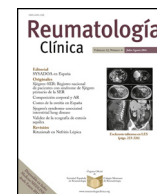




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## Special Article

### Update of the Consensus Statement of the Spanish Society of Rheumatology on the use of biological and synthetic targeted therapies in rheumatoid arthritis

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## ABSTRACT

**Objective:** To update the consensus document of the Spanish Society of Rheumatology (SER) regarding the use of targeted biological and synthetic therapies in rheumatoid arthritis (RA) with the aim of assisting clinicians in their therapeutic decisions.

**Methods:** A panel of 13 experts was assembled through an open call by SER. We employed a mixed adaptation-elaboration-update methodology starting from the 2015 Consensus Document of the Spanish Society of Rheumatology on the use of biological therapies in RA. Starting with systematic reviews (SR) of recommendations from EULAR 2019, American College of Rheumatology 2021, and GUIPCAR 2017, we updated the search strategies for the PICO questions of GUIPCAR. An additional SR was conducted on demyelinating disease in relation to targeted biological and synthetic therapies. Following the analysis of evidence by different panelists, consensus on the wording and level of agreement for each recommendation was reached in a face-to-face meeting.

**Results:** The panel established 5 general principles and 15 recommendations on the management of RA. These encompassed crucial aspects such as the importance of early treatment, therapeutic goals in RA, monitoring frequency, the use of glucocorticoids, the application of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs. Additionally, recommendations on dose reduction of these drugs in stable patients were included. This update also features recommendations on the use of bDMARDs and Janus Kinase inhibitors in some specific clinical situations, such as patients with lung disease, a history of cancer, heart failure, or demyelinating disease.

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**Conclusions:** This update provides recommendations on key aspects in the management of RA using targeted biological and synthetic therapies.

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## Actualización del Documento de Consenso de la Sociedad Española de Reumatología sobre el uso de terapias biológicas y sintéticas dirigidas en la artritis reumatoide

### R E S U M E N

#### Palabras clave:

Artritis reumatoide  
Fármacos biológicos  
Inhibidores de las JAK

**Objetivo:** Actualizar el consenso de la Sociedad Española de Reumatología (SER) sobre el uso de terapias biológicas y sintéticas dirigidas en la artritis reumatoide (AR) como medio de apoyo al clínico en sus decisiones terapéuticas.

**Métodos:** Se constituyó un panel de 13 expertos a través de convocatoria abierta en la SER. Se empleó una metodología mixta de adaptación-elaboración-actualización a partir del Documento de Consenso de la Sociedad Española de Reumatología sobre el uso de terapias biológicas en la AR publicado en 2015. Se partió de las revisiones sistemáticas (RS) de las recomendaciones de EULAR 2019, *American College of Rheumatology* 2021 y GUIPCAR 2017 y se actualizaron las estrategias de búsqueda de las preguntas PICO de GUIPCAR, elaborándose una RS adicional sobre enfermedad desmielinizante en relación con tratamientos biológicos y sintéticos dirigidos. Tras el análisis de la evidencia por los diferentes panelistas se consensuó en reunión presencial la redacción y el grado de acuerdo de cada una de las recomendaciones.

**Resultados:** El panel acordó 5 principios generales y 15 recomendaciones sobre el manejo de la AR. Estas incluyen aspectos como la importancia del tratamiento precoz, el objetivo terapéutico en la AR, la frecuencia de monitorización, el uso de glucocorticoides, la utilización de fármacos antirreumáticos modificadores de la enfermedad (FAME) sintéticos convencionales (FAMEsc), FAME biológicos (FAMEb) y FAME sintéticos dirigidos, así como la reducción de dosis de estos fármacos en pacientes estables. Además, en esta actualización se incluyen recomendaciones sobre el uso de FAMEb e inhibidores de Janus-kinasas en algunas situaciones clínicas especiales, como pacientes con enfermedad pulmonar, antecedente de cáncer, insuficiencia cardíaca o enfermedad desmielinizante.

**Conclusiones:** Esta actualización aporta recomendaciones sobre aspectos clave en el manejo de la AR con terapias biológicas y sintéticas dirigidas.

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## Introduction

The existence of multiple drugs for the treatment of rheumatoid arthritis (RA), together with the significant development of knowledge of the most suitable treatment strategies for its management, make it necessary to set out recommendations that help clinicians to select the most appropriate options for each situation. The Spanish Society of Rheumatology (SER in its Spanish acronym), in its desire to contribute to the improvement in the quality of life of patients with rheumatic and musculoskeletal diseases, has produced a number of consensus documents and updates on the treatment of RA with targeted biological and synthetic therapies since 2000.

The last consensus document was published in 2015;<sup>1</sup> this paper updates that consensus. Since then, new drugs have been approved and additional evidence has been found on the most appropriate treatment strategies for RA. A fundamental milestone has been the development of a large number of biosimilar drugs that are contributing to the reduction in the cost of these therapies, directly affecting one of the previous barriers to their use. A new inhibitor of the interleukin 6 receptor (IL-6R) has been available for years, new targeted synthetic therapies have been approved that augment existing options, and major studies have been published that analyse the safety profile of these treatments. This update builds on the structure of the previous document, in turn in line with the blueprint of the corresponding EULAR recommendations. After starting off with some general recommendations, aspects such as the importance of early treatment, the treatment objective in RA; the use of glucocorticoids (GC); and

the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) are analysed in this update. Of these drugs, in the case of RA, we have only Janus kinase inhibitors (JAKi). In addition, this update includes recommendations on the use of bDMARDs and JAKi in certain clinical situations.

This document aims to help health professionals involved in the care of patients with RA in treatment decision-making. Especially rheumatologists, who are the specialists usually involved in the treatment of this disease. Each of the recommendations has been made, after a detailed analysis of the evidence available, by the group of panellists competitively chosen from the SER, based on their experience on the subject. However, the level of evidence for several of these is limited, so the experience of the members of the panel has been key to the interpretation of the most uncertain or complex scenarios.

## Methodology

### Phases of the process

A series of steps have been followed in updating the consensus document that are described below (Table 1, Fig. 1).

1. *Creation of the working group.* The drafting of the document began with the formation of a panel of experts made up of 13 rheumatologists who are members of the SER. They were elected through an announcement to all SER members. The SER's Clinical Practice Guidelines (GPC in its Spanish acronym) and Recommendations

**Table 1**  
SER consensus over the use of bDMARDs and tsDMARDs in RA.

	Statistics	NE	DR
<b>Recommendations</b>			
<i>General recommendations</i>			
<i>Recommendation A.</i> Treatment of RA should be based on a shared decision between the patient and the rheumatologist	DA = 100%	SD = 0.49	NA NA
<i>Recommendation B.</i> Treatment decisions should be based on disease activity, safety of treatments, and other patient factors, such as comorbidities, progression of structural damage, or management preferences	DA = 100%	SD = 0.52	NA NA
<i>Recommendation C.</i> Rheumatologists are the specialists responsible for the care of patients with RA	DA = 92%	SD = 0.67	NA NA
<i>Recommendation D.</i> The heterogeneity and chronic course of RA make it necessary for patients to access multiple drugs with different mechanisms of action	DA = 100%	SD = 0.29	NA ON
<i>Recommendation E.</i> In the management of RA, the rheumatologist must take into account the high individual, social and healthcare cost that the disease entails	DA = 100%	SD = 0.49	ON ON
<i>Recommendations for the management of RA</i>			
<i>Recommendation 1.</i> Initiation of treatment with conventional synthetic DMARDs is recommended as soon as the diagnosis of RA is reached	DA = 83%	SD = 0.98	1a A
<i>Recommendation 2.</i> It is recommended that remission be achieved and maintained or, failing that, low disease activity as a treatment goal in RA	DA = 100%	SD = 0.29	1a A
<i>Recommendation 3a.</i> In patients with RA and active disease or recent changes to treatment, monitoring every 1-3 months is recommended	DA = 100%	SD = 0.39	2b B
<i>Recommendation 3b.</i> In patients with RA with stable disease, where the treatment goal has been achieved, monitoring every 3-6 months is recommended	DA = 100%	SD = 0.49	2b B
<i>Recommendation 4a.</i> In patients with RA, methotrexate is recommended as monotherapy, as the first choice DMARD	DA = 100%	SD = 0.00	1a A
<i>Recommendation 4b.</i> In the case of intolerance to methotrexate and/or adverse effects, leflunomide or sulfasalazine can be used	DA = 100%	SD = 0.00	1a A
<i>Recommendation 5a.</i> In patients with RA, considering the use of glucocorticoids is recommended as a bridging therapy in the initial treatment, or in the event of changes in csDMARD.	DA = 100%	SD = 0.51	1a A
<i>Recommendation 5b.</i> In patients on treatment with DMARDs and glucocorticoids in whom gradual tapering or withdrawal of glucocorticoids is not achieved, considering intensification or a change of DMARD is recommended	DA = 92%	SD = 1.08	5 D
<i>Recommendation 6a.</i> When the treatment goal has not been achieved with the first strategy using DMARDs, it is recommended that a bDMARD or a JAKi be added. In certain situations, another DMARD may be switched to as monotherapy or in combination	DA = 100%	SD = 0.51	1a A
<i>Recommendation 6b.</i> If it is decided to use a bDMARD, it should be chosen after considering the patient's characteristics, comorbidities, possibility of concomitant use of methotrexate, experience of use and cost	DA = 100%	SD = 0.51	5 D
<i>Recommendation 7.</i> In rheumatoid arthritis that requires combined therapy of a bDMARD/sd with a scDMARD, it is recommended to use methotrexate; When methotrexate is contraindicated or produces intolerance, leflunomide is recommended	DA = 100%	SD = 0.39	1a A
<i>Recommendation 8.</i> When a combination therapy of b/tsDMARD with methotrexate is initiated, it is recommended that the same dose of methotrexate be maintained	DA = 92%	SD = 0.90	1a A
<i>Recommendation 9.</i> Where using a b/tsDMARD as monotherapy, an anti-IL-6R or a JAKi is recommended	DA = 100%	SD = 0.29	1a A
<i>Recommendation 10a.</i> In patients with RA and previous failure of a first anti-TNF, a biologic with a different mechanism of action, a JAKi or even a second anti-TNF can be used	DA = 100%	SD = 0.39	1b A
<i>Recommendation 10b.</i> In patients with RA and previous failure of two or more anti-TNF drugs, the use of a biologic with a different mechanism of action or a JAKi is recommended	DA = 100%	SD = 0.29	1b A
<i>Recommendation 10c.</i> In patients with RA and failure of a non-anti-TNF biologic or a JAKi, any other DMARD or JAKi may be used	DA = 100%	SD = 0.39	4 C
<i>Recommendation 11.</i> In RA patients treated with bDMARD, in remission or with low disease activity for at least 6 months, dose reduction is recommended	DA = 100%	SD = 0.29	1b A
<i>Special recommendations</i>			
<i>Recommendation 12.</i> In patients with rheumatoid arthritis with an indication for tsDMARDs and diffuse interstitial lung disease, abatacept or rituximab or, alternatively, anti-IL-6R or iJAK are recommended	DA = 77%	SD = 0.74	4 C
<i>Recommendation 13.</i> In patients with RA and a history of cancer who are going to start biological or targeted treatment, it is recommended that an individualised decision be taken, agreed on with the patient and their oncologist	DA = 92%	SD = 0.58	4 C
<i>Recommendation 14.</i> In patients with RA and moderate or severe heart failure who require b/tsDMARDs, it is recommended that anti-TNF (NYHA class III or IV) and rituximab (NYHA class IV) be avoided	DA = 100%	SD = 0.39 SD = 0.29	4 C 4 C

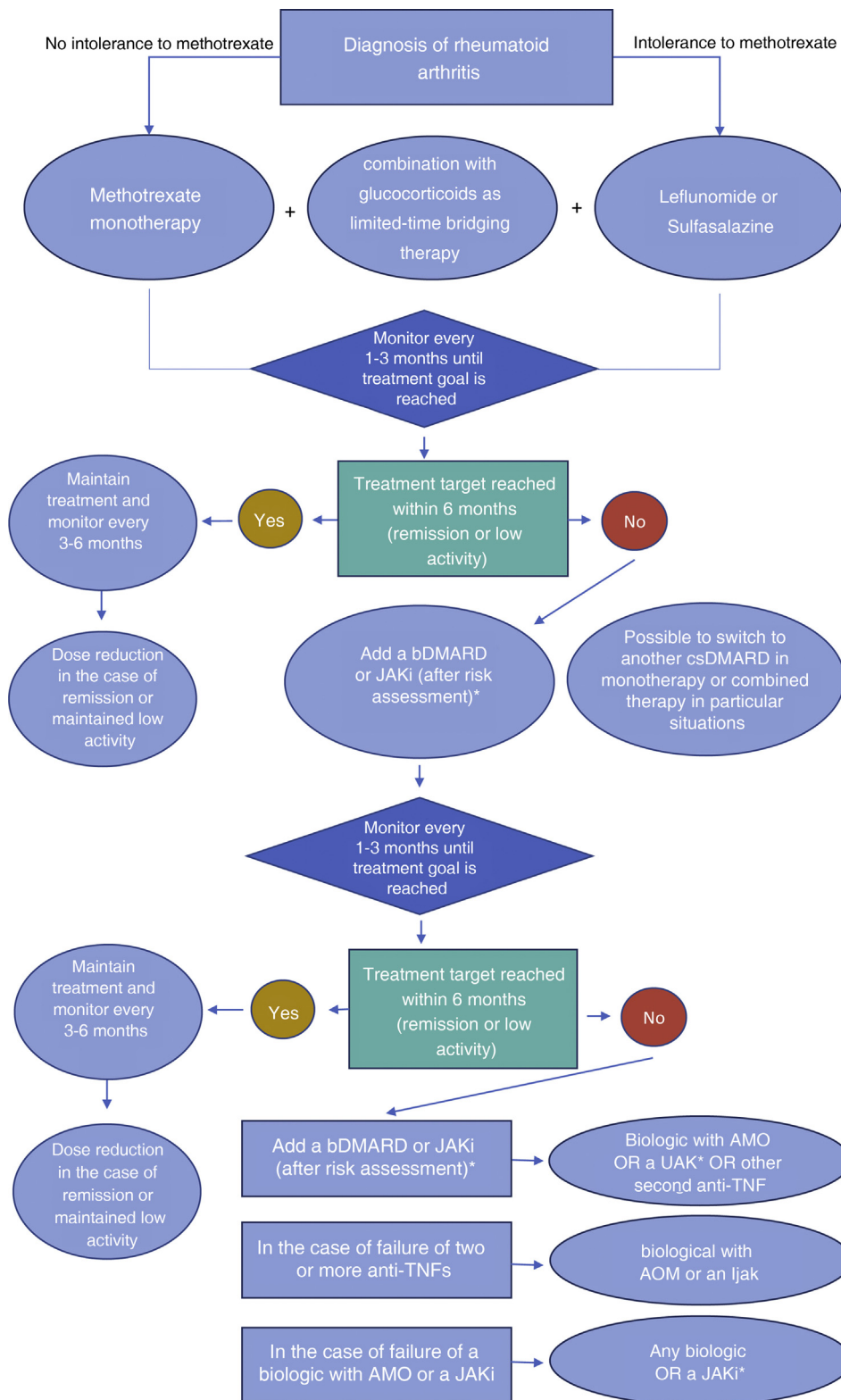
SD: standard deviation; DA: degree of agreement; DR: degree of recommendation from the SER, ACR, EULAR and GUIPCAR<sup>1-4</sup> Consensus documents; LE: Level of evidence from the SER, ACR, EULAR and GUIPCAR<sup>1-4</sup> Consensus documents.

