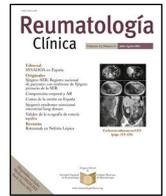




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Original Article

Expert recommendations on the interleukin 6 blockade in patients with rheumatoid arthritis[☆]



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ABSTRACT

Objective: To draft recommendations on interleukin 6 (IL-6) blockade in rheumatoid arthritis (RA), based on best evidence and experience.

Methods: A group of 10 experts on IL-6 blockade in RA was selected. The 2 coordinators formulated 23 questions about IL-6 blockade (indications, efficacy, safety, etc.). A systematic review was conducted to answer the questions. Using this information, inclusion and exclusion criteria were established, as were the search strategies (Medline, EMBASE and the Cochrane Library were searched). Two different reviewers selected the articles. Evidence tables were created. At the same time, European League Against Rheumatism and American College of Rheumatology abstracts were evaluated. Based on this evidence, the coordinators proposed preliminary recommendations that the experts discussed and voted on in a nominal group meeting. The level of evidence and grade of recommendation were established using the Oxford Centre for Evidence Based Medicine and the level of agreement with the Delphi technique (2 rounds). Agreement was established if at least 80% of the experts voted yes (yes/no).

Results: The 8 preliminary recommendations were accepted after the Delphi process. They covered aspects such as the use of these therapies in monotherapy, in combination, in patients with refractory disease or intolerant patients, response evaluation, optimisation and risk management.

Conclusions: The manuscript aims to solve frequently asked questions and aid in decision making strategies when treating RA patients with IL-6 blockade.

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Recomendaciones de experto sobre el bloqueo de la interleucina 6 en pacientes con artritis reumatoide

RESUMEN

Objetivo: Generar recomendaciones sobre el bloqueo de la interleucina 6 (IL-6) en pacientes con artritis reumatoide (AR), basadas en la mejor evidencia y experiencia.

Palabras clave:

Artritis reumatoide

Interleucina 6

Recomendaciones

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Métodos: Se seleccionó a 10 expertos reumatólogos en el manejo de los inhibidores de la IL-6. Los 2 coordinadores generaron 23 preguntas sobre el bloqueo de la IL-6 en la AR (perfiles de indicación, eficacia, seguridad, etc.) para ser contestadas mediante una revisión sistemática de la literatura. Con base en las preguntas se definieron los criterios de inclusión y exclusión, y las estrategias de búsqueda (para interrogar *Medline*, *Embase* y la *Cochrane Library*). Dos revisores seleccionaron los artículos resultantes de la búsqueda. Se generaron tablas de evidencia. Paralelamente, se evaluaron *abstracts* de congresos de EULAR y ACR. Con toda esta evidencia los coordinadores propusieron 8 recomendaciones preliminares que se evaluaron, discutieron y votaron en una reunión de grupo nominal con el resto de los expertos. Para cada recomendación se estableció el nivel de evidencia y grado de recomendación, y el grado de acuerdo mediante un Delphi. Se definió acuerdo si al menos el 80% de los participantes contestaban sí a la recomendación (sí o no).

Resultados: Las 8 recomendaciones preliminares se aceptaron tras el Delphi. Abarcan aspectos como su uso en monoterapia, en combinación, en pacientes refractarios o intolerantes, la evaluación de su respuesta, la optimización o la gestión del riesgo.

Conclusiones: Este documento pretende resolver algunos interrogantes clínicos habituales y facilitar la toma de decisiones con el bloqueo de la IL-6 en el manejo de la AR.

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Introduction

There have been major changes in the treatment of rheumatoid arthritis (RA) in recent years. New drugs and therapy strategies have completely changed the prognosis of these patients.^{1–4} The biological drugs have been a key element in this field.⁵ The first experience was with tumour necrosis factor (TNF) inhibitors, but in recent years drugs with different mechanisms of action have appeared, including the interleukin-6 (IL-6) inhibitors.^{6–18}

IL-6 is a pleiotropic cytokine that plays a central role in the pathogenesis of RA by contributing to the activation of T and B lymphocytes, the stimulation of synoviocytes, the maturation of osteoclasts and the production of acute-phase reactants. RA activity has been correlated with the serum elevation of both IL-6 and its soluble receptor (IL-6R), and therefore its blockade (both IL-6 and IL-6R) is considered a good therapeutic target in treatment of the disease.^{19,20}

