with csDMARDs. Lastly, a case-control study<sup>326</sup> explored the influence of bDMARDs on the development of cancer. None of these three studies found bDMARDs as a group to be associated with a higher risk of cancer than csDMARDs in patients with RA.

**c) What is the overall certainty of the evidence regarding the effects?**

- **Judgement:** Low/very low

The quality of evidence was rated as low or very low, given that it was based on uncontrolled observational studies.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above.

**d) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?**

The weight of the evidence indicates that RTX does not increase the risk of developing cancer of any type in patients with RA.

**JAK inhibitors**

JAK inhibitors vs TNF inhibitors

**b) What is the magnitude of the expected desirable effects?**

- **Judgement:** negligible

**Research-based evidence:**

The review identified six observational studies<sup>327-332</sup> assessing the risk of cancer in patients with RA treated with a JAK inhibitor compared to TNF inhibitors. The following table summarises the results by outcome.

Outcomes	Number of patients		Effect	Quality and importance of the outcome (GRADE)
	With JAK inhibitors	With TNF inhibitors	Relative effect (95% CI)	
<b>All types of cancer</b>				
(6 observational studies)	Huss 2023: 2,143 TOF: 377 BAR: 1676 UPA: 90	Huss 2023: 8,580	Huss 2023: <b>adjusted HR</b> 0.94 (0.65 to 1.98)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
	Mok 2024: 551	Mok 2024: 1920	Mok 2024: <b>IRR</b> 0.65 (0.32 to 1.35)	
	Min 2023: Set 1: 245 Set 2: 2498	Min 2023: Set 1: 951 Set 2: 9267	Min 2023: <u>Set 1</u> : <b>IRR</b> 1.53 (0.81 to 2.87); Men <b>IRR</b> 0.83 (0.26 to 2.66); Women <b>IRR</b> 2.15 (0.98 to 4.73)	