Classification according to the Oxford Centre for Evidence-Based Medicine (CEBM) system.<sup>5</sup>

Committee evaluated the curriculum vitae of all applicants, in line with the objective criteria which contribute to the knowledge of RA. Coordination of the clinical and methodological aspects, respectively, was managed by one of these rheumatologists, as principal investigator (PI), as well as a specialist in methodology and a technician from the SER's Research Unit.

2. *Identification of key areas in order to update the previous consensus.* In the first working meeting all the panellists participated in the tasks of providing a structure for the document, as well as laying down the content and key aspects.
3. *Definition of the methodology to be followed in the consensus-building process.* It was decided to use a mixed adaptation-

drafting-updating methodology. To this end, the starting point was the document prepared in 2014 (*2014 Update of the Consensus Document of the Spanish Society of Rheumatology on the use of biological therapies in rheumatoid arthritis*).<sup>1</sup> In addition, it was decided to take into account the revisions and recommendations already included in three other documents: a) 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis;<sup>2</sup> b) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update,<sup>3</sup> and c) GUIPCAR (SER's clinical practice guidelines for the management of patients with RA) 2017.<sup>4</sup> The process was



**Fig. 1.** Rheumatoid arthritis treatment algorithm.

DMARD: disease-modifying drug. B: biologic. CS: Conventional synthetic. AMO: Another mechanism of action.

JAKi: Janus kinase inhibitor\*: Limit the use of JAKi in patients of 65 years and over; those with risk factors for cardiovascular or thromboembolic disease; smokers; or those with additional risk factors for cancer.

completed by also assessing the *EULAR article recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update*.

4. *Bibliographical search.* The search strategies for the PICO questions from GUIPCAR were updated. It was decided to set the starting date for the search from 2019, the date of the ACR update, or 2016 for which there were no ACR data. The database



used was Pubmed (Medline). An additional SR was drafted to respond to a new clinical question posed by the expert panel: "In patients with RA, what is the risk of developing demyelinating disease from treatments with biological DMARDs or targeted synthetic DMARDs?"

5. *Analysis of the evidence.* The rheumatologists in the working group were in charge of reviewing the studies identified and selecting the most relevant ones. The information available on the subject was then summarised, including a draft of the relevant results.
6. *Formulation of recommendations.* At a second meeting, draft proposals were presented for each of the recommendations in order to reach a final proposal for drafting. Through the face-to-face meeting, interaction between the experts gave rise to a deeper understanding of all the most relevant issues. Using the modified nominal consensus technique, the degree of the experts' agreement with the wording of each of the recommendations was decided upon by consensus. Agreement was assessed using responses to the Likert scale. The score of "1" indicated complete disagreement with what was expressed in the text and the score of "5" indicated complete agreement with this statement. A high degree of consensus over the wording was defined as the percentage of panellists who gave values  $\geq 4$  on the Likert scale, equal to or greater than 75%. In addition to collecting statistical information on the degree of agreement reached by the panellists over each recommendation, the final recommendations were included in a table that also shows the levels of evidence and the degrees of recommendation, following the classification by the Oxford Centre for Evidence Based Medicine (CEBM).<sup>5</sup>

## Results and discussion

### General principles

- A) Treatment of RA should be based on a shared decision between the patient and the rheumatologist. DA 100%; SD = 0.49.
- B) Treatment decisions should be based on disease activity, safety of treatments, and other patient factors, such as comorbidities, progression of structural damage, or patients' administration preferences. DA 100%; SD = 0.52.
- C) Rheumatologists are the specialists responsible for the care of patients with RA. DA 92; SD = 0.67.
- D) The heterogeneity and chronic course of RA make it necessary for patients to access multiple drugs with different mechanisms of action. DA 100%; SD = 0.29.
- E) In the management of RA, the rheumatologist must take into account the high individual, social and healthcare costs that this disease entails. DA 100%; SD = 0.49.

For the first time, a series of general principles, for which there is no verifiable evidence, are included in this consensus document. These principles establish a framework for the management of RA, based fundamentally on the opinion of the panellists.

The first principle emphasizes the decisive role that the patient must play when participating in the choice of the most appropriate treatment for his or her disease, a fundamental principle in the current concept of medical practice. Principle B lists the key elements that must be considered when choosing a treatment, including aspects such as the patient's preference for the route of administration, its frequency, etc. Principle C stresses the central role of the rheumatologist in the management of RA; this does not, however, question the fact that, in areas where there is no access to a rheumatologist, some other specialist could take over the treatment of these patients. General principle D is also of great importance, in the sense that, given the complexity of RA and its chronic course, with a

frequent need to change the treatment throughout the patient's life, the availability of different bDMARDs or JAKi should not be limited, using the argument that other accessible drugs already exist. The last general principle stresses the need to incorporate the economic factor within the different elements, when choosing a treatment. This has a twofold perspective: on the one hand, the high cost of some therapies must be considered in terms of long-term savings on disability and job losses; on the other hand, the cost of medicines must be taken into account when choosing between two drugs with the same efficacy and safety profile, prioritising the one with the lower cost.

### Recommendations

*Recommendation 1. Initiation of treatment with conventional synthetic DMARDs is recommended as soon as the diagnosis of RA is reached. DA 83%; SD = 0.98.*

The systematic review for the update of RA treatment by SER 2014, the ACR 2021<sup>2</sup> and EULAR 2022<sup>6</sup> shows that treatment with csDMARDs improves the symptoms and signs of RA, and that this should be started as soon as the diagnosis of RA is reached. In addition, the importance of early diagnosis and treatment of the disease is emphasised, given that numerous studies, clinical trials, and meta-analyses<sup>7,8</sup> show that the duration of the disease before the start of treatment is associated with radiographical progression and with a lower probability of achieving remission.

Although the anti-TNF, tocilizumab (TCZ) and abatacept (ABA) would be indicated in the summary of product characteristics in patients with onset RA not previously treated with csDMARDs, and some studies and meta-analyses show that initial treatment with bDMARDs could have better clinical outcomes,<sup>9–11</sup> the strategy of initiating therapy with bDMARDs is not considered in the current recommendations. There are several reasons why the panel proposes the initiation of treatment with csDMARDs. In addition to safety and cost, a large number of patients can achieve clinical remission with methotrexate (MTX), without the need for a bDMARD or JAKi.<sup>12,13</sup> Two panellists disagreed with this recommendation, arguing that patients with pre-arthritis or undifferentiated arthritis should be included. This alternative is based on the EULAR 2016 recommendations for the management of early arthritis,<sup>14</sup> which include the possibility of extending the prescription of csDMARDs to patients with undifferentiated arthritis, if the rheumatologist has a major suspicion that it may evolve to RA.<sup>15–18</sup> Finally, it was decided that pre-arthritis or undifferentiated arthritis was beyond the objective of the document, which does not mean that the panel was against the possible early use of csDMARDs for this patient profile.

*Recommendation 2. It is recommended that full remission be achieved and maintained or, failing that, a low level of disease, as a treatment goal in RA. DA 100%; SD = 0.29.*

Remission is the most important treatment goal, according to treat-to-target (T2T) recommendations, as well as guidelines published by different organisations.<sup>4,19,20</sup> It has been shown that patients who achieve remission demonstrate better physical function, have better quality of life, greater productivity, less progression of structural damage, fewer orthopaedic surgeries and lower cost per patient, even when compared to other positive conditions such as low disease activity.<sup>21–23</sup>

However, remission or low RA activity as targets is a source of debate. The ACR recommendations prefer low activity as a goal and then consider remission, as the more treatments that fail, the more difficult it is to achieve the treatment goal. Remission as a target is not recommended because, according to established criteria, it may not be achievable, and if it is not achieved, this may be daunting.<sup>2</sup> In the TITRATE study, patients with established, moderately active RA who were randomised to receive intensive treatment versus

usual treatment showed that, although remission was achieved in a greater number of patients in the intervention arm (32% vs. 18%), it was at the expense of significantly increasing expenditure. Severe disability prior to treatment or being overweight made it difficult to achieve remission.<sup>24</sup> Despite these considerations, the panel considered remission to be the most desirable goal, especially in patients with a relatively short duration of disease.

DAS28, SDAI, CDAI, or Boolean criteria were used to describe remission. However, RA patients in whom synovitis was suppressed may still have significant pain or fatigue that is not explained by disease activity. This should be taken into account when interpreting RA activity rates.

**Recommendation 3a.** *In patients with RA and active disease or recent treatment changes, monitoring every 1-3 months is recommended. DA 100%; SD = 0.39.*

**Recommendation 3b.** *In RA patients with stable disease, in whom the treatment goal has been achieved, monitoring every 3-6 months is recommended. DA 100%; SD = 0.49.*

Sustained inflammatory activity in patients with RA can have irreversible consequences, so it is essential to adopt a treat-to-target strategy with adequate monitoring.<sup>25</sup> This has demonstrated long- and medium-term benefits in the overall evolution of the disease, regardless of the drug used.<sup>26–28</sup>

There is no specific data on the most appropriate frequency of monitoring clinical activity in patients with RA, since most studies are not designed to evaluate this.<sup>29,30</sup> Most publications propose monitoring periods ranging from 4 weeks to 4 months.<sup>31–43</sup>

The expert panel proposes that, in recent initiation of—or changes in—DMARD treatment, the optimal range of clinical monitoring should be between 1 and 3 months. In a stable clinical situation, it is recommended that this monitoring be spaced out to every 3-6 months. On the other hand, the panel considered that, in special situations where the disease is controlled in a sustained manner and there is the support of a health care professional (primary care physician) who runs intermediate analytical controls, monitoring could be extended to a maximum of 9 months.

Conversely, the growing development in information and communication technologies (ICTs) is ushering in a revolution in the management of patients in different areas of medicine.<sup>44</sup> The panel of experts recognises that there are certain circumstances where patients with chronic diseases could benefit from telematic monitoring, supported by the use of ICTs, thus avoiding face-to-face visits. Recently, EULAR published recommendations on how remote monitoring should be undertaken in patients with rheumatic diseases.<sup>45</sup> This document highlights the importance of having the necessary equipment and adequately trained professionals to handle remote control of the disease. Current evidence on models for the implementation of these tools in the hospital setting is still scarce, although there is very promising data.<sup>46,47</sup> Nevertheless, the successful implementation of these techniques requires the development of high-quality digital solutions that have been rigorously evaluated in a clinical setting.<sup>48</sup>

**Recommendation 4a.** *In patients with RA, methotrexate is recommended as a monotherapy, as the first choice DMARD. DA 100%; SD = 0.0.*

**Recommendation 4b.** *In the case of intolerance and/or adverse effects from methotrexate, alternatively leflunomide or sulfasalazine can be used. DA 100%; SD = 0.0.*

The panel considered that the current data clearly reinforce the use of MTX ahead of other csDMARDs, taking into account its proven effectiveness, much more frequently contrasted than that of hydroxychloroquine (HCQ), sulfasalazine (SSZ) or leflunomide (LEF), as well as dose flexibility and experience in different clinical scenarios of the disease.<sup>2,49,50</sup> Oral administration is preferable, thanks to its ease of use, good safety profile and bioavailability at initial doses of the drug. However, there are other studies that sug-

gest that the efficacy of subcutaneous administration is greater, although the cost of this is a factor to be considered.<sup>51–54</sup> The dose of MTX was not discussed in detail, referring to previous versions.<sup>55</sup> Briefly, it is considered appropriate to use it in rapid dosage escalation, starting at 10–15 mg and working the way up to around 25 mg weekly.

MTX monotherapy was considered to be of choice because the greater burden of combination therapy (e.g., multiple medications, higher cost, more adverse effects) outweighed the moderate-quality evidence, suggesting improvements in disease activity associated with the csDMARD combination. However, the panel considered it acceptable to choose csDMARDs in combination, in some situations, in order to obtain a greater response, despite the additional burden of taking multiple tablets.<sup>56</sup>

Some panellists considered the use of HCQ, ahead of MTX, acceptable in RA with a low inflammatory load and with no poor prognostic factors, due to its good safety profile,<sup>57,58</sup> although there were differences in criteria on this point.