Tocilizumab (TCZ) was the first IL-6 inhibitor approved and marketed in Spain, for which there is much short and long-term evidence.^{7,14–18} The EMA has also approved sarilumab (SAR),^{9–13} another monoclonal antibody against IL-6R, and there are other IL-6 inhibitors such as olokizumab,^{21,22} clazakizumab,²³ and sirukumab,^{24,25} at different stages of clinical development; however, the latter in the end will not be registered for RA treatment.

The aim of this paper was to generate recommendations based on the best possible evidence and experience with the use of IL-6 inhibitors in patients with RA.

Methods

The nominal group and Delphi technique were used to prepare the consensus.²⁶ The document was entirely prepared by distribution of tasks and comments to the parties, with the help of a systematic literature review and an expert methodologist.

Selection of experts

First, a group of 10 rheumatologists was formed, with recognised experience in the management of RA patients and the use of IL-6 inhibitors. A *Medline* search was carried out to identify Spanish rheumatologists with publications on the subject of this paper. Submission of papers to the national congress of the Spanish Society of Rheumatology was also considered. All the results were discussed with the coordinators who, in addition to the aforementioned, considered as experts those who regularly attended specific

forums, those considered opinion leaders on this subject, who those had been speakers, etc. Finally, the selection sought to achieve the greatest geographical representativeness.

Systematic literature review

The project coordinators generated 23 questions to be answered by a systematic review of the literature (Table 1). Since they all referred to different aspects of the same topic, it was decided that one review should be carried out. The inclusion and exclusion criteria were defined with these questions. We searched for articles that included patients with RA under treatment with any IL-6 inhibitor, irrespective of the dose or specific administration route. In addition, these studies had to analyse (depending on the question) different aspects of the efficacy and safety of the drug therapy. In the end, only studies with the following designs were included: meta-analyses, systematic reviews and clinical trials. A search was performed of the literature databases *Medline* (from its launch until October 2017), *Embase* (from its launch until October 2017), and the *Cochrane Library* (from its launch until October 2017). Mesh and free text terms were used, and the search strategy was executed with the help of an expert documentalist. For each review, two reviewers (EL, TO) independently analysed the articles resulting from the search strategy in the different literature databases, and also carried out a detailed analysis of the articles included. In the event of discrepancy, a third person, LC, resolved any conflict. The grey literature in EULAR and ACR congresses over the past 2 years was reviewed as well as documents from the coordinators (articles and abstracts from congresses and other forums of interest, related to the subject of the consensus). Then, a secondary manual search was undertaken of the references of the articles that were eventually included. The Jadad scale was used for the clinical trials (RCT),²⁷ to evaluate the methodological quality of the studies included. Evidence and results tables were created describing the main features and results of the studies included.

Nominal group meeting and Delphi technique (2 rounds)

The group of experts held a nominal group meeting. Prior to the meeting, the result of the systematic review of the literature and a summary of the evidence found were sent in order to answer the questions posed by the coordinators. The recommendations and evidence were presented and discussed at the meeting.

This led to the formulation of the final recommendations, which were then dealt with through a Delphi vote (first round), using the televoting system, to assess the grade of agreement (GA).

Table 1
Questions formulated to be answered by means of a systematic review of the literature.