	<p>Uchida 2023: 296</p> <p><u>Khosrow-Khavar 2023:</u> Optum: 3,301 MarketScan: 4,499 Medicare: 2,689</p> <p><u>Song 2022:</u> Before IPTW: 1,064 After IPTW: 4,101</p>	<p>Uchida 2023: 203</p> <p><u>Khosrow-Khavar 2023:</u> Optum: 21,934 MarketScan: 24,960 Medicare: 25,673</p> <p><u>Song 2022:</u> Before IPTW: 3,865 After IPTW: 5,131</p>	<p><u>Set 2:</u> <b>IRR</b> 1.02 (0.81 to 1.29); Men <b>IRR</b> 0.72 (0.41 to 1.26); Women <b>IRR</b> 1.12 (0.87 to 1.45)</p> <p>Uchida 2023: <b>HR</b> 0.385 (0.095 to 1.552)</p> <p><u>Khosrow-Khavar 2023:</u> Optum: <b>adjusted HR</b> 1.14 (0.82 to 1.59) MarketScan: <b>adjusted HR</b> 0.65 (0.42 to 1.02) Medicare: <b>adjusted HR</b> 1.09 (0.83 to 1.45) Combined dataset: <b>adjusted HR</b> 1.01 (0.83 to 1.22)</p> <p><u>Song 2022:</u> Before IPTW: <b>adjusted HR</b> 0.69 (0.30 to 1.56) After IPTW: <b>adjusted HR</b> 0.83 (0.55 to 1.27)</p>	
NMSC				
(4 observational studies)	<p><u>Huss 2023:</u> 2,143 TOF: 377 BAR: 1676 UPA: 90</p> <p><u>Min 2023:</u> Set 2: 2,498</p> <p><u>Khosrow-Khavar 2023:</u> Optum: 3,301 MarketScan: 4,499 Medicare: 2,689</p> <p><u>Song 2022:</u> 1,064</p>	<p><u>Huss 2023:</u> 8,580</p> <p><u>Min 2023:</u> Set 2: 9,267</p> <p><u>Khosrow-Khavar 2023:</u> Optum: 21,934 MarketScan: 24,960 Medicare: 25,673</p> <p><u>Song 2022:</u> 3,865</p>	<p><u>Huss 2023:</u> <b>adjusted HR</b> 1.39 (1.01 to 1.91)</p> <p><u>Min 2023:</u> Set 2: Men: <b>IRR</b> 2.27 (0.25 to 20.28) Women: <b>IRR</b> 0.87 (0.20 to 3.75)</p> <p><u>Khosrow-Khavar 2023:</u> Optum: <b>adjusted HR</b> 1.15 (0.80 to 1.64) MarketScan: <b>adjusted HR</b> 1.25 (0.89 to 1.75) Medicare: <b>adjusted HR</b> 1.09 (0.83 to 1.45) Combined dataset: <b>adjusted HR</b> 1.15 (0.96 to 1.39)</p> <p><u>Song 2022:</u> <b>adjusted HR</b> 3.46 (0.59 to 20.26)</p>	⊕⊕⊕⊕ VERY LOW <sup>a</sup> Critical
Haematopoietic cancer				
(3 observational studies)	<p><u>Huss 2023:</u> 2,143 TOF: 377 BAR: 1676 UPA: 90</p> <p><u>Khosrow-Khavar 2023:</u> Optum: 3,301 MarketScan: 4,499 Medicare: 2,689</p> <p><u>Song 2022:</u> Before IPTW: 1064 After IPTW: 4101</p>	<p><u>Huss 2023:</u> 8,580</p> <p><u>Khosrow-Khavar 2023:</u> Optum: 21,934 MarketScan: 24,960 Medicare: 25,673</p> <p><u>Song 2022:</u> Before IPTW: 3865 After IPTW: 5131</p>	<p>Huss 2023: <b>adjusted HR</b> 1.90 (0.70 to 5.16)</p> <p><u>Khosrow-Khavar 2023:</u> Optum: <b>adjusted HR</b> 0.44 (0.10 to 1.97) MarketScan: <b>adjusted HR</b> 1.33 (0.49 to 3.61) Medicare: <b>adjusted HR</b> 0.88 (0.43 to 1.84) Combined dataset: <b>adjusted HR</b> 0.91 (0.53 to 1.98)</p> <p><u>Song 2022:</u> Before IPTW: <b>adjusted HR</b> 2.41 (0.15 to 37.99) After IPTW: <b>adjusted HR</b> 2.86 (0.41 to 20.00)</p>	⊕⊕⊕⊕ VERY LOW <sup>b</sup> Critical
Lung cancer				
(3 observational studies)	<p><u>Huss 2023:</u> 2,143 TOF: 377 BAR: 1676 UPA: 90</p> <p><u>Khosrow-Khavar 2023:</u> Optum: 3,301 MarketScan: 4,499 Medicare: 2,689</p> <p><u>Song 2022:</u> 1,064</p>	<p><u>Huss 2023:</u> 8,580</p> <p><u>Khosrow-Khavar 2023:</u> Optum: 21,934 MarketScan: 24,960 Medicare: 25,673</p> <p><u>Song 2022:</u> 3,865</p>	<p>Huss 2023: <b>adjusted HR</b> 1.15 (0.57 to 2.32)</p> <p><u>Khosrow-Khavar 2023:</u> Optum: <b>adjusted HR</b> 1.60 (0.70 to 3.66) MarketScan: <b>adjusted HR</b> 1.05 (0.38 to 2.91) Medicare: <b>adjusted HR</b> 1.07 (0.58 to 2.00) Combined dataset: <b>adjusted HR</b> 1.20 (0.77 to 1.87)</p>	⊕⊕⊕⊕ LOW <sup>a</sup> Critical