If MTX cannot be used, LEF has demonstrated its efficacy in RA, at a dose of 20 mg daily in monotherapy, both from the clinical and the radiological progression point of view. This efficacy is similar to that of MTX, although it has been debated whether the doses of MTX used in comparative studies were optimal for this drug.<sup>59,60</sup> LEF is also effective in combination with biological agents<sup>61,62</sup> and JAKi63, although with less evidence than that available on MTX. For these reasons, LEF can be considered as the first alternative to MTX in the case of intolerance to or contraindication for MTX.<sup>64</sup>

Enteric-coated SSZ at doses of 2 g per day, escalated according to tolerance to 3–4 g, has demonstrated efficacy similar to MTX, from the clinical and radiological point of view.<sup>65–70</sup> Furthermore, it is safe during pregnancy. However, since there is no enteric-coated SSZ in Spain, the poor tolerability of the 3–4 g doses limits the use of this drug.<sup>64,71</sup>

Finally, chloroquine (CQ) and basically HCQ, are drugs whose use in monotherapy in RA is practically ruled out, without prejudice to what has been mentioned above in mild patients. Its use in RA has been practically limited to combined therapy with SSZ and MTX. HCQ, like SSZ, is a safe drug in pregnancy.<sup>72</sup>

In patients with MTX-induced nodulosis, a change of DMARD should be considered, although information on the efficacy of LEF or SSZ in this situation is limited.<sup>73</sup>

**Recommendation 5a.** *In patients with RA, it is recommended that the use of glucocorticoids be considered as bridging therapy in the initial treatment or in the event of a change in csDMARD. DA 100%; SD = 0.51.*

**Recommendation 5b.** *In those patients treated with DMARDs and glucocorticoids in whom gradual tapering or withdrawal of glucocorticoids is not achieved, it is recommended that intensification or a change of DMARD be considered. DA 92%; SD = 1.08.*

There is evidence that low-dose GCs are often necessary as initial treatment to relieve symptoms before the onset of csDMARDs.

Although the optimal duration of treatment is not known, the latest ACR 2021 and EULAR 2019 recommendations suggest, based on expert opinion, that if necessary this treatment should not be prolonged for more than 3 months due to its significant toxicity.<sup>2,3</sup> Thus, treatment with GC should be limited to the minimum effective dose with the shortest possible duration.

According to the latest EULAR 2019 recommendations, there was unanimity that these drugs should be used primarily as bridging therapy until csDMARDs demonstrate their efficacy, and with rapid tapering.<sup>3</sup>

Failure to maintain the treatment goal in the gradual tapering or withdrawal of GC after the bridging therapy phase should be considered as a failure of this treatment phase and therefore the initiation of a bDMARD or a JAKi added to the csDMARD should be considered.

As regards the debate on the preference of treatment with bDMARDs or JAKi over treatment with csDMARDs plus GC, at least three clinical trials have shown similar responses when MTX plus GC was compared with MTX plus DMARD.<sup>38,74,75</sup> However, it has been shown that prolonged use of GC after the bridging period (less than 3 months) leads to the negative impact of GCs with undesirable effects on patients in the long term, including the risk of infections, osteoporosis and cardiovascular diseases, RA and other rheumatic diseases, supported by growing evidence.<sup>76–81</sup>

*Recommendation 6a. When the treatment goal has not been achieved with the first strategy using csDMARDs, it is recommended that a bDMARD or a JAKi be added. In certain situations, another csDMARD may be switched to as monotherapy or combination. DA 100%; SD = 0.51.*

*Recommendation 6b. If it is decided to use a bDMARD, it should be chosen after considering the patient's characteristics, comorbidities, possibility of concomitant use of methotrexate, experience of use and cost. DA 100%; SD = 0.51.*

The panel considers that risk stratification is an aspect of the utmost relevance in the management of RA. A state of great activity, positivity of the rheumatoid factor and/or anti-citrullinated protein antibodies (ACPA); failure to perform two or more csDMARDs; and the presence of erosions are all factors of poor prognosis in RA.<sup>82,83</sup> In addition, panellists consider that an inadequate response (IR) to MTX represents in itself a factor of poor prognosis in RA.

In patients with a poor prognostic factor, it is recommended that a bDMARD or a JAKi be added, after an adequate evaluation of the patient's risk factors (see below). The term "add" reflects the consensus that it is recommended that b/tsDMARD be used in combination with csDMARDs, unless there is intolerance or contraindication, given the demonstrated superiority of combination therapy over b/tsDMARD monotherapy, particularly for anti-TNF drugs.<sup>84,85</sup>

All bDMARDs show comparable efficacy in the treatment of RA with an IR to MTX.<sup>30</sup>

It is common to initiate biological therapy with an anti-TNF agent combined with MTX for a variety of reasons including clinicians' experience, more long-term safety information, and the availability of lower-cost biosimilars. The choice of ABA, rituximab (RTX), or IL-6R inhibitors depends on a number of factors: patient preferences, drug cost, comorbidities, route of administration, clinician experience, and indications (RTX is not approved for first-line indication after MTX failure).

In RA, four JAKi (tofacitinib, baricitinib, upadacitinib, and filgotinib) have demonstrated efficacy and safety with RCTs of high methodological quality in different clinical situations.<sup>86–106</sup>

The results of the *Oral-Surveillance RCT*<sup>107</sup> have recently been published, failing to demonstrate the non-inferiority of tofacitinib compared to etanercept or adalimumab (ADA) with respect to the occurrence of cancer and relevant cardiovascular events in patients over 50 years of age with some cardiovascular risk factor. Another observational study on clinical practice has identified an increased risk of venous thromboembolism in patients treated with baricitinib versus anti-TNF.<sup>108</sup> Following these results, the European Medicines Agency (EMA) Committee for Risk Assessment (PRAC) has concluded that the increased risk of major cardiovascular events, thromboembolic disease, cancer, serious infections and all-cause mortality identified in these studies should be considered a class effect for all JAKi, given the similarity of all these drugs in their mechanism of action. For all these reasons, the EMA recommends that, in patients aged 65 years or older, those with a history or risk factors of cardiovascular disease, smokers or ex-smokers who smoked for a long time or with additional risk factors for cancer, JAKi should be used only when adequate treatment alternatives are not available. Likewise, the EMA recommends that, in patients at risk of thromboembolic disease, JAKi should be used

with caution.<sup>51</sup> This panel considers that JAKi are a reasonable alternative to bDMARDs in RA and that they can be used after a careful evaluation of the existence of the risk factors described.

In patients with no poor prognostic factors, with an inadequate response to a first strategy with csDMARDs (which practically always includes MTX), another strategy with csDMARDs could be considered as monotherapy (LEF or SSZ) or in combination (MTX + HCQ + SSZ –triple therapy– or MTX + LEF).<sup>12,30,51,52,109</sup> There is no RCT data on the use of MTX + LEF compared to the addition of a bDMARD or a JAKi in this context, so this panel cannot recommend its use, based on the existing scientific evidence. However, the panel is aware of the frequent intolerance to triple therapy, as well as the widespread use in our setting of the MTX + LEF combination, so in selected cases, this combination could be a reasonable alternative.

*Recommendation 7. In rheumatoid arthritis requiring combination therapy of a b/tsDMARD with a csDMARD, methotrexate is recommended; When methotrexate is contraindicated or produces intolerance, leflunomide is recommended. DA 92%; SD = 0.39.*

A clinical trial<sup>110</sup> and different cohort studies<sup>62,111–113</sup> have analysed various combinations of treatment of csDMARDs (including MTX, LEF and others) with anti-TNF agents, concluding that most of them and potentially other csDMARDs are as effective and safe as MTX in combination with different anti-TNFs.

In a large collaborative cohort study<sup>114</sup> between European registers, the percentage of patients who achieved a good EULAR response at 6 months in the RTX + LEF group (29.1%) was statistically higher than that of RTX + MTX (21.1%) and RTX monotherapy (19.3%). Similar results were observed at 12 months, with a similar frequency of adverse effects (AEs) between groups. An analysis of the RABBIT<sup>115</sup> register in patients with RA who had not previously received MTX concluded that, for patients intolerant to MTX, the combination RTX + LEF is a good option also in the long term. A Spanish cohort study<sup>116</sup> showed that the efficacy and safety of TCZ combined with MTX was similar to that of LEF combined.

A recently reported SR + meta-analysis<sup>117</sup> analysed which was the best csDMARD (MTX or LEF/other) to combine with a biologic DMARD/JAKi. For RTX, a significantly better EULAR response (RR = 1.46,  $p < 0.001$ ) and better safety (not significant) were observed with LEF than with MTX. With respect to subjects who received anti-TNF, the probability of achieving a good or moderate EULAR response was somewhat higher when combined with MTX than with other synthetic DMARDs.

Data on ABA, TCZ or JAKi<sup>4,63</sup> were insufficient to draw conclusions.

*Recommendation 8. When a combination therapy of b/tsDMARD with methotrexate is initiated, it is recommended that the same dose of methotrexate be maintained. DA 100%; SD = 0.90.*

An SR<sup>118</sup> established that in multiple RCTs and observational studies on bDMARDs (many of them in patients with IR-MTX) the maximum dose of MTX that was combined with the biological agent at the start of therapy was 25 mg weekly for oral administration and 15 mg for parenteral administration, with mean doses of 12.5–15 mg weekly.

The CONCERTO<sup>119</sup> study investigated the efficacy and safety of increasing weekly doses of MTX in combination with ADA in RA. Their results suggest that the doses of 10 and 20 mg weekly of MTX when combined with ADA are similar, with doses of 2.5 and 5 mg per week showing less efficacy. The MUSICA study<sup>120</sup> investigated the usefulness of reducing the dosage of MTX (7.5 mg weekly vs. 20 mg weekly) when initiating its combination with ADA in patients with previous failure of this drug. Their results did not support routine dose reduction of MTX when ADA combination therapy was initiated. The interpretation and application of these studies to practice gave rise to an interesting debate within the group that drafted these recommendations; some members considered that



the evidence could support the reduction of MTX doses to 10 mg when the combination with an anti-TNF is initiated. However, the group agreed that, when MTX is combined with anti-TNF, the starting dose of MTX should be at least 10 mg weekly.

There are no studies comparing different doses of MTX when combined with JAKi. Therefore, the panel recommends continuing with the same dose of MTX that the patient previously received. In the pivotal RCTs on tofacitinib (as well as in real-world studies) the pooled dose of MTX ranged from 7.5 to 25 mg weekly,<sup>87,90,91,121</sup> and in baricitinib RCTs, from 10–25 mg every 7 days.<sup>93</sup>

It has also been suggested that spreading the total weekly dose of MTX over 2–3 oral doses every 2–3 days may be better than giving it all together and similar to the use of the parenteral route, in terms of efficacy and tolerability.<sup>122</sup>

**Recommendation 9.** *In the case of using a b/tsDMARD as monotherapy, an anti-IL-6R or a JAKi is recommended. DA 100%; SD = 0.29.*

All the b/tsDMARDs are more effective when combined with MTX or another csDMARD compared to their individual prescription.<sup>123</sup> However, unlike monotherapy with anti-TNF, ABA, and RTX, the isolated use of antibodies against the IL-6 receptor (sarilumab, tocilizumab [TCZ]) and JAKi can achieve an adequate treatment effect, similar to that achieved when combined with MTX and superior to monotherapy with other biological agents.<sup>124–129</sup>

Different studies have compared combined TCZ + MTX therapy versus TCZ monotherapy, demonstrating that there are no significant differences between the two groups in efficacy, especially in the short term.<sup>130,131</sup> However, in other studies, TCZ + MTX combination therapy appeared to be significantly superior in the medium/long term in the rate of Boolean remission and radiological progression.<sup>132</sup> TCZ or sarilumab monotherapy is superior to ADA monotherapy.<sup>128,129</sup>

Regarding JAKi, all of them have demonstrated their efficacy in monotherapy.<sup>95,97,106,127,133,134</sup> The comparison of the combined treatment of tofacitinib and MTX with tofacitinib alone demonstrates the efficacy of the latter, although this is slightly less than that of combined therapy.<sup>127</sup> Baricitinib has demonstrated efficacy in monotherapy similar to that of combined treatment with MTX in patients with RA-onset.<sup>95,133</sup> Upadacitinib and filgotinib have also demonstrated their efficacy as monotherapy, although there are no direct comparative studies with their use in combination with MTX.<sup>97,134</sup>

**Recommendation 10a.** *In patients with RA and failure prior to a first anti-TNF, a biologic with a different mechanism of action, a JAKi or even a second anti-TNF can be used. DA 100%; SD = 0.39.*

**Recommendation 10b.** *In patients with RA and previous failure of two or more anti-TNF drugs, the use of a biologic with a different mechanism of action or a JAKi is recommended. DA 100%; SD = 0.29.*

**Recommendation 10c.** *In patients with RA and failure of a non-anti-TNF biologic or a JAKi, any other DMARD or JAKi can be used. DA 100%; SD = 0.39.*

In clinical practice, the need to change biologics or JAKi is very frequently raised due, in most cases, to inefficacy.<sup>135–137</sup> In addition, it is known that the survival of the different drugs is lower as the lines of treatment used increase.<sup>138</sup> Within this general situation, the panel evaluated three different possible scenarios. The first two focussed on evaluating the response, persistence and/or costs of DMARDs (including another anti-TNF) or JAKi after failure of anti-TNF therapy.<sup>136–175</sup> With regard to switching to a second biologic after failure of a first anti-TNF, different studies, both clinical trials and cohort studies<sup>142,143,146,148,149,153,156–158,160,164,165,168,170,172</sup> have demonstrated the efficacy of a biologic with another mechanism of action (AMO), a JAKi or even a second anti-TNF. This backing from the evidence facilitated a good degree of agreement among the panellists when issuing the recommendation. Although several of these studies show some variance between the different treatment options, the available evidence does not

allow the choice of one specific drug to be recommended rather than another, so the panel decided to establish a certain priority between the drugs in the drafting of the recommendation, giving preference to the change of treatment target, but without establishing a clear hierarchy and leaving open the choice of one or other drug, depending on the individualised assessment of each patient. Somewhat clearer is the available evidence of the treatment to be chosen after failure of two or more anti-TNF drugs.<sup>136–141,145,147,150–152,154,155,159,161–163,166,167,169,171,173–176</sup>

This evidence shows greater efficacy after switching to a drug with AOM compared to a third or successive anti-TNF. The panel recommends this change of mechanism of action after failure of two or more anti-TNFs with a high degree of agreement although, as in the previous scenario, the existing evidence does not permit one mechanism of action to be recommended over another, so the choice is left open to the individualised assessment of each case. The third part of the recommendation includes patients in whom at least one previous treatment with non-anti-TNF or JAKi biologics has failed. Studies of different quality from the point of view of scientific evidence have analysed the treatment of patients in whom AMO has failed<sup>177–185</sup> and they demonstrate a number of advantages—especially from the point of view of survival—of treatment with another drug with AMO or JAKi, compared to an anti-TNF drug. However, the variability in the drugs used in the different studies again prevents the recommendation of a hierarchy in the choice of drug. Finally, looking at the scenario of patients with treatment failure with a JAKi, different studies, generally of low quality from the point of view of evidence-based medicine,<sup>177,181,183,184</sup> have shown the efficacy of a second JAKi similar to that of anti-TNF drugs or AMO, although with certain advantages in the persistence of treatment in the first of these. The available evidence, which does not permit stratification of treatment with anti-TNF drugs, with AOM or JAKi after the failure of these last two, led the panel to issue a single recommendation for this scenario, with a lower degree of agreement than in other cases, without prioritising the choice between them. This should be subject to the individual assessment of the patient in each case.