N	Question
1	What clinical advantages does the therapeutic blockade of IL-6 in monotherapy have vs other therapies (other than IL-6 blockade) in monotherapy for patients with RA who cannot take MTX (intolerance, lack of adherence or medical judgement)?
2	Can therapeutic blockade be prescribed for patients with heart failure?
3	Is IL-6 blockade safe in subjects with demyelinating disease?
4	What is the therapeutic effect of IL-6 blockade on structural joint damage in RA?
5	What are the consequences of IL-6 blockade on general mortality and that of cardiovascular cause in patients with RA?
6	Is there a relationship between IL-6 blockade and the induction of neoplasia (skin, solid organ, lymphomas) in patients with RA?
7	Is there any special clinical profile (in which its efficacy has been demonstrated as superior) or clinical manifestations of RA in which IL-6 blockade is particularly useful?
8	What is the risk of pulmonary involvement, deriving from IL-6 blockade, in subjects with RA?
9	Does therapeutic IL-6 blockade have any effect on the hydrocarbon metabolism of individuals with RA?
10	Which clinical profiles of children with JIA (systemic or polyarticular) could benefit from therapeutic IL-6 blockade, and to what extent (efficacy)?
11	What are the advantages (whether it is more effective), in a patient with RA and primary/secondary failure with an anti-TNF α of switching to therapeutic IL-6 blockade or trying a second anti-TNF α agent?
12	What is the evidence (efficacy and safety) for IL-6 blockade optimisation in RA?
13	Which is the best disease activity index to use in patients treated with IL-6? Is CRP the best disease activity index in RA with the use of anti-IL-6?
14	What is the efficacy of inhibition of IL-6 in RA in patients with RA after failure with synthetic DMARDs or MTX compared to other biologics or kinase inhibitors?
15	Do remission percentages increase in patients treated with IL-6 inhibitors due to their effect on CRP or ESR?
16	Do IL-6 inhibitors increase the risk of bowel perforation?
17	How do weight, smoking or the presence of RF and anti-CCP antibodies affect therapeutic response to IL-6 inhibition?
18	Are there differences between the different IL-6 inhibitors (efficacy, safety)?
19	How does IL-6 inhibition affect extra-articular manifestations of RA?
20	What is the efficacy and safety of IL-6 blockade in patients previously treated with non anti-TNF α biologics?
21	What is the effect of biological drugs or kinase inhibitors in patients who do not respond to IL-6 blockade?
22	Is one administration route safer and more effective than another?
23	What is the safest and most effective dose of an IL-6 inhibitor?

JIA: juvenile idiopathic arthritis; anti-CCP: anti-citrullinated proteins; RA: rheumatoid arthritis; disease-modifying antirheumatic drugs; RF: rheumatoid factor; IL-6: interleukin-6; MTX: methotrexate; CPR: C reactive protein; TNF α : tumour necrosis factor α ; ESR: erythrocyte sedimentation rate.

Agreement was defined if at least 80% of the participants answered yes to the recommendation (yes or no). The Delphi results were shown to the experts. In a second Delphi round, votes that reached a sufficient grade of agreement were again voted from 1 to 10 (1: totally disagree; 10: totally agree).

Final consensus document

The final document was drawn up with all this information. Each of the recommendations, with the assistance of the methodologist, was assigned a level of evidence (LE) and a grade of recommendation (GR) according to the recommendations of the Oxford Centre for Evidence-Based Medicine.²⁸ Allocation of GA was as described. The paper was circulated among the experts for final appraisal and final comments.

Results

Two IL-6 inhibitors have currently been approved in our country: TCZ (marketed) and SAR (in the process of marketing), whose main characteristics are shown in [Table 2](#).

TCZ has been available to clinical rheumatologists since 2009, and both its intravenous (iv) and subcutaneous (sc) formulations are available. There is therefore a large amount of both short-term and long-term information from RCTs and observational studies. They have been studied in early RA, established RA, RA naïve to traditional or biological disease modifying drugs, refractory/intolerant RA, in monotherapy, and in combination.^{18,29–38} We also have data on the effect of TCZ in monotherapy once its use has been discontinued,³⁹ and on its efficacy when reintroduced.⁴⁰ It has been shown to achieve clinical remission or low activity in a significant percentage of patients.^{18,29,30,32,33,38} It can be observed at 2 weeks, and can last up to several years.^{32,33,36,41} TCZ IV in monotherapy is superior to adalimumab,²⁹ methotrexate (MTX)^{34,35} and other traditional DMARDs⁴² in monotherapy. When combined with another