			<u>Song 2022</u> : <b>adjusted HR</b> 0.96 (0.31 to 2.96)	
<b>Breast cancer</b>				
(3 observational studies)	<u>Huss 2023</u> : 2,143 TOF: 377 BAR: 1,676 UPA: 90  <u>Khosrow-Khavar 2023</u> : Optum: 3,301 MarketScan: 4,499 Medicare: 2,689  <u>Song 2022</u> : 1,064	<u>Huss 2023</u> : 8,580  <u>Khosrow-Khavar 2023</u> : Optum: 21,934 MarketScan: 24,960 Medicare: 25,673  <u>Song 2022</u> : 3,865	Huss 2023: <b>adjusted HR</b> 0.73 (0.29 to 1.86)  <u>Khosrow-Khavar 2023</u> : Optum: <b>adjusted HR</b> 0.99 (0.42 to 2.34) MarketScan: <b>adjusted HR</b> 0.66 (0.27 to 1.60) Medicare: <b>adjusted HR</b> 0.92 (0.43 to 2.00) Combined dataset: <b>adjusted HR</b> 0.85 (0.53 to 1.38)  <u>Song 2022</u> : <b>adjusted HR</b> 1.92 (0.94 to 3.90)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<b>Cancer-related death</b>				
(1 observational study)	Mok 2024: 551	Mok 2024: 1,920	Mok 2024: <b>IRR</b> 0.70 (0.15 to 3.38)	⊕⊕⊕⊖ VERY LOW <sup>c</sup> Critical
<b>Abbreviations</b> CI: confidence interval; HR: hazard ratio; IPTW: inverse probability of treatment weighting; IRR: incidence rate ratio; JAK: Janus kinase				
<b>Explanations</b> a. Very wide CIs in Min et al. (2023) and Song et al. (2022) b. Very wide CIs in Son et al. (2022) and somewhat narrower in that Huss et al. (2023) c. Wide CIs for death in Mok et al. (2024)  - Evidence based on uncontrolled observational studies. Considered to be at high risk of bias by default.				

### Tofacitinib vs. TNF inhibitors

The review identified one observational study<sup>327</sup> and one RCT<sup>382</sup> assessing the risk of cancer in patients with RA treated with TOF compared to TNF inhibitors. The following table summarises the results by outcome:

Outcomes	Number of patients		Effect Relative effect (95% CI)	Quality and importance of the outcome (GRADE)
	With TOF	With TNF inhibitors		
<b>All types of cancer</b>				
(1 observational study)	<u>Huss 2023</u> : 377	<u>Huss 2023</u> : 8,580	Huss 2023: <b>adjusted HR</b> 1.08 (0.52 to 2.24)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<b>All types of cancer except NMSC</b>				
(1 RCT)	<u>Curtis 2023</u> : TOF 5 mg: 1,455	<u>Curtis 2023</u> : 1451	<u>Curtis 2023</u> : TOF (either dose): <b>HR</b> 1.48 (1.04 to 2.09)	⊕⊕⊕⊕ High