In all these scenarios, the recommendation discussed above to limit the use of JAKi in patients over 65 years of age, with a history or risk factors of cardiovascular disease or cancer, should be taken into account.

**Recommendation 11.** *In patients with RA treated with b/tsDMARDs, in remission or with low activity for at least 6 months, it is recommended that dose reduction be considered. DA 77%; SD = 0.29.*

For some time, the suspension or progressive reduction of the dose has been proposed in those patients who are in remission or in a low disease activity state, which would mean a lower risk for the patient, in addition to a reduction in expenditure.

In a high proportion of patients, the suspension of biological treatment entails reactivation of the disease and greater irreversible damage, so this is not advisable.<sup>186–196</sup> However, there is evidence that patients with RA in remission or with low disease activity for at least 6 months may reduce the dose of b/tsDMARDs. These studies have been conducted with both anti-TNF and other targeted treatments. Most of the results concur that dose reduction in patients who have achieved the treatment goal in a sustained manner maintains remission or low activity in most cases, with disease control being restored with intensification of treatment in the case of reactivation.<sup>192,196–209</sup>

As for the different strategies for reducing doses or spacing them, there were no differences in the results.<sup>210</sup>

Several studies identify profiles and markers associated with greater success in reducing treatment: short-course RA, male patients, early remission or low activity, low or negative titres of rheumatoid factor, and combination with MTX, other csDMARDs, or GC.<sup>6,50,211–213</sup>



For the situation of patients with RA in remission or low activity who receive combined MTX therapy with bDMARDs or tsDMARDs, there is no difference as regards which of the two strategies is reduced first, so cost and other factors such as comorbidities, antidrug antibody formation, and patient opinion should be taken into account in this decision.<sup>214–218</sup>

Some uncertainties as regards this recommendation highlight the importance of the decision to reduce or space a b/tsDMARD to be shared between rheumatologists and patients.

### Special recommendations

**Recommendation 12.** In patients with RA indicated for b/tsDMARD and diffuse interstitial lung disease, abatacept or rituximab or, alternatively, anti-IL-6R or JAKi are recommended. DA 77%; SD = 0.74.

RA-associated diffuse interstitial lung disease (RA-ILD) is the most common pulmonary manifestation in patients with RA, and causes high morbidity and mortality.<sup>219,220</sup> Both the new recommendations by SER-SEPAR for the management of RA-ILD,<sup>221</sup> as well as the SER's clinical practice guidelines for the management of patients with RA (GUIPCAR), and the guidelines from the British Society of Rheumatology,<sup>222</sup> concur in pointing out in their SR that ABA and RTX are the biological agents with the most evidence of safety in these patients,<sup>223–225</sup> while anti-TNF drugs could be associated with a risk of worsening of a pre-existing RA-ILD (with a low level of evidence).<sup>226</sup> The Spanish experience of using ABA in clinical practice supports the safety of its use in RA-ILD.<sup>223–225</sup> In addition, in a study that analysed safety data from 3173 patients included in pivotal studies with ABA, the incidence of ILD was 1.1/1000 patient-years, a figure similar to that estimated for RA.<sup>227</sup> Likewise, there are observational studies with RTX that confirm its safety and its possible usefulness in stabilising or improving lung function in these patients.<sup>224,228,229</sup>

On the other hand, the published evidence with IL-6 inhibitors in patients with RA-EPID is limited to TCZ and, although some studies have been contradictory,<sup>230,231</sup> others show an adequate safety profile.<sup>232</sup> Regarding JAKi, although cases of ILD were reported in RCTs for the development of tofacitinib, in a *post hoc* analysis the incidence of ILD was similar to that estimated in AR.<sup>233</sup> Similarly, existing information with baricitinib has not detected an increased risk of developing or exacerbating ILD in clinical trials.<sup>234</sup>

In this context, the panel considers that, with the available information, it is reasonable to prioritise the use of ABA or RTX in these patients, however maintaining TCZ or JAKi as appropriate alternatives.

**Recommendation 13.** In patients with RA and a history of cancer who are going to start biological or targeted treatment, it is recommended that an individualised decision be taken, agreed jointly with the patient and their oncologist. DA 92%; SD = 0.58.

The panel considers that the existing literature does not allow for a more specific answer to this question. Some observational studies in patients with RA and cancer who have received bDMARD nevertheless provide interesting information.

Several posts in European registries have found no differences in cancer recurrence among RA patients treated with anti-TNF, RTX, or csDMARDs,<sup>235–238</sup> or even with other pathologies such as psoriasis and inflammatory bowel disease.<sup>239</sup> A meta-analysis published in 2020<sup>240</sup> confirmed that patients with RA and a previous neoplasm treated with bDMARDs did not have an increased risk of developing cancer compared to patients treated with csDMARDs. Other studies that have evaluated patients with head and neck cancer<sup>241</sup> and breast cancer<sup>242,243</sup> treated with anti-TNF have not found a higher rate of recurrence either.

There are no longitudinal observational studies looking at the risk of cancer recurrence in patients treated with non-anti-TNF (other than RTX and anakinra) or JAKi. Studies on cancer inci-

dence in RA patients with no history of cancer do not show an increased risk with non-anti-TNF bDMARDs, except with ABA. A post-marketing study<sup>244</sup> showed a slight increase in melanoma in patients treated with ABA compared to other bDMARDs, and an SR<sup>245</sup> found an increased risk of cancer overall, compared with anti-TNF and non-melanoma skin cancer compared with anti-TNFs.<sup>17,245–247</sup> With respect to JAKi, two previous meta-analyses<sup>17,248</sup> had not detected an increase in cancer incidence. However, in the ORAL Surveillance randomised clinical trial,<sup>107,249</sup> tofacitinib did not meet non-inferiority criteria in terms of cancer incidence compared to anti-TNFs.

Given these findings, the development group considered that it was reasonable to use b/tsDMARDs in patients with a history of cancer. The safety data on ABA and JAKi suggest that these drugs should be reserved for patients who are unable to receive an anti-cytokine drug (TNF or IL-6) or RTX. However, since these findings have not been obtained in populations of patients with a previous neoplasm—the object of this recommendation—this recommendation was not established in the end, leaving the decision as the result of consensus between the rheumatologist, the oncologist and the patient. Factors such as the nature and stage of the previous cancer (not all cancers have the same risk of recurrence or the same time horizon), the treatment received, or RA<sup>250</sup> activity should be taken into account.

**Recommendation 14.** In patients with RA and moderate or severe heart failure who require b/tsDMARDs, it is recommended that anti-TNF (New York Heart Association [NYHA] class III or IV) and rituximab be avoided (NYHA class IV). DA 100%; SD = 0.39.

To date, there is not much evidence supporting this research question other than that provided in the latest ACR 20212 guidelines.

Different RCTs with anti-TNF therapy in patients with moderate-to-severe chronic heart failure (HF) have shown an increased risk of adverse clinical events. There have been three trials with etanercept: RENAISSANCE, RECOVER and RENEWAL, in moderate to severe HF, without RA, which demonstrated no clinical benefit in HF patients and suggested that etanercept may adversely affect the course of HF.<sup>251–253</sup> Another RCT with infliximab, ATTACH, concluded that anti-TNF with infliximab did not improve HF and negatively affected the clinical status of patients with moderate to severe HF.<sup>254</sup> Cases of worsening congestive HF have also been reported with ADA.<sup>255</sup>

In this regard, it is recommended that anti-TNF should be used with caution in patients with mild congestive HF (NYHA class I/II), and these patients should be closely monitored, while anti-TNF should be avoided in patients with moderate-to-severe HF (NYHA class III/IV).<sup>251–256</sup> Studies with RTX in patients with severe chronic HF have shown an increased risk of adverse clinical events and this is contraindicated in patients with RA and severe HF (NYHA class IV) or severe uncontrolled heart disease.<sup>257</sup>

On the other hand, in line with this recommendation, for patients with RA who are already on treatment with an anti-TNF or RTX who develop moderate/severe or severe HF, in the case of RTX, the panel considers the switch to non-anti-TNF bDMARDs or tsDMARDs to be appropriate.<sup>252,255–257</sup>

**Recommendation 15.** In patients with RA and demyelinating disease, it is recommended that the use of anti-TNF be avoided. DA 100%; SD = 0.29.

This recommendation stems from a cautious attitude, given the limited evidence, also considering the multiple treatment options in RA patients.

RA is not associated with an increased risk of multiple sclerosis (MS);<sup>258</sup> however, anti-TNF treatment may increase flare-ups in MS patients. Multiple case series of demyelinating disease have been published in patients with RA and anti-TNF treatment; however, it is unclear whether these induce the onset of MS or unmask

a previous demyelinating disease. Several more recent epidemiological studies have attempted to clarify this association. Data from the 2021 British registry did not show an increase in risk, which was only marginal in men, and possibly associated with increased smoking in this group.<sup>259</sup> Similar results have been obtained in a study with patients from Denmark's registers (DANBIO) and also Sweden's (ARTIS), published in 2020, with a total of 111,455 patients. In this study, an increased risk of demyelinating disease was observed in patients treated with anti-TNF and spondylarthritis, and psoriatic arthritis, but not in RA.<sup>259</sup> This study was proposed after an increased risk observed in men in a 2016 DANBIO study without sufficient statistical power.<sup>260</sup> On the other hand, there are two case-control studies, one from Canada in 2022, with 296,918 patients, and another from the Mayo Clinic (USA) in 2020, with 212 patients, in which an increased risk of MS<sup>261</sup> and demyelinating events<sup>262</sup> was observed with the use of anti-TNF in a mixed population of rheumatic diseases without specific analysis for RA.

In conclusion, demyelinating events with anti-TNF in RA are very rare and it is not clear whether there is an increased risk associated with its use, except perhaps in men and related to smoking. No data are available for treatment targets other than anti-TNF. On the other hand, there is insufficient evidence to establish whether it is safe to restart anti-TNF in patients who develop demyelinating disease. In this context of limited evidence and given that alternative treatment targets are available in RA, the panel recommends not restarting anti-TNF against this scenario.

Finally, the panel considers that, since demyelinating diseases have an insidious onset of symptoms and slow progression, it is important to be alert to possible warning symptoms in patients who start treatment with anti-TNF, since rapid discontinuation of the drug improves the prognosis.

### Ethical responsibilities

Protection of people and animals. The authors state that no experiments have been run on humans or animals for this research.

Data confidentiality. The authors state that no patient data appears in this article.

Right to privacy and informed consent. The authors state that no patient data appears in this article.