DMARDs, the percentages of remission increases, although this is not statistically significant.^{32,33,36,41} Radiological progression was analysed in 5 articles,^{31,43} with plain radiography or magnetic resonance imaging.³¹ TCZ IV in monotherapy delays radiological progression at least to one year of treatment. This effect is greater for RA with a greater risk of unfavourable outcome.⁴³ The efficacy of TCZ in RA has also been demonstrated in other variables such as functional capacity,^{30,32–35,41,42,44,45} bone metabolism,^{30,44} fatigue, C reactive protein (CRP), quality of life, pain, morning stiffness and anaemia.^{18,29,32,33,35–38,41,44,45}

SAR^{9,46–49} was studied in established cases of RA refractory/intolerant to MTX, other traditional DMARDs and TNF inhibitors, in monotherapy or in combination with MTX. SAR (200 mg every 2 weeks) achieves clinical remission or low activity in a significant percentage of patients; it improves functional capacity and other patient-related outcomes (PRO), and reduces radiographic progression for up to 52 weeks of treatment. There is also intermediate data showing maintained efficacy at two years.⁴⁹ Like TCZ, its efficacy in monotherapy was superior to adalimumab in monotherapy for most of the variables studied.¹⁰ Finally, other variables studied with a good response to SAR were, for example, fatigue, CRP, anaemia, and fasting blood sugar and glycated haemoglobin.^{9,46–49}

Below, we discuss the recommendations and full evidence with the use of IL-6 inhibitors (see [Table 3](#) for the full Delphi results).

Recommendation 1: In patients with RA and insufficient response to conventional synthetic MTX/other DMARDs, for whom it is decided to prescribe a drug that blocks IL-6, use in combination is recommended (LE1b; GR A; GA 90%).

The panel first wants to stress that it is important that this option is individualised for each case assessing the balance between risk (toxicity) and benefit (magnitude of effect, if clinically relevant). Also, most of the evidence comes from combining with MTX, although we also have evidence (far less) with leflunomide, salazopyrine and antimalarials.^{15,50}

Table 2
Main characteristics of tocilizumab and sarilumab.

Characteristic	Tocilizumab	Sarilumab
Molecule	Recombinant human IgG monoclonal antibody	Recombinant human IgG monoclonal antibody
Mechanism of action	Blockade of both soluble IL-6 and membrane-bound receptors	Blockade of both soluble IL-6 and membrane-bound receptors
Administration route	IV, SC	SC
Steady-state half life	12 days	21 days
Treatment dose	IV formulation 8 mg/kg every 4 weeks SC formulation 162 mg every week	SC formulation 200 mg every 2 weeks
Presentation	Infusion vial Preloaded syringe	Pre-filled syringe and pen
Indication on technical datasheet	-In combination with MTX for: • Severe, active and progressive RA in adults not treated previously with MTX • Active, moderate-severe RA in adult patients who have not responded appropriately, or who are intolerant to ≥ 1 DMARD or TNF antagonists -TCZ can be administered as monotherapy if there is intolerance to MTX or when continuous treatment with MTX is inappropriate	-In combination with MTX for: • Active, moderate-severe RA in adult patients who have not responded appropriately, or who are intolerant to ≥ 1 DMARD -SAR can be administered in monotherapy in the case of intolerance to MTX or when treatment with MTX is not appropriate

RA: rheumatoid arthritis; DMARDs: disease-modifying antirheumatic drugs; IV: intravenous; kg: kilogramme; mg: milligram; MTX: methotrexate; SC: subcutaneous; TNF: tumour necrosis factor.

Table 3
Delphi technique (1st and 2nd round) results of the recommendations on the use of IL-6 inhibitors in patients with RA.