	TOF 10 mg: 1,456		TOF 5 mg: <b>HR</b> 1.47 (1.00 to 2.18) TOF 10 mg: <b>HR</b> 1.48 (1.00 to 2.19)	
<b>Nonmelanoma skin cancer</b>				
(1 RCT)	<u>Curtis 2023</u> : TOF 5 mg: 1,455 TOF 10 mg: 1,456	<u>Curtis 2023</u> : 1451	<u>Curtis 2023</u> : TOF (either dose): <b>HR</b> 2.02 (1.17 to 3.50) TOF 5 mg: <b>HR</b> 1.90 (1.04 to 3.47) TOF 10 mg: <b>HR</b> 2.16 (1.19 to 3.92)	⊕⊕⊕⊕ High
(1 observational study)	<u>Huss 2023</u> : 377	<u>Huss 2023</u> : 8,580	Huss 2023: <b>adjusted HR</b> 1.56 (0.83 to 2.92)	⊕⊕⊕⊖ LOW <sup>a</sup> Critical
<b>Breast cancer</b>				
(1 RCT)	<u>Curtis 2023</u> : TOF 5 mg: 1,455 TOF 10 mg: 1,456	<u>Curtis 2023</u> : 1451	<u>Curtis 2023</u> : TOF (either dose): <b>HR</b> 0.83 (0.38 to 1.82) TOF 5 mg: <b>HR</b> 0.95 (0.39 to 2.28) TOF 10 mg: <b>HR</b> 0.71 (0.27 to 1.87)	⊕⊕⊕⊕ High
<b>Lymphoma</b>				
(1 RCT)	<u>Curtis 2023</u> : TOF 5 mg: 1,455 (4 events) TOF 10 mg: 1,456 (6 events)	<u>Curtis 2023</u> : 1451 (1 event)	<u>Curtis 2023</u> : TOF (either dose): <b>HR</b> 5.09 (0.65 to 39.78) TOF 5 mg: <b>HR</b> 3.99 (0.45 to 35.70) TOF 10 mg: <b>HR</b> 6.24 (0.75 to 51.86)	⊕⊕⊕○ Moderate
<b>Lung cancer</b>				
(1 RCT)	<u>Curtis 2023</u> : TOF 5 mg: 1455 TOF 10 mg: 1456	<u>Curtis 2023</u> : 1451	<u>Curtis 2023</u> : TOF (either dose): <b>HR</b> 2.17 (0.95 to 4.93) TOF 5 mg: <b>HR</b> 1.84 (0.74 to 4.62) TOF 10 mg: <b>HR</b> 2.50 (1.04 to 6.02)	⊕⊕⊕⊕ High
<b>Melanoma</b>				
(1 RCT)	<u>Curtis 2023</u> : TOF 5 mg: 1455 TOF 10 mg: 1456	<u>Curtis 2023</u> : 1451	<u>Curtis 2023</u> : TOF (either dose): <b>HR</b> 0.20 (0.04 to 1.04) TOF 5 mg: <b>HR</b> 0.20 (0.02 to 1.71) TOF 10 mg: <b>HR</b> 0.20 (0.02 to 1.75)	⊕⊕⊕⊕ High
<b>Abbreviations</b> CI: confidence interval; HR: hazard ratio; TOF: tofacitinib				
<b>Explanations</b> <sup>a</sup> Very wide CIs				

### *Baricitinib vs. TNF inhibitors*

The review identified one observational study<sup>327</sup> assessing the risk of cancer in patients with RA treated with JAK inhibitors compared to TNF inhibitors. The following table summarises the results by outcome:

Outcomes	Number of patients		Effect	Quality and importance of the outcome (GRADE)
	With baricitinib	With TNF inhibitors	Relative effect (95% CI)	
<b>All types of cancer</b>				

(1 observational study)	<u>Huss 2023</u> : 1,676	<u>Huss 2023</u> : 8,580	Huss 2023: <b>adjusted HR</b> 0.92 (0.61 to 1.38)	⊕⊕⊖⊖ LOW <sup>a</sup> Critical
<b>Nonmelanoma skin cancer</b>				
(1 observational study)	<u>Huss 2023</u> : 1,676	<u>Huss 2023</u> : 8,580	Huss 2023: <b>adjusted HR</b> 1.37 (0.97 to 1.92)	⊕⊕⊖⊖ LOW <sup>a</sup> Critical
<b>Haematopoietic cancer</b>				
	<u>Huss 2023</u> : 1,676	<u>Huss 2023</u> : 8,580	Huss 2023: <b>adjusted HR</b> 1.96 (0.66 to 5.79)	⊕⊕⊖⊖ LOW <sup>a</sup> Critical
<b>Breast cancer</b>				
(1 observational study)	<u>Huss 2023</u> : 1,676	<u>Huss 2023</u> : 8,580	Huss 2023: <b>adjusted HR</b> 0.77 (0.29 to 2.06)	⊕⊕⊖⊖ LOW <sup>a</sup> Critical
<b>Lung cancer</b>				
(1 observational study)	<u>Huss 2023</u> : 1,676	<u>Huss 2023</u> : 8,580	Huss 2023: <b>adjusted HR</b> 0.98 (0.44 to 2.23)	⊕⊕⊖⊖ LOW <sup>a</sup> Critical
<b>Abbreviations</b> CI: confidence interval; HR: hazard ratio				
<b>Explanations</b> a. Evidence based on uncontrolled observational studies. Considered to be at high risk of bias by default.				