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## References

- Sanmartí R, García-Rodríguez S, Álvaro-Gracia JM, Andreu JL, Balsa A, Cáliz R, et al. 2014 Update of the Consensus Statement of the Spanish Society of Rheumatology on the use of biological therapies in rheumatoid arthritis. *Rheumatol Clin*. 2015;11:279–94.
- Fraenkel L, Bathon JM, England BR, St Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2021;73:924–39.
- Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis*. 2020;79:685–99.
- Grupo de trabajo de la GUIPCAR. Guía de Práctica Clínica para el Manejo de Pacientes con Artritis Reumatoide. Madrid: Sociedad Española de Reumatología; 2019.
- OCFe-bM. Centre for evidence based medicine – levels of evidence (March 2009). Available from: <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>.
- Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis*. 2023;82:3–18.
- Van Nies JA, Krabben A, Schoones JW, Huizinga TW, Kloppenburg M, van der Helm-van Mil AH. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. *Ann Rheum Dis*. 2014;73:861–70.
- Burgers LE, Raza K, der Helm-van Mil AH. Window of opportunity in rheumatoid arthritis – definitions and supporting evidence: from old to new perspectives. *RMD Open*. 2019;5:e000870.
- Emamikia S, Arkema EV, Györi N, Detert J, Chatzidionysiou K, Dougados M, et al. Induction maintenance with tumour necrosis factor-inhibitor combination therapy with discontinuation versus methotrexate monotherapy in early rheumatoid arthritis: a systematic review and meta-analysis of efficacy in randomised controlled trials. *RMD Open*. 2016;2:e000323.
- Bijlsma JWJ, Welsing PMJ, Woodworth TG, Middelink LM, Pethö-Schramm A, Bernasconi C, et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. *Lancet*. 2016;388:343–55.
- Allaart CF, Breedveld FC, Dijkmans BA. Treatment of recent-onset rheumatoid arthritis: lessons from the BeSt study. *J Rheumatol Suppl*. 2007;80:25–33.
- Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. *Arthritis Rheum*. 2012;64:2824–35.
- Soubrier M, Puéchal X, Sibilia J, Mariette X, Meyer O, Combe B, et al. Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. *Rheumatology (Oxford)*. 2009;48:1429–34.
- Combe B, Landewe R, Daien CI, Hua C, Aletaha D, Álvaro-Gracia JM, et al. 2016 update of the EULAR recommendations for the management of early arthritis. *Ann Rheum Dis*. 2017;76:948–59.
- Muilu P, Rantalaiho V, Kautiainen H, Virta LJ, Eriksson JG, Puolakka K. First-year drug therapy of new-onset rheumatoid and undifferentiated arthritis: a nationwide register-based study. *BMC Rheumatol*. 2020;4:34.
- Verstappen M, Matthijssen XME, van der Helm-van Mil AHM. Undifferentiated arthritis: a changing population who did not benefit from enhanced disease-modifying anti-rheumatic drug strategies—results from a 25 year longitudinal inception cohort. *Rheumatology (Oxford)*. 2022;61:3212–22.
- Sepriano A, Kerschbaumer A, Smolen JS, van der Heijde D, Dougados M, van Vollenhoven R, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis*. 2020;79:760–70.
- Wevers-de Boer KV, Heimans L, Huizinga TW, Allaart CF. Drug therapy in undifferentiated arthritis: a systematic literature review. *Ann Rheum Dis*. 2013;72:1436–44.
- Aletaha D, Smolen JS. Remission in rheumatoid arthritis: missing objectives by using inadequate DAS28 targets. *Nat Rev Rheumatol*. 2019;15:633–4.
- Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis*. 2016;75:3–15.
- Radner H, Smolen JS, Aletaha D. Remission in rheumatoid arthritis: benefit over low disease activity in patient-reported outcomes and costs. *Arthritis Res Ther*. 2014;16:R56.
- Ruyssen-Witrand A, Guernec G, Nigon D, Tobon G, Jamard B, Rat AC, et al. Aiming for SDAI remission versus low disease activity at 1 year after inclusion in ESPOIR cohort is associated with better 3-year structural outcomes. *Ann Rheum Dis*. 2015;74:1676–83.
- Nikiphorou E, Norton S, Young A, Carpenter L, Dixey J, Walsh DA, et al. Association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds. *Ann Rheum Dis*. 2016;75:2080–6.
- Scott DL, Ibrahim F, Hill H, Tom B, Prothero L, Baggott RR, et al. Intensive therapy for moderate established rheumatoid arthritis: the TITRATE research programme. In: Programme Grants for Applied Research. Southampton (UK): NIHR Journals Library; 2021. <http://dx.doi.org/10.3310/pgfar09080>.
- Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis*. 2010;69:631–7.
- Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet*. 2004;364:263–9.
- Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis*. 2007;66:1443–9.
- Fransen J, Moens HB, Speyer I, van Riel PL. Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial. *Ann Rheum Dis*. 2005;64:1294–8.
- Gaujoux-Viala C, Nam J, Ramiro S, Landewé R, Buch MH, Smolen JS, et al. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis*. 2014;73:510–5.
- Nam JL, Ramiro S, Gaujoux-Viala C, Takase K, Leon-Garcia M, Emery P, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis*. 2014;73:516–28.
- Smolen JS, Emery P, Fleischmann R, van Vollenhoven RF, Pavelka K, Durez P, et al. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. *Lancet*. 2014;383:321–32.
- Combe B, Dasgupta B, Louw I, Pal S, Wollenhaupt J, Zerbini CA, et al. Efficacy and safety of golimumab as add-on therapy to disease-modifying antirheumatic drugs: results of the GO-MORE study. *Ann Rheum Dis*. 2014;73:1477–86.
- Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum*. 2005;52:3381–90.
- Heimans L, Wevers-de Boer KV, Koudijs KK, Visser K, Goekoop-Ruiterman YP, Harbers JB, et al. Health-related quality of life and functional ability in patients with early arthritis during remission steered treatment: results of the IMPROVED study. *Arthritis Res Ther*. 2013;15:R173.
- Heimans L, Wevers-de Boer KV, Visser K, Goekoop RJ, van Oosterhout M, Harbers JB, et al. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. *Ann Rheum Dis*. 2014;73:1356–61.
- Hørslev-Petersen K, Hetland ML, Junker P, Pødenphant J, Ellingsen T, Ahlquist P, et al. Adalimumab added to a treat-to-target strategy with methotrexate and intra-articular triamcinolone in early rheumatoid arthritis increased remission rates, function and quality of life. The OPERA study: an investigator-



- initiated, randomised, double-blind, parallel-group, placebo-controlled trial. *Ann Rheum Dis.* 2014;73:654–61.
37. Leirisalo-Repo M, Kautiainen H, Laasonen L, Korpela M, Kauppi MJ, Kaipiainen-Seppänen O, et al. Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomised, double-blind, placebo-controlled study (the NEO-RACO study). *Ann Rheum Dis.* 2013;72:851–7.
  38. Nam JL, Villeneuve E, Hensor EM, Conaghan PG, Keen HI, Buch MH, et al. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naïve, rheumatoid arthritis (the IDEA study). *Ann Rheum Dis.* 2014;73:75–85.
  39. Nam JL, Villeneuve E, Hensor EM, Wakefield RJ, Conaghan PG, Green MJ, et al. A randomised controlled trial of etanercept and methotrexate to induce remission in early inflammatory arthritis: the EMPIRE trial. *Ann Rheum Dis.* 2014;73:1027–36.
  40. Smolen JS, Emery P, Ferraccioli GF, Samborski W, Berenbaum F, Davies OR, et al. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial. *Ann Rheum Dis.* 2015;74:843–50.
  41. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Ewals JA, Han KH, Hazes JM, et al. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. *Arthritis Rheum.* 2009;61:4–12.
  42. van Eijk IC, Nielen MM, van der Horst-Bruinsma I, Tjuijthuis GJ, Boers M, Dijkman BA, et al. Aggressive therapy in patients with early arthritis results in similar outcome compared with conventional care: the STREAM randomized trial. *Rheumatology (Oxford).* 2012;51:686–94.
  43. Van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Güler-Yüksel M, Zwiderman AH, Kerstens PJ, et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis.* 2009;68:914–21.
  44. Solomon DH, Rudin RS. Digital health technologies: opportunities and challenges in rheumatology. *Nat Rev Rheumatol.* 2020;16:525–35.
  45. de Thurah A, Bosch P, Marques A, Meissner Y, Mukhtyar CB, Knitza J, et al. 2022 EULAR points to consider for remote care in rheumatic and musculoskeletal diseases. *Ann Rheum Dis.* 2022;81:1065–71.
  46. McDougall JA, Ferucci ED, Glover J, Fraenkel L. Telerheumatology: a systematic review. *Arthritis Care Res (Hoboken).* 2017;69:1546–57.
  47. Salaffi F, Carotti M, Ciapetti A, Di Carlo M, Gasparini S, Farah S, et al. Effectiveness of a telemonitoring intensive strategy in early rheumatoid arthritis: comparison with the conventional management approach. *BMC Musculoskelet Disord.* 2016;17:146.
  48. Najm A, Gossec L, Weill C, Benoist D, Berenbaum F, Nikiphorou E. Mobile health apps for self-management of rheumatic and musculoskeletal diseases: systematic literature review. *JMIR Mhealth Uhealth.* 2019;7:e14730.
  49. Curtis JR, Palmer JL, Reed GW, Greenberg J, Pappas DA, Harrold LR, et al. Real-world outcomes associated with methotrexate, sulfasalazine, and hydroxychloroquine triple therapy versus tumor necrosis factor inhibitor/methotrexate combination therapy in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2021;73:1114–24.
  50. Erhardt DP, Cannon GW, Teng CC, Mikuls TR, Curtis JR, Sauer BC. Low persistence rates in patients with rheumatoid arthritis treated with triple therapy and adverse drug events associated with sulfasalazine. *Arthritis Care Res (Hoboken).* 2019;71:1326–35.
  51. Van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. *Lancet.* 2012;379:1712–20.
  52. O'Dell JR, Curtis JR, Mikuls TR, Cofield SS, Bridges SL Jr, Ranganath VK, et al. Validation of the methotrexate-first strategy in patients with early, poor-prognosis rheumatoid arthritis: results from a two-year randomized, double-blind trial. *Arthritis Rheum.* 2013;65:1985–94.
  53. Braun J. Optimal administration and dosage of methotrexate. *Clin Exp Rheumatol.* 2010;28 5 Suppl 61:S46–51.
  54. Bujor AM, Janjua S, LaValley MP, Duran J, Braun J, Felson DT. Comparison of oral versus parenteral methotrexate in the treatment of rheumatoid arthritis: a meta-analysis. *PLoS One.* 2019;14:e0221823.
  55. Sanmartí R, García-Rodríguez S, Álvaro-Gracia JM, Andreu JL, Balsa A, Cáliz R, et al. Actualización 2014 del Documento de Consenso de la Sociedad Española de Reumatología sobre el uso de terapias biológicas en la artritis reumatoide. *Reumatol Clin.* 2015;11:279–94.
  56. Katchamart W, Trudeau J, Phumethum V, Bombardier C. Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and meta-analysis. *Ann Rheum Dis.* 2009;68:1105–12.
  57. Katz SJ, Russell AS. Re-evaluation of antimalarials in treating rheumatic diseases: re-appreciation and insights into new mechanisms of action. *Curr Opin Rheumatol.* 2011;23:278–81.
  58. Suarez-Almazor ME, Belseck E, Shea B, Homik J, Wells G, Tugwell P. Antimalarials for treating rheumatoid arthritis. *Cochrane Database Syst Rev.* 2000;CD000959.
  59. Sharp JT, Strand V, Leung H, Hurley F, Loew-Friedrich I. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis: results from three randomized controlled trials of leflunomide in patients with active rheumatoid arthritis. *Leflunomide Rheumatoid Arthritis Investigators Group. Arthritis Rheum.* 2000;43:495–505.
  60. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Leflunomide Rheumatoid Arthritis Investigators Group. Arch Intern Med.* 1999;159:2542–50.
  61. Burmester GR, Mariette X, Montecucco C, Monteagudo-Sáez I, Malaise M, Tzioufas AG, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the research in Active Rheumatoid Arthritis (ReAct) trial. *Ann Rheum Dis.* 2007;66:732–9.
  62. Strangfeld A, Hieber F, Kekow J, von Hineuber U, Tony HP, Dockhorn R, et al. Comparative effectiveness of tumour necrosis factor alpha inhibitors in combination with either methotrexate or leflunomide. *Ann Rheum Dis.* 2009;68:1856–62.
  63. Kvacsakay P, Blank N, Lorenz HM, Merkt W. Leflunomide in combination with JAK inhibitors in the treatment of rheumatoid arthritis: a case series. *Rheumatology (Oxford).* 2022;61:e280–1.
  64. Sociedad Española de Reumatología. Proyecto EMAR II. Variabilidad en el manejo de la artritis reumatoide y las espondiloartritis en España. Informe de resultados. Madrid: SER; 2011 [updated February 2011]. Available from: <http://www.ser.es/ArchivosDESCARGABLES/Proyectos/Emar/EMARInforme.pdf>
  65. Capell HA. Clinical efficacy of sulphasalazine – a review. *Br J Rheumatol.* 1995;34 Suppl 2:35–9.
  66. Van der Heijde DM, van Riel PL, Nuvér-Zwart IH, Gribnau FW, van de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet.* 1989;1:1036–8.
  67. Van Riel PL, van Gestel AM, van de Putte LB. Long-term usage and side-effect profile of sulphasalazine in rheumatoid arthritis. *Br J Rheumatol.* 1995;34 Suppl 2:40–2.
  68. Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. *European Leflunomide Study Group. Lancet.* 1999;353:259–66.
  69. Boers M, Verhoeven AC, Markuse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet.* 1997;350:309–18.
  70. Neumann VC, Grindulis KA, Hubbard S, McConkey B, Wright V. Comparison between penicillamine and sulphasalazine in rheumatoid arthritis: Leeds-Birmingham trial. *Br Med J (Clin Res Ed).* 1983;287:1099–102.
  71. González-Alvaro I, Descalzo MA, Carmona L. Trends towards an improved disease state in rheumatoid arthritis over time: influence of new therapies and changes in management approach: analysis of the EMECAR cohort. *Arthritis Res Ther.* 2008;10:R138.
  72. Partlett R, Roussou E. The treatment of rheumatoid arthritis during pregnancy. *Rheumatol Int.* 2011;31:445–9.
  73. Patatanian E, Thompson DF. A review of methotrexate-induced accelerated nodulosis. *Pharmacotherapy.* 2002;22:1157–62.
  74. Lund Hetland M, Haavardsholm E, Rudin A, Nordström D, Nurmohamed M, Gudbjörnsson B, et al. NORD-STAR Study Group. A multicenter randomized study in early rheumatoid arthritis to compare active conventional therapy versus three biological treatments: 24 week efficacy and safety results of the NORD-STAR Trial [abstract]. *Arthritis Rheumatol.* 2019;71 Suppl 10 [Accessed 17 July 2023]. <https://acrabstracts.org/abstract/a-multicenter-randomized-study-in-early-rheumatoid-arthritis-to-compare-active-conventional-therapy-versus-three-biological-treatments-24-week-efficacy-and-safety-results-of-the-nord-star-trial/>
  75. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med.* 2007;146:406–15.
  76. Sun T, Wang J, Zhang R, Li Y. A systematic review and meta-analysis: effects of glucocorticoids on rheumatoid arthritis and systemic lupus erythematosus. *Ann Palliat Med.* 2021;10:7977–91.
  77. Einarsson MJ, Ekman P, Molin M, Trimpou P, Olsson DS, Johannsson G, et al. High mortality rate in oral glucocorticoid users: a population-based matched cohort study. *Front Endocrinol (Lausanne).* 2022;13:918356.
  78. Moshayedi S, Tasorian B, Almasi-Hashiani A. The prevalence of osteoporosis in rheumatoid arthritis patient: a systematic review and meta-analysis. *Sci Rep.* 2022;12:15844.
  79. del Rincón I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. *Arthritis Rheumatol.* 2014;66:264–72.
  80. Billsma JWJ, Buttgerit F. Adverse events of glucocorticoids during treatment of rheumatoid arthritis: lessons from cohort and registry studies. *Rheumatology (Oxford).* 2016;55 Suppl 2:ii3–5.
  81. Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Rheum.* 2006;55:420–6.
  82. Vastesaeger N, Xu S, Aletaha D, St Clair EW, Smolen JS. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. *Rheumatology (Oxford).* 2009;48:1114–21.
  83. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ronday HK, Seys PE, Kerstens PJ, et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic



- treatment strategies: post hoc analyses from the BeSt study. *Ann Rheum Dis*. 2010;69:1333–7.
84. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum*. 2006;54:26–37.
  85. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet*. 2004;363:675–81.
  86. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet*. 2013;381:451–60.
  87. Kremer J, Li ZC, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2013;159:253–61.
  88. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med*. 2014;370:2377–86.
  89. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med*. 2012;367:495–507.
  90. Van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum*. 2013;65:559–70.
  91. Van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Mejiade JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med*. 2012;367:508–19.
  92. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med*. 2016;374:1243–52.
  93. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med*. 2017;376:652–62.
  94. Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis*. 2017;76:88–95.
  95. Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Rheumatol*. 2017;69:506–17.
  96. Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. *Ann Rheum Dis*. 2015;74:333–40.
  97. Smolen JS, Pangan AL, Emery P, Rigby W, Tanaka Y, Vargas JJ, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. *Lancet*. 2019;393:2303–11.
  98. Burmester GR, Kremer JM, van den Bosch F, Kivitz A, Bessette L, Li Y, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2018;391:2503–12.
  99. Genovese MC, Fleischmann R, Combe B, Hall S, Rubbert-Roth A, Zhang Y, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet*. 2018;391:2513–24.
  100. Fleischmann R, Pangan AL, Song IH, Mysler E, Bessette L, Peterfy C, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. *Arthritis Rheumatol*. 2019;71:1788–800.
  101. Fleischmann RM, Genovese MC, Enejosa JV, Mysler E, Bessette L, Peterfy C, et al. Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. *Ann Rheum Dis*. 2019;78:1454–62.
  102. Rubbert-Roth A, Enejosa J, Pangan AL, Haraoui B, Rischmueller M, Khan N, et al. Trial of upadacitinib or abatacept in rheumatoid arthritis. *N Engl J Med*. 2020;383:1511–21.
  103. Combe B, Kivitz A, Tanaka Y, van der Heijde D, Simon JA, Baraf HSB, et al. Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. *Ann Rheum Dis*. 2021;80:848–58.
  104. Genovese MC, Kalunian K, Gottenberg JE, Mozaffarian N, Bartok B, Matzkies F, et al. Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the FINCH 2 randomized clinical trial. *JAMA*. 2019;322:315–25.
  105. Westhovens R, Rigby WFC, van der Heijde D, Ching DWT, Stohl W, Kay J, et al. Filgotinib in combination with methotrexate or as monotherapy versus methotrexate monotherapy in patients with active rheumatoid arthritis and limited or no prior exposure to methotrexate: the phase 3, randomised controlled FINCH 3 trial. *Ann Rheum Dis*. 2021;80:727–38.
  106. Van Vollenhoven R, Takeuchi T, Pangan A, Friedman A, Chen S, Rischmueller M, et al. Monotherapy with upadacitinib in MTX-naïve patients with rheumatoid arthritis: results at 48 weeks [abstract]. *Arthritis Rheumatol*. 2019;71 Suppl 10 [Accessed 15 February 2023]. <https://acrabstracts.org/abstract/monotherapy-with-upadacitinib-in-mtx-naive-patients-with-rheumatoid-arthritis-results-at-48-weeks/>
  107. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med*. 2022;386:316–26.
  108. Janus kinase inhibitors (JAKi); 2023. Available from: <https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki>
  109. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. *N Engl J Med*. 2013;369:307–18.
  110. Finckh A, Dehler S, Gabay C. The effectiveness of leflunomide as a co-therapy of tumour necrosis factor inhibitors in rheumatoid arthritis: a population-based study. *Ann Rheum Dis*. 2009;68:33–9.
  111. De Stefano R, Frati E, Nargi F, Baldi C, Menza L, Hammoud M, et al. Comparison of combination therapies in the treatment of rheumatoid arthritis: leflunomide-anti-TNF-alpha versus methotrexate-anti-TNF-alpha. *Clin Rheumatol*. 2010;29:517–24.
  112. Hyrich KL, Symmons DP, Watson KD, Silman AJ. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum*. 2006;54:1786–94.
  113. Manders SH, Kievit W, Jansen TL, Stolk JN, Visser H, Schilder AM, et al. Effectiveness of tumor necrosis factor inhibitors in combination with various csDMARD in the treatment of rheumatoid arthritis: data from the DREAM registry. *J Rheumatol*. 2016;43:1787–94.
  114. Chatzidionysiou K, Lie E, Nasonov E, Lukina G, Hetland ML, Tarp U, et al. Effectiveness of disease-modifying antirheumatic drug co-therapy with methotrexate and leflunomide in rituximab-treated rheumatoid arthritis patients: results of a 1-year follow-up study from the CERERRA collaboration. *Ann Rheum Dis*. 2012;71:374–7.
  115. Richter A, Strangfeld A, Herzer P, Wilden E, Bussmann A, Listing J, et al. Sustainability of rituximab therapy in different treatment strategies: results of a 3-year followup of a German biologics register. *Arthritis Care Res (Hoboken)*. 2014;66:1627–33.
  116. Narváez J, Díaz-Torné C, Magallares B, Hernández MV, Reina D, Corominas H, et al. Comparative effectiveness of tocilizumab with either methotrexate or leflunomide in the treatment of rheumatoid arthritis. *PLoS One*. 2015;10:e0123392.
  117. Decarriere G, Barnetteche T, Lukas C, Gaujoux-Viala C, Combe B, Morel J, et al. Should we prefer leflunomide to methotrexate in combination with biologics? A systematic review and a meta-analysis [abstract]. *Arthritis Rheumatol*. 2018;70 Suppl 9 [Accessed 23 November 2023]. <https://acrabstracts.org/abstract/should-we-prefer-leflunomide-to-methotrexate-in-combination-with-biologics-a-systematic-review-and-a-meta-analysis/>
  118. Durán J, Bockorny M, Dalal D, LaValley M, Felson DT. Methotrexate dosage as a source of bias in biological trials in rheumatoid arthritis: a systematic review. *Ann Rheum Dis*. 2016;75:1595–8.
  119. Burmester GR, Kivitz AJ, Kupper H, Arulmani U, Florentinus S, Goss SL, et al. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. *Ann Rheum Dis*. 2015;74:1037–44.
  120. Kaeley GS, Evangelisto AM, Nishio MJ, Goss SL, Liu S, Kalabic J, et al. Methotrexate dosage reduction upon adalimumab initiation: clinical and ultrasonographic outcomes from the randomized noninferiority MUSICA trial. *J Rheumatol*. 2016;43:1480–9.
  121. Caporali R, Zavaglia D. Real-world experience with tofacitinib for the treatment of rheumatoid arthritis. *Clin Exp Rheumatol*. 2019;37:485–95.
  122. Dhaon P, Das SK, Srivastava R, Agarwal G, Asthana A. Oral Methotrexate in split dose weekly versus oral or parenteral methotrexate once weekly in rheumatoid arthritis: a short-term study. *Int J Rheum Dis*. 2018;21:1010–7.
  123. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. *JAMA*. 2018;320:1360–72.
  124. Burmester GR, Rigby WF, van Vollenhoven RF, Kay J, Rubbert-Roth A, Kelman A, et al. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. *Ann Rheum Dis*. 2016;75:1081–91.
  125. Emery P, Burmester GR, Bykerk VP, Combe BG, Furst DE, Barré E, et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. *Ann Rheum Dis*. 2015;74:19–26.
  126. Kaneko Y, Atsumi T, Tanaka Y, Inoo M, Kobayashi-Haraoka H, Amano K, et al. Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study). *Ann Rheum Dis*. 2016;75:1917–23.

127. Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. *Lancet*. 2017;390:457–68.
128. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet*. 2013;381:1541–50.
129. Burmester GR, Lin Y, Patel R, van Adelsberg J, Mangan EK, Graham NM, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. *Ann Rheum Dis*. 2017;76:840–7.
130. Emery P, Pope JE, Kruger K, Lippe R, DeMasi R, Lula S, et al. Efficacy of monotherapy with biologics and JAK inhibitors for the treatment of rheumatoid arthritis: a systematic review. *Adv Ther*. 2018;35:1535–63.
131. Huizinga TW, Conaghan PG, Martin-Mola E, Schett G, Amital H, Xavier RM, et al. Clinical and radiographic outcomes at 2 years and the effect of tocilizumab discontinuation following sustained remission in the second and third year of the ACT-RAY study. *Ann Rheum Dis*. 2015;74:35–43.
132. Dougados M, Kissel K, Conaghan PG, Mola EM, Schett G, Gerli R, et al. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. *Ann Rheum Dis*. 2014;73:803–9.
133. Schiff M, Takeuchi T, Fleischmann R, Gaich CL, DeLozier AM, Schlichting D, et al. Patient-reported outcomes of baricitinib in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Res Ther*. 2017;19:208.
134. Kavanaugh A, Kremer J, Ponce L, Cseuz R, Reshetko OV, Stanislavchuk M, et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). *Ann Rheum Dis*. 2017;76:1009–19.
135. Fletcher A, Lassere M, March L, Hill C, Barrett C, Carroll G, et al. Patterns of biologic and targeted-synthetic disease-modifying antirheumatic drug use in rheumatoid arthritis in Australia. *Rheumatology (Oxford)*. 2022;61:3939–51.
136. Ebina K, Hirano T, Maeda Y, Yamamoto W, Hashimoto M, Murata K, et al. Drug retention of 7 biologics and tofacitinib in biologics-naïve and biologics-switched patients with rheumatoid arthritis: the ANSWER cohort study. *Arthritis Res Ther*. 2020;22:142.
137. Bonafede MM, Curtis JR, McMorrow D, Mahajan P, Chen CI. Treatment effectiveness and treatment patterns among rheumatoid arthritis patients after switching from a tumor necrosis factor inhibitor to another medication. *Clinicoecon Outcomes Res*. 2016;8:707–15.
138. Kondo M, Yamada H. Drug survival rates of biological disease-modifying antirheumatic drugs and Janus kinase-inhibitor therapy in 801 rheumatoid arthritis patients: a 14 year-retrospective study from a rheumatology clinic in Japan. *Mod Rheumatol*. 2019;29:928–35.
139. Beresniak A, Baerwald C, Zeidler H, Krüger K, Neubauer AS, Dupont D, et al. Cost-effectiveness simulation model of biologic strategies for treating to target rheumatoid arthritis in Germany. *Clin Exp Rheumatol*. 2013;31:400–8.
140. Best JH, Vlad SC, Tomina L, Abbasi I. Real-world persistence with tocilizumab compared to other subcutaneous biologic disease-modifying antirheumatic drugs among patients with rheumatoid arthritis switching from another biologic. *Rheumatol Ther*. 2020;7:345–55.
141. Blom M, Kievit W, Donders AR, den Broeder AA, Straten VH, Kuper I, et al. Effectiveness of a third tumor necrosis factor- $\alpha$ -blocking agent compared with rituximab after failure of 2 TNF-blocking agents in rheumatoid arthritis. *J Rheumatol*. 2011;38:2355–61.
142. Bogas P, Plasencia-Rodriguez C, Navarro-Compán V, Tornero C, Novella-Navarro M, Nuño L, et al. Comparison of long-term efficacy between biological agents following tumor necrosis factor inhibitor failure in patients with rheumatoid arthritis: a prospective cohort study. *Ther Adv Musculoskelet Dis*. 2021;13, 1759720x211060910.
143. Brown S, Everett CC, Naraghi K, Davies C, Dawkins B, Hulme C, et al. Alternative tumour necrosis factor inhibitors (TNFi) or abatacept or rituximab following failure of initial TNFi in rheumatoid arthritis: the SWITCH RCT. *Health Technol Assess*. 2018;22:1–280.
144. Chastek B, Becker LK, Chen CI, Mahajan P, Curtis JR. Outcomes of tumor necrosis factor inhibitor cycling versus switching to a disease-modifying anti-rheumatic drug with a new mechanism of action among patients with rheumatoid arthritis. *J Med Econ*. 2017;20:464–73.
145. Chastek B, Chen CI, Proudfoot C, Shinde S, Kuznik A, Wei W. Treatment persistence and healthcare costs among patients with rheumatoid arthritis changing biologics in the USA. *Adv Ther*. 2017;34:2422–35.
146. Chatzidionysiou K, van Vollenhoven RF. Rituximab versus anti-TNF in patients who previously failed one TNF inhibitor in an observational cohort. *Scand J Rheumatol*. 2013;42:190–5.
147. Choi S, Ghang B, Jeong S, Choi D, Lee JS, Park SM, et al. Association of first, second, and third-line bDMARDs and tsDMARD with drug survival among seropositive rheumatoid arthritis patients: cohort study in a real world setting. *Semin Arthritis Rheum*. 2021;51:685–91.
148. Choquette D, Bessette L, Alemão E, Haraoui B, Postema R, Raynaud JP, et al. Persistence rates of abatacept and TNF inhibitors used as first or second biologic DMARDs in the treatment of rheumatoid arthritis: 9 years of experience from the Rhumadata® clinical database and registry. *Arthritis Res Ther*. 2019;21:138.
149. Emery P, Gottenberg JE, Rubbert-Roth A, Sarzi-Puttini P, Choquette D, Taboada VM, et al. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. *Ann Rheum Dis*. 2015;74:979–84.
150. Finckh A, Ciurea A, Brulhart L, Möller B, Walker UA, Courvoisier D, et al. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? *Ann Rheum Dis*. 2010;69:387–93.
151. Finckh A, Tellenbach C, Herzog L, Scherer A, Moeller B, Ciurea A, et al. Comparative effectiveness of antitumour necrosis factor agents, biologics with an alternative mode of action and tofacitinib in an observational cohort of patients with rheumatoid arthritis in Switzerland. *RMD Open*. 2020;6:e001174.
152. Gharaibeh M, Bonafede M, McMorrow D, Hernandez EJM, Stolshek BS. Effectiveness and costs among rheumatoid arthritis patients treated with targeted immunomodulators using real-world U.S. data. *J Manag Care Spec Pharm*. 2020;26:1039–49.
153. Gottenberg JE, Brocq O, Perdriger A, Lassoued S, Berthelot JM, Wendling D, et al. Non-TNF-targeted biologic vs a second anti-TNF drug to treat rheumatoid arthritis in patients with insufficient response to a first anti-TNF drug: a randomized clinical trial. *JAMA*. 2016;316:1172–80.
154. Gottenberg JE, Morel J, Perrodeau E, Bardin T, Combe B, Dougados M, et al. Comparative effectiveness of rituximab, abatacept, and tocilizumab in adults with rheumatoid arthritis and inadequate response to TNF inhibitors: prospective cohort study. *BMJ*. 2019;364:167.
155. Humby F, Durez P, Buch MH, Lewis MJ, Rizvi H, Rivellese F, et al. Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial. *Lancet*. 2021;397:305–17.
156. Karpes Matusевич AR, Duan Z, Zhao H, Lal LS, Chan W, Suarez-Almazor ME, et al. Treatment sequences after discontinuing a tumor necrosis factor inhibitor in patients with rheumatoid arthritis: a comparison of cycling versus swapping strategies. *Arthritis Care Res (Hoboken)*. 2021;73:1461–9.
157. Lopatina E, Marshall DA, Coupl L, Le Lorier J, Choquette D. Cost-utility analysis of second-line therapy with rituximab compared to tumour necrosis factor inhibitors in rheumatoid arthritis. *Curr Med Res Opin*. 2021;37:157–66.
158. Manders SH, Kievit W, Adang E, Brus HL, Moens HJ, Hartkamp A, et al. Cost-effectiveness of abatacept, rituximab, and TNFi treatment after previous failure with TNFi treatment in rheumatoid arthritis: a pragmatic multi-centre randomised trial. *Arthritis Res Ther*. 2015;17:134.
159. Park JA, Lee MY, Nam JH, Shin JY, Wood R, Holbrook T, et al. Real-world treatment persistence of non-tumor necrosis factor inhibitors versus tumor necrosis factor inhibitors among patients with rheumatoid arthritis in South Korea. *Curr Med Res Opin*. 2020;36:343–51.
160. Smolen JS, Burmester GR, Combe B, Curtis JR, Hall S, Haraoui B, et al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXCELERATE study. *Lancet*. 2016;388:2763–74.
161. Takabayashi K, Ando F, Suzuki T. Comparing the effectiveness of biological disease-modifying antirheumatic drugs using real-world data. *Mod Rheumatol*. 2019;29:87–97.
162. Backhaus M, Kaufmann J, Richter C, Wassenberg S, Roske AE, Hellmann P, et al. Comparison of tocilizumab and tumour necrosis factor inhibitors in rheumatoid arthritis: a retrospective analysis of 1603 patients managed in routine clinical practice. *Clin Rheumatol*. 2015;34:673–81.
163. Elmedany SH, Mohamed AE, Galil SMA. Efficacy and safety profile of intravenous tocilizumab versus intravenous abatacept in treating female Saudi Arabian patients with active moderate-to-severe rheumatoid arthritis. *Clin Rheumatol*. 2019;38:2109–17.
164. Favalli EG, Biggoggero M, Marchesoni A, Meroni PL. Survival on treatment with second-line biologic therapy: a cohort study comparing cycling and swap strategies. *Rheumatology (Oxford)*. 2014;53:1664–8.
165. Frisell T, Dehlin M, Di Giuseppe D, Feltelius N, Turesson C, Askling J. Comparative effectiveness of abatacept, rituximab, tocilizumab and TNFi biologics in RA: results from the nationwide Swedish register. *Rheumatology (Oxford)*. 2019. <http://dx.doi.org/10.1093/rheumatology/key433>.
166. Harold LR, Reed GW, Kremer JM, Curtis JR, Solomon DH, Hochberg MC, et al. The comparative effectiveness of abatacept versus anti-tumour necrosis factor switching for rheumatoid arthritis patients previously treated with an anti-tumour necrosis factor. *Ann Rheum Dis*. 2015;74:430–6.
167. Harold LR, Reed GW, Magner R, Shewade A, John A, Greenberg JD, et al. Comparative effectiveness and safety of rituximab versus subsequent anti-tumour necrosis factor therapy in patients with rheumatoid arthritis with prior exposure to anti-tumour necrosis factor therapies in the United States Corrona registry. *Arthritis Res Ther*. 2015;17:256.
168. Hirabara S, Takahashi N, Fukaya N, Miyake H, Yabe Y, Kaneko A, et al. Clinical efficacy of abatacept, tocilizumab, and etanercept in Japanese rheumatoid arthritis patients with inadequate response to anti-TNF monoclonal antibodies. *Clin Rheumatol*. 2014;33:1247–54.
169. Lauper K, Nordström DC, Pavelka K, Hernández MV, Kvien TK, Kristianslund EK, et al. Comparative effectiveness of tocilizumab versus TNF inhibitors as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis after the use of at least one biologic disease-modifying antirheumatic drug: analyses from the pan-European TOCERRA register collaboration. *Ann Rheum Dis*. 2018;77:1276–82.