N	Recommendation	1st round ^a			2nd round ^b				Oxford ^c	
		GA	Mean (SD)	Median	p25–p75	Min	Max	% ≥ 7	LE	GR
1	In patients with RA and insufficient response to MTX/other conventional synthetic DMARDs in whom it is decided to prescribe a drug that blocks IL-6, its use in combination is recommended	100%	8.6 (2.8)	9	8–9.7	6	10	90%	1b	A
2	In patients with active RA who cannot take MTX and it is decided to prescribe a biological therapy in monotherapy, using IL-6 blockade preferentially is recommended	90%	8.6 (2.8)	8.5	8–9.7	6	10	90%	1a	A
3	In patients with RA with insufficient primary response to a first TNF inhibitor, therapeutic target change including IL-6 blockade is recommended	100%	8.7 (2.8)	9	8.2–9.7	6	10	90%	2b	B
4	Assessment of the use of IL-6 blockers is recommended in patients with RA with an important systemic component.	90%	7.9 (3.5)	8	7.2–8.7	5	10	80%	1a	B
5	When evaluating response to treatment in patients with an IL-6 blocking drug, using an disease activity index is recommended that does not include an acute phase reactant, such as CDAI	100%	8.7 (2.1)	9	8.2–	7	10	100%	2a	B
6	In patients with RA in remission/low disease activity maintained with an IL-6 blocker, adjusting the dose of the drug is recommended	100%	9.2 (2.1)	10	9–9	7	10	100%	2a	B
7	In a patient with IL-6 blockage, special monitoring of neutrophil, lipid, and transaminase levels is recommended. Special caution should also be taken if there is a history of diverticulitis, due to the risk of bowel perforation.	100%	8.7 (2.1)	9	8–10	7	10	100%	5	D
8	IL-6 blockade in RA is not associated with an increased risk of cardiovascular disease, therefore no special action is required other than the usual	100%	9(2.1)	9	9–9.7	7	10	100%	5	D

RA: rheumatoid arthritis; CDAI: *Clinical Disease Activity Index*; SD: standard deviation; DMARDs: disease-modifying antirheumatic drugs; GA: grade of agreement; GR: grade of recommendation; IL-6: interleukin-6; Max: maximum; Min: minimum; MTX: methotrexate; LE: level of evidence; p25–p75: percentiles 25 and 75; TNF: tumour necrosis factor.

^a The grade of agreement was established in the first Delphi round if at least 80% voted yes (yes/no).

^b The grade of agreement was graded in the second Delphi round from 1 (total disagreement) to 10 (total agreement).

^c The LE and GR were established according to the Oxford levels of evidence.

For TCZ, we have many RCT in which, in terms of activity or harm, no statistically significant differences were generally found between monotherapy and combination with MTX or DMARDs. However the trend and absolute numbers favour combination, especially with prominent variables such as ACR70, longer-term

radiological damage or for patients who are refractory to TNF inhibitors.^{51–54,43,55}

With respect to SAR, it has been published that, in patients with established RA refractory to MTX, the combined use of SAR and MTX is associated with a greater reduction in the Sharp/van der Heijde

index at 52 weeks compared to the MTX in monotherapy group.¹²

Recommendation 2: In patients with active RA who cannot take MTX and those for whom prescription of a biological drug in monotherapy has been decided, it is recommended that agents that block IL-6 should be used preferentially (LE1a; GR A; GA 90%).

It should be noted that the criteria for not prescribing MTX would be contraindication, intolerance or medical judgement. Most of the evidence refers to patients who cannot take specific MTX, although this could probably be extended to other synthetic DMARDs.

The panel wishes to point out that there are other therapeutic options in addition to IL-6 blockade for these types of patients, an indication included in its technical data sheets, but for which there is less evidence regarding its use in monotherapy.^{56–58}

In terms of the evidence, in patients with established, active RA who are intolerant or for whom it is inappropriate to continue with MTX and compared with adalimumab,^{29,59} TCZ IV was superior (at 24 weeks) in variables such as clinical remission, low disease activity or Clinical Disease Activity Index (CDAI). On the other hand, no significant differences were observed between adalimumab and TCZ in improvement in the Health Assessment Questionnaire (HAQ), fatigue, or the health-related quality of life questionnaire (SF 36). In a similar patient profile, which also included patients refractory to MTX10, SAR was superior (at 24 weeks) in clinical remission, CDAI remission and low disease activity, at week 12 and at week 24, with statistical significance, the HAQ and SF-36 (physical component). However, there was no significant difference between adalimumab and SAR in the improvement of fatigue and the SF-36 mental component. There are preliminary data with other IL-6 blockers that point in the same direction.^{21,23}

Recommendation 3: In patients with RA with insufficient primary response to a first TNF inhibitor, a change of therapeutic target is recommended, including IL-6 blockade (LE 2b; GR B; GA 90%).