### c) What is the overall certainty of the evidence regarding the effects?

- **Judgement:** High/moderate/low/very low

The quality of the evidence was rated as high/moderate for the RCT, given the wide 95% CIs for some outcome measures, and low/very low for observational studies that have an inherently high risk of bias.

- **Research-based evidence:** See the “Quality and importance of the outcome” column in the table of evidence above

### c) Does the balance of expected desirable and undesirable effects favour the intervention or the comparator?

The weight of the evidence indicates that TOF does increase the risk of NMSC in patients with RA, and at a dose of 10 mg twice daily, it may increase the risk of lung cancer, compared to that with TNF inhibitors.

## Appendix 5. Declaration of interests

Alejandro Balsa Criado Alejandro Balsa Criado has received funding for attending courses/conferences from AbbVie, Lilly, Pfizer, and Sandoz; speaker fees from AbbVie, Biogen, BMS, Galápagos, Lilly, Nordic, Pfizer, Sandoz, Sanofi and UCB; funding for educational programmes and courses from Pfizer and UCB; grants for research projects from AbbVie, Novartis and UCB; and fees for consultancy services for pharmaceutical and technology sectors from AbbVie, Biogen, Galápagos, Lilly, Nordic, Pfizer, Sanofi, Sandoz and UCB. He has also received a grant for a research project from UCB and funding for educational programmes and courses for his unit/department from Novartis, Sandoz and UCB.

Petra Díaz del Campo works in the SER research unit overseeing the development of clinical practice guidelines, and this work is supported by funding from numerous sources in the pharmaceutical sector.

Laly Alcaide Cornejo has received funding for organising educational programmes for patients' associations from AbbVie and Boehringer Ingelheim. As the national arthritis coordinator for ConArtritis, she has also received funding for running awareness campaigns from AbbVie, Alfasigma, Amgen, Biogen, BMS, Boehringer Ingelheim, Galápagos, Gebro Pharma, Janssen, Johnson & Johnson, Lilly, MSD, Nordic Pharma, Pfizer, Roche, Sandoz, Sanofi and UCB.

José Luis Andreu Sánchez has received funding for attending conferences/symposia from AbbVie, Janssen, Lilly, Novartis, Pfizer and UCB; speaker fees from AstraZeneca and GSK; and fees for consultancy services for pharmaceutical and technology sectors from AstraZeneca and UCB. He has also received funding for educational programmes and courses for his unit/department from AbbVie, Amgen, AstraZeneca, BMS, Biogen, GSK, Janssen, Lilly, Novartis, Pfizer and UCB.

Laura Cano García has received funding for attending courses/conferences from Gebro, Novartis, Pfizer and UCB; and speaker fees from Biogen, Fresenius Kabi, GSK, Novartis, Sandoz and Theramex.

Carlos González Juanatey has received funding for attending courses/conferences from Daiichi Sankyo; speaker fees from AbbVie, Astra-Zeneca and Novartis; and funding for consultancy services for pharmaceutical and technology sectors from Novartis. He has also received funding from Abbott and Medtronic for acquiring equipment and from Medtronic for hiring staff for his department/unit.

M. Vanesa Hernández Hernández has received funding for attending courses/conferences and speaker fees from AbbVie, Bristol Myers, Grünenthal, Johnson & Johnson, Novartis, Pfizer and UCB; funding for educational programmes and courses from Bristol Myers Squibb, Grünenthal and Novartis; grants for research projects from AbbVie, Johnson & Johnson and Novartis; and fees for consultancy services for pharmaceutical and technology sectors from Amgen and UCB.

Fernando León Vázquez has received funding for attending courses/conferences from SEMFYC; speaker fees from Editorial Panamericana, Elsevier, Esteve Pharmaceuticals, Galapagos, Glaxo, Lilly, Lundbeck, Madrid Region Health Service and World Health Management; and a grant for a research project from Lilly.

