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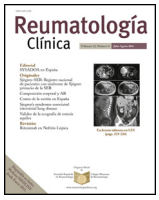

Special Article

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.

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

Palabras clave:
Artritis reumatoide
Fármacos biológicos
Inhibidores de las JAK

R E S U M E N

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 cardiaca o enfermedad desmielinizante.

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

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;[1] 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
Recommendations				
General recommendations				
Recommendation A. Treatment of RA should be based on a shared decision between the patient and the rheumatologist	DA = 100%	SD = 0.49	NA	NA
Recommendation B. 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
Recommendation C. Rheumatologists are the specialists responsible for the care of patients with RA	DA = 92%	SD = 0.67	NA	NA
Recommendation 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	NA	ON
Recommendation E. 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
Recommendations for the management of RA				
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	1a	A
Recommendation 2. 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
Recommendation 3a. 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
Recommendation 3b. 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
Recommendation 4a. In patients with RA, methotrexate is recommended as monotherapy, as the first choice DMARD	DA = 100%	SD = 0.00	1a	A
Recommendation 4b. In the case of intolerance to methotrexate and/or adverse effects, leflunomide or sulfasalazine can be used	DA = 100%	SD = 0.00	1a	A
Recommendation 5a. 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
Recommendation 5b. 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
Recommendation 6a. 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
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	5	D
Recommendation 7. 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
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 = 92%	SD = 0.90	1a	A
Recommendation 9. Where using a b/tsDMARD as monotherapy, an anti-IL-6R or a JAKi is recommended	DA = 100%	SD = 0.29	1a	A
Recommendation 10a. 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
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	1b	A
Recommendation 10c. 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
Recommendation 11. 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
Special recommendations				
Recommendation 12. 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
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 on with the patient and their oncologist	DA = 92%	SD = 0.58	4	C
Recommendation 14. 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 4	C C

SD: standard deviation; DA: degree of agreement; DR: degree of recommendation from the SER, ACR, EULAR and GUIPCAR[1–4] Consensus documents; LE: Level of evidence from the SER, ACR, EULAR and GUIPCAR[1–4] Consensus documents.
Classification according to the Oxford *Centre for Evidence-Based Medicine* (CEBM) system.[5]

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).*[1] 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*;[2] b) EULAR *recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update*,[3] and c) GUIPCAR (SER's clinical practice guidelines for the management of patients with RA) 2017.[4] The process was