It has been demonstrated in the literature that TCZ is effective in patients refractory to TNF^{30,35–37} both in the short⁶⁰ and long term.⁶¹ The efficacy of SAR (along with a conventional DMARD) has also been analysed in these patients, at least in the short term.¹¹ SAR was superior to placebo in both disease activity and response rates (DAS 28-PCR, ACR 20/50/70), as well as functional capacity (HAQ)¹¹ and patient-perceived health variables, including work productivity.⁴⁷ There is some short-term (12 weeks) data for olokizumab on its superiority to placebo in these patients.^{21,22} We also have similar data for sirukumab,²⁴ although this drug is not going to be marketed for the time being.

The panel also considers that, in cases of inefficacy secondary to TNF inhibitor, the decision to change therapeutic target is not as clear, and is not supported by the evidence. Therefore, for example, in cases where this is due to immunogenicity, another TNF inhibitor can be tested. However, this does not preclude a change of TNF inhibitor target.

In cases of class adverse events, such as demyelinating disease with TNF inhibitors, the panel also recommends a change of therapeutic target.

Recommendation 4: It is recommended that the use of IL-6 blockade in patients with RA with a significant systemic component should be assessed (LE 1a; GR A; GA 80).

The panel defined a clinically important systemic component (clinically significant anaemia due to disease, fatigue, and fever/slight fever).

The literature confirmed that patients with anaemia had a significant increase in haemoglobin levels with TCZ compared to those treated with MTX (1.19 vs .10 g/dL),³⁵ whereas in other studies the increase was 6–7 g/L compared to placebo.⁵¹ There are similar results with other IL-6 inhibitors such as SAR.⁶² There are also

data on the efficacy of IL-6 inhibitors in fatigue,^{15,22,36,63,64,51,65,66} pain,^{15,46,51,65–68} morning stiffness,^{15,66} and depression.^{64,66}

On the other hand, with regard to other clinical profiles such as patients with amyloidosis, case series of patients with this manifestation under treatment with TCZ have been published and no problems recorded.⁶⁹ In patients with lung disease, the use of an IL-6 blocking agent has not been clinically shown to cause a specific lung disease, nor has it been shown to be associated with the development or exacerbation of a lung disease.^{70–73} Finally, in terms of bone metabolism, there are data indicating that TCZ in monotherapy,^{30,44} and SAR in monotherapy and combined therapy may have a beneficial effect in this regard.^{9,74}

Little information is currently available on the effect of these drugs on hydrocarbon metabolism. There is a small observational study with TCZ, where it appears that the drug could improve insulin sensitivity (decrease resistance).⁷⁵ It has also been seen in RCT subanalysis of SAR^{48,76} that, in patients with RA with or without diabetes, the use of SAR with traditional DMARDs decreased fasting blood sugar and glycated haemoglobin levels. The decrease in glycated haemoglobin in diabetic patients compared to placebo was very significant.

Recommendation 5: When evaluating response to treatment in patients with an IL-6 blocking drug, use of a disease activity index is recommended that does not include an acute-phase reactant, such as CDAI (LE 2b; GR B; GA 100%).

IL-6 blockade has been shown to directly and rapidly inhibit the production of acute phase reactants, especially CRP.^{13,22,25,50,77} Therefore, CRP and the indices containing this reactant may not be good indices for monitoring the efficacy of these drugs. Thus, the European consensus document on IL-6 blockade and related documents⁷⁸ propose the use of CDAI as a compound index to monitor disease activity. This same document also considers better indices that use erythrocyte sedimentation rate instead of CRP.⁷⁹

Recommendation 6: In patients with RA in remission/low activity with IL-6 blockade, the panel recommends assessing adjustment of the drug dose (LE 2a; GR B; GA 100%).

First, the panel considered that the patient should have been in remission/low disease activity on a sustained basis (6 months) to consider dose adjustment.