Francisco Javier Narvárez García has received funding for attending courses/conferences from AbbVie, Astra Zeneca, Lilly, Pfizer and UCB; speaker fees from AbbVie, Astra Zeneca, Boehringer, Bristol, Galápagos, Gebro pharma, GSK, Sanofi, Lilly, Pfizer and Fresenius; grants from research projects for Astra Zeneca, Boehringer and Novartis; and fees for consultancy services for pharmaceutical and technology sectors from AbbVie, Astra Zeneca, Boehringer, Galápagos, GSK, Lilly, Sanofi and Fresenius.

María Asunción Nieto Barbero has received funding for attending courses/conferences from Boehringer Ingelheim; speaker fees from BMS, Ferrer, Janssen and Roche; funding for educational programmes and courses from Boehringer Ingelheim; fees for consultancy services for pharmaceutical and technology sectors from Boehringer Ingelheim and Roche; and funding for educational programmes and courses for her unit/department from Astra Zeneca and Boehringer Ingelheim.

Ana Ortiz García has received funding for attending courses/conferences from AbbVie, Asacpharma and Pfizer; speaker fees from Pfizer and Sanofi; and grants for research projects from AbbVie, Alfasigma, Gebro Pharma and Pfizer.

Lucía Silva Fernández has received funding for attending courses/conferences from Gebro Lilly, Nordic, Novartis, Pfizer and UCB; speaker fees from Amgen, FAES, Grünenthal, GSK, Janssen, Lilly, Novartis, Pfizer and hUCB; grants for research projects from BMS and Galapagos; and fees for consultancy services for pharmaceutical and technology sectors from Janssen, Novartis, Pfizer and Sanofi.

## Appendix 6. Drugs for RA. Pregnancy and breastfeeding

**Table 11.** Drugs used in RA for women during pregnancy

Drugs compatible with pregnancy	Drugs that women can use if needed to control their disease	Drugs used to treat severe maternal disease	Drugs that women should stop before conception due to teratogenicity concerns	Drugs that women should avoid due to a lack of safety data
HCQ and chloroquine	IL-6R inhibitors	Pulsed methylprednisolone	Cyclophosphamide	JAK inhibitors
SSZ	IL-1 inhibitors	IV immunoglobulins	MTX	LEF (wait 5 half-lives before conception or complete a washout period)
AZA	Costimulation modulator (ABA)		MMF	
Ciclosporin and tacrolimus	Anti-CD20 (RTX)			
TNF inhibitors				
NSAIDs (preferably ibuprofen or diclofenac and discontinue by week 28 of pregnancy)				
Low-dose prednisone and prednisolone				

**Table 12.** Drugs used in RA for women during breastfeeding

Drugs compatible with breastfeeding		Drugs that women can use during breastfeeding if there are no alternatives available to control their disease	Drugs that women should avoid during breastfeeding due to a lack of safety data
HCQ and chloroquine	Pulsed methylprednisolone	MTX	LEF
SSZ	IV immunoglobulins		JAK inhibitors
AZA	IL-6R inhibitors		Cyclophosphamide
Ciclosporin and tacrolimus	IL-1 inhibitors		Etoricoxib
Biological TNF inhibitors	Costimulation modulator (ABA)		MMF
NSAIDs (preferably ibuprofen or celecoxib)	Anti-CD20 (RTX)		
Prednisone and prednisolone			

Table 13. Drugs used in RA for men seeking fatherhood

Drugs compatible with seeking fatherhood in men		Drugs that men seeking fatherhood should avoid, if possible, due to scarce evidence	Drugs that men should stop before seeking fatherhood
HCQ and chloroquine	Pulsed methylprednisolone	JAK inhibitors	Cyclophosphamide
SSZ	IV immunoglobulins	Etoricoxib	
AZA	TNF inhibitors		
Ciclosporin and tacrolimus	IL-6R inhibitors		

MMF	IL-1 inhibitors		
NSAIDs (preferably ibuprofen or celecoxib)	Costimulation modulator (ABA)		
Prednisone and prednisolone	Anti-CD20 (RTX)		
MTX			
LEF			

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