170. Santos-Faria D, Tavares-Costa J, Eusébio M, Leite Silva J, Ramos Rodrigues J, Sousa-Neves J, et al. Tocilizumab and rituximab have similar effectiveness and are both superior to a second tumour necrosis factor inhibitor in rheumatoid arthritis patients who discontinued a first TNF inhibitor. *Acta Reumatol Port.* 2019;44:103–13.
171. Sung YK, Lee YH. Comparative effectiveness and safety of non-tumour necrosis factor biologics and Janus kinase inhibitors in patients with active rheumatoid arthritis showing insufficient response to tumour necrosis factor inhibitors: a Bayesian network meta-analysis of randomized controlled trials. *J Clin Pharm Ther.* 2021;46:984–92.
172. Torrente-Segarra V, Acosta Pereira A, Morla R, Ruiz JM, Clavaguera T, Figuls R, et al. VARIAR study: assessment of short-term efficacy and safety of rituximab compared to a tumor necrosis factor alpha antagonists as second-line drug therapy in patients with rheumatoid arthritis refractory to a first tumor necrosis factor alpha antagonist. *Reumatol Clin.* 2016;12:319–22.
173. Vieira MC, Zwillich SH, Jansen JP, Smiechowski B, Spurden D, Wallenstein GV. Tofacitinib versus biologic treatments in patients with active rheumatoid arthritis who have had an inadequate response to tumor necrosis factor inhibitors: results from a network meta-analysis. *Clin Ther.* 2016;38:2628–41.e5.
174. Wei W, Knapp K, Wang L, Chen CI, Craig GL, Ferguson K, et al. Treatment persistence and clinical outcomes of tumor necrosis factor inhibitor cycling or switching to a new mechanism of action therapy: real-world observational study of rheumatoid arthritis patients in the united states with prior tumor necrosis factor inhibitor therapy. *Adv Ther.* 2017;34:1936–52.
175. Roodenrijs NMT, Hamar A, Kedves M, Nagy G, van Laar JM, van der Heijde D, et al. Pharmacological and non-pharmacological therapeutic strategies in difficult-to-treat rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis. *RMD Open.* 2021;7.
176. Gomez-Reino JJ, Maneiro JR, Ruiz J, Roselló R, Sanmarti R, Romero AB. Comparative effectiveness of switching to alternative tumour necrosis factor (TNF) antagonists versus switching to rituximab in patients with rheumatoid arthritis who failed previous TNF antagonists: the MIRAR study. *Ann Rheum Dis.* 2012;71:1861–4.
177. Amstad A, Papagiannoulis E, Scherer A, Rubbert-Roth A, Finckh A, Mueller R, et al. Comparison of drug retention of TNF inhibitors, other biologics and JAK inhibitors in RA patients who discontinued JAK inhibitor therapy. *Rheumatology (Oxford).* 2022;62:89–97.
178. Bonafede MMK, McMorrow D, Proudfoot C, Shinde S, Kuznik A, Chen CI. Treatment persistence and healthcare costs among patients with rheumatoid arthritis after a change in targeted therapy. *Am Health Drug Benefits.* 2018;11:192–202.
179. Das S, Vital EM, Horton S, Bryer D, El-Sherbiny Y, Rawstron AC, et al. Abatacept or tocilizumab after rituximab in rheumatoid arthritis? An exploratory study suggests non-response to rituximab is associated with persistently high IL-6 and better clinical response to IL-6 blocking therapy. *Ann Rheum Dis.* 2014;73:909–12.
180. Ebina K, Hirano T, Maeda Y, Yamamoto W, Hashimoto M, Murata K, et al. Drug retention of secondary biologics or JAK inhibitors after tocilizumab or abatacept failure as first biologics in patients with rheumatoid arthritis — the ANSWER cohort study. *Clin Rheumatol.* 2020;39:2563–72.
181. Fitton J, Melville AR, Emery P, Nam JL, Buch MH. Real-world single centre use of JAK inhibitors across the rheumatoid arthritis pathway. *Rheumatology (Oxford).* 2021;60:4048–54.
182. Pascart T, Philippe P, Drumez E, Deprez X, Cortet B, Duhamel A, et al. Comparative efficacy of tocilizumab, abatacept and rituximab after non-TNF inhibitor failure: results from a multicentre study. *Int J Rheum Dis.* 2016;19:1093–102.
183. Pombo-Suarez M, Sanchez-Piedra C, Gómez-Reino J, Lauper K, Mongin D, Iannone F, et al. After JAK inhibitor failure: to cycle or to switch, that is the question — data from the JAK-pot collaboration of registries. *Ann Rheum Dis.* 2023;82:175–81.
184. Retuerto M, Trujillo E, Valero C, Fernandez-Espartero C, Soletto CY, Garcia-Valle A, et al. Efficacy and safety of switching Jak inhibitors in rheumatoid arthritis: an observational study. *Clin Exp Rheumatol.* 2021;39:453–5.
185. Sebastiani M, Venerito V, Bugatti S, Bazzani C, Biggioggero M, Petricca L, et al. Retention rate of a second line with a biologic DMARD after failure of a first-line therapy with abatacept, tocilizumab, or rituximab: results from the Italian GISEA registry. *Clin Rheumatol.* 2021;40:4039–47.
186. Brocq O, Millasseau E, Albert C, Grisot C, Flory P, Roux CH, et al. Effect of discontinuing TNFalpha antagonist therapy in patients with remission of rheumatoid arthritis. *Joint Bone Spine.* 2009;76:350–5.
187. Harigai M, Takeuchi T, Tanaka Y, Matsubara T, Yamanaka H, Miyasaka N. Discontinuation of adalimumab treatment in rheumatoid arthritis patients after achieving low disease activity. *Mod Rheumatol.* 2012;22:814–22.
188. Nawata M, Saito K, Nakayamada S, Tanaka Y. Discontinuation of infliximab in rheumatoid arthritis patients in clinical remission. *Mod Rheumatol.* 2008;18:460–4.
189. Tanaka Y, Hirata S, Kubo S, Fukuyo S, Hanami K, Sawamukai N, et al. Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study. *Ann Rheum Dis.* 2015;74:389–95.
190. Tanaka Y, Takeuchi T, Mimori T, Saito K, Nawata M, Kameda H, et al. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis: RRR (remission induction by Remicade in RA) study. *Ann Rheum Dis.* 2010;69:1286–91.
191. Van der Maas A, Kievit W, van den Bemt BJ, van den Hoogen FH, van Riel PL, den Broeder AA. Down-titration and discontinuation of infliximab in rheumatoid arthritis patients with stable low disease activity and stable treatment: an observational cohort study. *Ann Rheum Dis.* 2012;71:1849–54.
192. Mori S, Okada A, Koga T, Ueki Y. Long-term outcomes after discontinuing biological drugs and tofacitinib in patients with rheumatoid arthritis: a prospective cohort study. *PLoS One.* 2022;17:e0270391.
193. Baillet A, Gossec L, Carmona L, Wit M, van Eijk-Hustings Y, Bertheussen H, et al. Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. *Ann Rheum Dis.* 2016;75:965–73.
194. Van Vollenhoven R.F., Østergaard M., Leirisalo-Repo M., Uhlig T., Jansson M., Klackenbergh A., et al. In rheumatoid arthritis patients with stable low disease activity on methotrexate plus etanercept, continuation of etanercept 50 mg weekly or 25 mg weekly are both clinically superior to discontinuation: results from a randomized, 3-armed, double-blind clinical trial. Meeting: 2012 ACR/ARHP. Annual Meeting. Abstract oral session.
195. Weinblatt ME, Bingham CO 3rd, Burmester GR, Bykerk VP, Furst DE, Mariette X, et al. A phase III study evaluating continuation, tapering, and withdrawal of certolizumab pegol after one year of therapy in patients with early rheumatoid arthritis. *Arthritis Rheumatol.* 2017;69:1937–48.
196. van Vollenhoven RF, Østergaard M, Leirisalo-Repo M, Uhlig T, Jansson M, Larsson E, et al. Full dose, reduced dose or discontinuation of etanercept in rheumatoid arthritis. *Ann Rheum Dis.* 2016;75:52–8.
197. Chen DY, Chen YM, Hsieh TY, Hung WT, Hsieh CW, Chen HH, et al. Drug trough levels predict therapeutic responses to dose reduction of adalimumab for rheumatoid arthritis patients during 24 weeks of follow-up. *Rheumatology (Oxford).* 2016;55:143–8.
198. Plasencia C, Wolbink G, Krieckaert CL, Kneepkens EL, Turk S, Jurado T, et al. Comparing a tapering strategy to the standard dosing regimen of TNF inhibitors in rheumatoid arthritis patients with low disease activity. *Clin Exp Rheumatol.* 2016;34:655–62.
199. Van Herwaarden N, van der Maas A, Minten MJ, van den Hoogen FH, Kievit W, van Vollenhoven RF, et al. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. *BMJ.* 2015;350:h1389.
200. Westhovens R, Robles M, Ximenes AC, Wollenhaupt J, Durez P, Gomez-Reino J, et al. Maintenance of remission following 2 years of standard treatment then dose reduction with abatacept in patients with early rheumatoid arthritis and poor prognosis. *Ann Rheum Dis.* 2015;74:564–8.
201. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet.* 2013;381:918–29.
202. Haschka J, Englbrecht M, Hueber AJ, Manger B, Kleyer A, Reiser M, et al. Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping antirheumatic therapy: interim results from the prospective randomised controlled RETRO study. *Ann Rheum Dis.* 2016;75:45–51.
203. Inciarte-Mundo J, Hernández MV, Rosario V, Ruiz-Esquide V, Cabrera-Villalba S, Ramírez J, et al. Reduction of biological agent dose in rheumatic diseases: descriptive analysis of 153 patients in clinical practice conditions. *Reumatol Clin.* 2014;10:10–6.
204. Bertias A, Avgoustidis N, Papalopoulos I, Repa A, Kougkas N, Kalogiannaki E, et al. Rheumatoid arthritis patients initiating rituximab with low number of previous bDMARDs failures may effectively reduce rituximab dose and experience fewer serious adverse events than patients on full dose: a 5-year cohort study. *Arthritis Res Ther.* 2022;24:132.
205. Pavelka K, Akkoç N, Al-Maini M, Zerbini CAF, Karateev DE, Nasonov EL, et al. Maintenance of remission with combination etanercept-DMARD therapy versus DMARDs alone in active rheumatoid arthritis: results of an international treat-to-target study conducted in regions with limited biologic access. *Rheumatol Int.* 2017;37:1469–79.
206. Emery P, Burmester GR, Naredo E, Sinigaglia L, Lagunes I, Koenigsbauer F, et al. Adalimumab dose tapering in patients with rheumatoid arthritis who are in long-standing clinical remission: results of the phase IV PREDICTRA study. *Ann Rheum Dis.* 2020;79:1023–30.
207. Bertrand D, Stouten V, De Cock D, Pazmino S, Doumen M, de Wergifosse I, et al. Tapering of etanercept is feasible in patients with rheumatoid arthritis in sustained remission: a pragmatic randomized controlled trial. *Scand J Rheumatol.* 2021;51:470–80.
208. Vasconcelos LB, Silva MT, Galvao TF. Reduction of biologics in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatol Int.* 2020;40:1949–59.
209. Pavelka K, Burgos-Vargas R, Miranda P, Guzman R, Yen JH, Izzi MA, et al. Etanercept in moderate rheumatoid arthritis: PRESERVE study results from central/eastern Europe, Latin America and Asia. *Int J Clin Rheumatol.* 2014;9:415–30.
210. Dierckx S, Sokolova T, Lauwerys BR, Avramovska A, de Bellefont LM, Toukap AN, et al. Tapering of biological antirheumatic drugs in rheumatoid arthritis patients is achievable and cost-effective in daily clinical practice: data from the Brussels UCLouvain RA Cohort. *Arthritis Res Ther.* 2020;22:96.
211. Arnold S, Jaeger VK, Scherer A, Ciurea A, Walker UA, Kyburz D. Discontinuation of biologic DMARDs in a real-world population of patients with rheumatoid arthritis in remission: outcome and risk factors. *Rheumatology (Oxford).* 2021;61:131–8.