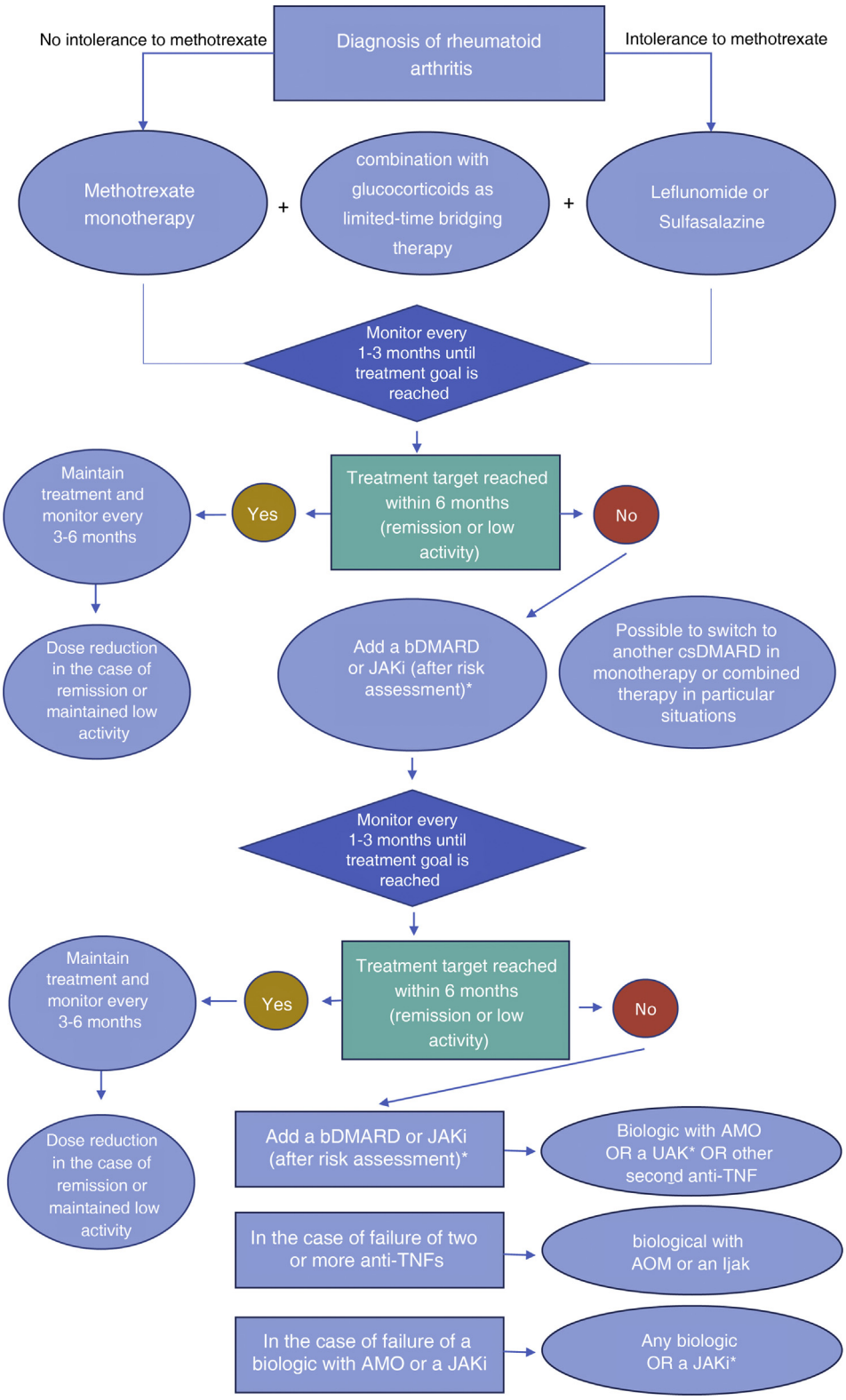

Fig. 1. Rheumatoid arthritis treatment algorithm.
DMARD: disease-modifying drug. B: biologic. CS: Conventional synthetic. AMO: Another mechanism of action.
JAKi: Janus kinase inhibitor*: Limit the use of JAKi in patients of 65 years and over; those with risk factors for cardiovascular or thromboembolic 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 ≥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).[5]

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[2] and EULAR 2022[6] 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[7,8] 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,[9–11] 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.[12,13] 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,[14] 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.[15–18] 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.[4,19,20] 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.[21–23]

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.[2] 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.[24] 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.[25] This has demonstrated long- and medium-term benefits in the overall evolution of the disease, regardless of the drug used.[26–28]

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.[29,30] Most publications propose monitoring periods ranging from 4 weeks to 4 months.[31–43]

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.[44] 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.[45] 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.[46,47] Nevertheless, the successful implementation of these techniques requires the development of high-quality digital solutions that have been rigorously evaluated in a clinical setting.[48]

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.[2,49,50] 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 suggest that the efficacy of subcutaneous administration is greater, although the cost of this is a factor to be considered.[51–54] The dose of MTX was not discussed in detail, referring to previous versions.[55] 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.[56]

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,[57,58] 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.[59,60] LEF is also effective in combination with biological agents[61,62] 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.[64]

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.[65–70] 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.[64,71]

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.[72]

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.[73]

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.[2,3] 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.[3]

Failure to maintain the treatment goal in the gradual trapering 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.[38,74,75] 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.[76–81]

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.[82,83] 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.[84,85]

All bDMARDs show comparable efficacy in the treatment of RA with an IR to MTX.[30]

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.[86–106]

The results of the *Oral-Surveillance RCT*[107] 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.[108] 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.[51] 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).[12,30,51,52,109] 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 = 039.

A clinical trial[110] and different cohort studies[62,111–113] 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[114] 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[115] 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[116] showed that the efficacy and safety of TCZ combined with MTX was similar to that of LEF combined.

A recently reported SR + meta-analysis[117] 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[4,63] 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[118] 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[119] 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[120] 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,[87,90,91,121] and in baricitinib RCTs, from 10-25 mg every 7 days.[93]

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.[122]

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.[123] 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.[124–129]

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.[130,131] 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.[132] TCZ or sarilumab monotherapy is superior to ADA monotherapy.[128,129]

Regarding JAKi, all of them have demonstrated their efficacy in monotherapy.[95,97,106,127,133,134] 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.[127] Baricitinib has demonstrated efficacy in monotherapy similar to that of combined treatment with MTX in patients with RA-onset.[95,133] Upadacitinib and filgotinib have also demonstrated their efficacy as monotherapy, although there are no direct comparative studies with their use in combination with MTX.[97,134]

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.[135–137] In addition, it is known that the survival of the different drugs is lower as the lines of treatment used increase.[138] 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.[136–175] With regard to switching to a second biologic after failure of a first anti-TNF, different studies, both clinical trials and cohort studies[142,143,146,148,149,153,156–158,160,164,165,168,170,172] 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.[136–141,145,147,150–152,154,155,159,161–163,166,167,169,171,173–176]

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[177–185] 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,[177,181,183,184] 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.[186–196] 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.[192,196–209]

As for the different strategies for reducing doses or spacing them, there were no differences in the results.[210]

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.[6,50,211–213]

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.[214–218]

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.[219,220] Both the new recommendations by SER-SEPAR for the management of RA-ILD,[221] 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,[222] concur in pointing out in their SR that ABA and RTX are the biological agents with the most evidence of safety in these patients,[223–225] while anti-TNF drugs could be associated with a risk of worsening of a pre-existing RA-ILD (with a low level of evidence).[226] The Spanish experience of using ABA in clinical practice supports the safety of its use in RA-ILD.[223–225] 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.[227] Likewise, there are observational studies with RTX that confirm its safety and its possible usefulness in stabilising or improving lung function in these patients.[224,228,229]

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,[230,231] others show an adequate safety profile.[232] 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.[233] Similarly, existing information with baricitinib has not detected an increased risk of developing or exacerbating ILD in clinical trials.[234]

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,[235–238] or even with other pathologies such as psoriasis and inflammatory bowel disease.[239] A meta-analysis published in 2020[240] 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[241] and breast cancer [242,243] 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 incidence 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[244] showed a slight increase in melanoma in patients treated with ABA compared to other bDMARDs, and an SR[245] found an increased risk of cancer overall, compared with anti-TNF and non-melanoma skin cancer compared with anti-TNFs.[17,245–247] With respect to JAKi, two previous meta-analyses[17,248] had not detected an increase in cancer incidence. However, in the ORAL Surveillance randomised clinical trial,[107,249] 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[250] 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.[251–253] 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.[254] Cases of worsening congestive HF have also been reported with ADA.[255]

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).[251–256] 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.[257]

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.[252,255–257]

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);[258] 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.[259] 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.[259] This study was proposed after an increased risk observed in men in a 2016 DANBIO study without sufficient statistical power.[260] 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[261] and demyelinating events[262] 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.

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