212. Brahe CH, Krabbe S, Østergaard M, Ørnbjerg L, Glinatsi D, Røgind H, et al. Dose tapering and discontinuation of biological therapy in rheumatoid arthritis patients in routine care – 2-year outcomes and predictors. *Rheumatology (Oxford)*. 2019;58:110–9.
213. Alperi-López M, Alonso-Castro S, Morante-Bolado I, Queiro-Silva R, Riestra-Noriega JL, Arboleya L, et al. Biological dose tapering in daily clinical practice: a 10 year follow-up study. *Reumatol Clin (Engl Ed)*. 2020;16 5 Pt 1:319–23.
214. Chandramohan P, Jain A, Antony G, Krishnan N, Shenoy P. Low-dose rituximab protocol in rheumatoid arthritis-outcome and economic impact. *Rheumatol Adv Pract*. 2021;5: rkaa077.
215. Lamberg T, Sipponen T, Valtanen S, Eklund KK, Mälkönen T, Aalto K, et al. Short interruptions of TNF-inhibitor treatment can be associated with treatment failure in patients with immune-mediated diseases. *Autoimmunity*. 2022;55:275–84.
216. Pope J, Rampakakis E, Vaillancourt J, Bessette L, Lazovskis J, Haraoui B, et al. An open-label randomized controlled trial of DMARD withdrawal in RA patients achieving therapeutic response with certolizumab pegol combined with DMARDs. *Rheumatology (Oxford)*. 2020;59:1522–8.
217. Asai S, Hayashi M, Hanabayashi M, Kanayama Y, Takemoto T, Yabe Y, et al. Discontinuation of concomitant methotrexate in Japanese patients with rheumatoid arthritis treated with tocilizumab: an interventional study. *Mod Rheumatol*. 2020;30:434–41.
218. Van Mulligen E, de Jong PHP, Kuijper TM, van der Ven M, Appels C, Bijkerk C, et al. Gradual tapering TNF inhibitors versus conventional synthetic DMARDs after achieving controlled disease in patients with rheumatoid arthritis: first-year results of the randomised controlled TARA study. *Ann Rheum Dis*. 2019;78:746–53.
219. Mori S, Cho I, Koga Y, Sugimoto M. Comparison of pulmonary abnormalities on high-resolution computed tomography in patients with early versus longstanding rheumatoid arthritis. *J Rheumatol*. 2008;35:1513–21.
220. Bilgici A, Ulusoy H, Kuru O, Celenk C, Unsal M, Danaci M. Pulmonary involvement in rheumatoid arthritis. *Rheumatol Int*. 2005;25:429–35.
221. Narváez J, Díaz Del Campo Fontecha P, Brito García N, Bonilla G, Aburto M, Castéllví I, et al. SER-SEPAR recommendations for the management of rheumatoid arthritis-related interstitial lung disease. Part 2: treatment. *Reumatol Clin (Engl Ed)*. 2022;18:501–12.
222. Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis-Executive summary. *Rheumatology (Oxford)*. 2019;58:220–6.
223. Fernández-Díaz C, Castañeda S, Melero-González RB, Ortiz-Sanjuán F, Juan-Mas A, Carrasco-Cubero C, et al. Abatacept in interstitial lung disease associated with rheumatoid arthritis: national multicenter study of 263 patients. *Rheumatology (Oxford)*. 2020;59:3906–16.
224. Narváez J, Robles-Pérez A, Molina-Molina M, Vicens-Zygmunt V, Luburich P, Yañez MA, et al. Real-world clinical effectiveness of rituximab rescue therapy in patients with progressive rheumatoid arthritis-related interstitial lung disease. *Semin Arthritis Rheum*. 2020;50:902–10.
225. Mena-Vázquez N, Rojas-Gimenez M, Fuego-Varela C, García-Studer A, Perez-Gómez N, Romero-Barco CM, et al. Safety and effectiveness of abatacept in a prospective cohort of patients with rheumatoid arthritis-associated interstitial lung disease. *Biomedicines*. 2022;10:1480.
226. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDs and biologic agents in rheumatoid arthritis: a systematic literature review. *Semin Arthritis Rheum*. 2014;43:613–26.
227. Weinblatt ME, Moreland LW, Westhovens R, Cohen RB, Kelly SM, Khan N, et al. Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. *J Rheumatol*. 2013;40:787–97.
228. Vadillo C, Nieto MA, Romero-Bueno F, Leon L, Sanchez-Pernaute O, Rodriguez-Nieto MJ, et al. Comment on: Efficacy of rituximab in slowing down progression of rheumatoid arthritis-related interstitial lung disease: data from the NEREA Registry: reply. *Rheumatology (Oxford)*. 2020;59:2181–2.
229. Fui A, Bergantini L, Selvi E, Mazzei MA, Bennett D, Pieroni MG, et al. Rituximab therapy in interstitial lung disease associated with rheumatoid arthritis. *Intern Med J*. 2020;50:330–6.
230. Hadjinicolaou AV, Nisar MK, Bhagat S, Parfrey H, Chilvers ER, Ostör AJ. Non-infectious pulmonary complications of newer biological agents for rheumatic diseases – a systematic literature review. *Rheumatology (Oxford)*. 2011;50:2297–305.
231. Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor  $\alpha$  agents, a retrospective cohort study. *Arthritis Res Ther*. 2015;17:319.
232. Manfredi A, Cassone G, Furini F, Gremese E, Venerito V, Atzeni F, et al. Tocilizumab therapy in rheumatoid arthritis with interstitial lung disease: a multicenter retrospective study. *Intern Med J*. 2020;50:1085–90.
233. Citera G, Mysler E, Madariaga H, Cardiel MH, Castañeda O, Fischer A, et al. Incidence rates of interstitial lung disease events in tofacitinib-treated rheumatoid arthritis patients: post hoc analysis from 21 clinical trials. *J Clin Rheumatol*. 2021;27:e482–90.
234. Salvarani C, Sebastiani M, Dieude P, Garcia M, Deberdt W, Rogai V, et al. Baricitinib and the risk of incident interstitial lung disease: a descriptive clinical case report from clinical trials. *Rheumatol Ther*. 2021;8:1435–41.
235. Silva-Fernández L, Lunt M, Kearsley-Fleet L, Watson KD, Dixon WG, Symmons DP, et al. The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis. *Rheumatology (Oxford)*. 2016;55:2033–9.
236. Strangfeld A, Hieser F, Rau R, Burmester GR, Krummel-Lorenz B, Demary W, et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. *Arthritis Res Ther*. 2010;12:R5.
237. Dreyer L, Cordtz RL, Hansen IMJ, Kristensen LE, Hetland ML, Mellekjær L. Risk of second malignant neoplasm and mortality in patients with rheumatoid arthritis treated with biological DMARDs: a Danish population-based cohort study. *Ann Rheum Dis*. 2018;77:510–4.
238. Raaschou P, Söderling J, Turesson C, Askling J. Tumor necrosis factor inhibitors and cancer recurrence in Swedish patients with rheumatoid arthritis: a nationwide population-based cohort study. *Ann Intern Med*. 2018;169:291–9.
239. Waljee AK, Higgins PDR, Jensen CB, Villumsen M, Cohen-Mekelburg SA, Wallace BI, et al. Anti-tumor necrosis factor- $\alpha$  therapy and recurrent or new primary cancers in patients with inflammatory bowel disease, rheumatoid arthritis, or psoriasis and previous cancer in Denmark: a nationwide, population-based cohort study. *Lancet Gastroenterol Hepatol*. 2020;5:276–84.
240. Xie W, Xiao S, Huang Y, Sun X, Gao D, Ji L, et al. A meta-analysis of biologic therapies on risk of new or recurrent cancer in patients with rheumatoid arthritis and a prior malignancy. *Rheumatology (Oxford)*. 2020;59:930–9.
241. Phillips C, Zeringue AL, McDonald JR, Eisen SA, Ranganathan P. Tumor necrosis factor inhibition and head and neck cancer recurrence and death in rheumatoid arthritis. *PLoS One*. 2015;10:e0143286.
242. Mamtani R, Clark AS, Scott FI, Brensinger CM, Boursi B, Chen L, et al. Association between breast cancer recurrence and immunosuppression in rheumatoid arthritis and inflammatory bowel disease: a cohort study. *Arthritis Rheumatol*. 2016;68:2403–11.
243. Raaschou P, Frisell T, Askling J. TNF inhibitor therapy and risk of breast cancer recurrence in patients with rheumatoid arthritis: a nationwide cohort study. *Ann Rheum Dis*. 2015;74:2137–43.
244. de Gernay S, Bagheri H, Despas F, Rousseau V, Montastruc F. Abatacept in rheumatoid arthritis and the risk of cancer: a world observational post-marketing study. *Rheumatology (Oxford)*. 2020;59:2360–7.
245. Xie W, Yang X, Huang H, Gao D, Ji L, Zhang Z. Risk of malignancy with non-TNFi biologic or tofacitinib therapy in rheumatoid arthritis: a meta-analysis of observational studies. *Semin Arthritis Rheum*. 2020;50:930–7.
246. Wang JL, Yin WJ, Zhou LY, Zhou G, Liu K, Hu C, et al. Risk of non-melanoma skin cancer for rheumatoid arthritis patients receiving TNF antagonist: a systematic review and meta-analysis. *Clin Rheumatol*. 2020;39:769–78.
247. Wadström H, Frisell T, Askling J. Malignant neoplasms in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors, tocilizumab, abatacept, or rituximab in clinical practice: a nationwide cohort study from Sweden. *JAMA Intern Med*. 2017;177:1605–12.
248. Solipuram V, Mohan A, Patel R, Ni R. Effect of janus kinase inhibitors and methotrexate combination on malignancy in patients with rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. *Auto Immun Highlights*. 2021;12:8.
249. Curtis JR, Yamaoka K, Chen YH, Bhatt DL, Gunay LM, Sugiyama N, et al. Malignancy risk with tofacitinib versus TNF inhibitors in rheumatoid arthritis: results from the open-label, randomised controlled ORAL Surveillance trial. *Ann Rheum Dis*. 2023;82:331–43.
250. Elandt K, Aletaha D. Treating rheumatic patients with a malignancy. *Arthritis Res Ther*. 2011;13:223.
251. Anker SD, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. *Int J Cardiol*. 2002;86:123–30.
252. Coletta AP, Clark AL, Banarjee P, Cleland JG. Clinical trials update: RENEWAL (RENAISSANCE and RECOVER) and ATTACH. *Eur J Heart Fail*. 2002;4:559–61.
253. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation*. 2004;109:1594–602.
254. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor- $\alpha$ , in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation*. 2003;107:3133–40.
255. European Medicines Agency: humira (adalimumab). Available from: <https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information.es.pdf>.
256. European Medicines Agency: remicade (infliximab). Available from: <https://www.ema.europa.eu/en/documents/product-information/remicade-epar-product-information.es.pdf>.
257. European Medicines Agency: MabThera (rituximab). Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/mabthera430>.
258. Dobson R, Giovannoni G. Autoimmune disease in people with multiple sclerosis and their relatives: a systematic review and meta-analysis. *J Neurol*. 2013;260:1272–85.
259. Taylor TRP, Galloway J, Davies R, Hyrich K, Dobson R. Demyelinating Events Following Initiation of Anti-TNF $\alpha$  Therapy in the British Society for Rheumatology Biologics Register in Rheumatoid Arthritis. *Neurol Neuroimmunol Neuroinflamm*. 2021;8:e992.
260. Dreyer L, Magyari M, Laursen B, Cordtz R, Sellebjerg F, Locht H. Risk of multiple sclerosis during tumour necrosis factor inhibitor treatment for arthritis: a



- population-based study from DANBIO and the Danish Multiple Sclerosis Registry. *Ann Rheum Dis.* 2016;75:785–6.
261. Li L, Aviña-Zubieta JA, Bernstein CN, Kaplan GG, Tremlett H, Xie H, et al. Risk of multiple sclerosis among users of antitumor necrosis factor  $\alpha$  in 4 Canadian provinces: a population-based study. *Neurology.* 2023;100:e558–67.
262. Kunchok A, Aksamit AJ Jr, Davis JM 3rd, Kantarci OH, Keegan BM, Pittock SJ, et al. Association between tumor necrosis factor inhibitor exposure and inflammatory central nervous system events. *JAMA Neurol.* 2020;77:937–46.