Several systematic reviews of the literature with TCZ (principally based on observational studies), including its used as a second line biologic, show that dose adjustment in patients in remission is reasonable.^{80,81} Similarly, a retrospective Spanish observational study maintains that optimisation in patients in remission is effective even when a change is made from IV to SC.⁸² Recently in an RCT, patients who were in sustained remission after 24 weeks of treatment with 162 mg of TCZ SC weekly (in monotherapy and in combination) were randomised to either continue this regimen or change to every 2 weeks. It was observed that after a further 24 weeks, the percentage of patients in clinical remission was 73.9% in those whose doses were adjusted.⁸³ We should point out that in the United States the approved dose of TCZ is 4 mg, based on RCTs in which this dose was effective in a significant percentage of patients.^{51,41} In the open phase of RCTs with SAR, the dose was reduced from 200 mg to 150 mg if there were laboratory abnormalities (neutropenia, thrombocytopenia or elevated transaminases), not for reasons of optimisation. On the other hand, an analysis found that this occurred in 17% of patients, in which, in addition to improving safety parameters, efficacy was maintained in the majority at 24 weeks.⁸⁴

Finally, no dose regimen adjustment is better than another (increasing the interval, reducing the dose). Different ways of doing this have been published, therefore the panel did not opt for any one in particular.⁸⁵ Some of the most described are, for TCZ IV, a

reduction in dose to 4 mg or 6 mg maintaining the interval and for TCZ SC, increasing the interval to 14 days.

The panel would like to comment that, in relation to other biological drugs, risk management in general is carried out in the same way. We shall go on to review this management and outline specific peculiarities that we found in the use of these drugs.

Recommendation 7: In a patient with IL-blockage, monitoring of neutrophil, lipid and transaminase levels especially is recommended. Special care is required if the patient has a history of diverticulitis, due to the risk of bowel perforation. (LE 5; GR D; GA 100%).

With the use of IL-6 inhibitors we can observe a marked decrease in neutrophils already in the first 4 weeks of treatment.^{10,25,47,51,86,87} However, clinically significant neutropenia occurs in ~3% of patients and is usually transient.^{12,13,86} In most cases, neutrophil counts return to normal even when the drug is continued. But most important in this regard is that there is no association between neutropenia and the onset or intensity of infections.^{10,25,47,51,86,87} Furthermore, the rate of serious infections is similar to that observed with other biologics such as TNF inhibitors.⁸⁸

For monitoring purposes, the panel recommends following the instructions given on the technical data sheet of these drugs and the recommendations of the SER.⁸⁹ And in the case of recurrent or major (not clinically significant) neutropenia, shortening the monitoring time will be assessed based on clinical judgement.

With regard to clinical monitoring, it is important to bear in mind that some symptoms or general signs of infection may not be present or may be masked by IL-6 blockade (acute phase reactants, fever or leucocytosis),⁹⁰ therefore, we need to be clinically cautious.

IL-6 inhibitors produce increases in the levels of the different serum lipids, but the overall atherogenic quotient is unchanged and there has been no evidence of an increase in cardiovascular events (even with long-term use).^{11,17,18,21,23,24,47,91,92} Lipids increase in the first few weeks after starting treatment and their levels remain stable over time. It should be noted that patients with hyperlipidaemia due to these drugs have an adequate response to statins.⁵⁰ The panel advises following the usual recommendations for hypercholesterolaemia.^{93,94}

An increase in transaminases is relatively frequent with IL-6 inhibitors, although the majority ($\geq 90\%$) are mild (< 3 LSN) and transient (even without suspension),^{7,10–12,18,23,25,47} and are easily managed following the usual monitoring recommendations.⁸⁹ Serious cases that are similar to those found in patients with RA treated with other biologics and traditional DMARDs are exceptional.⁹⁵ The elevation of transaminases is clearly higher in patients treated with TCZ in combination with MTX.^{95,96}

On the other hand, in studies published with TCZ,^{7,97–100} the rate of gastrointestinal perforation is very low 2.2/1000 patients/year in the SAR studies.^{10–12} Both have been associated with a history of diverticulitis, concomitant use of NSAIDs and corticosteroids, as well as a higher number of previous biological drugs.^{10,99,100} This risk is slightly increased compared to that found for the traditional DMARDs or TNF inhibitors, and is less than of corticosteroids.¹⁰⁰

Again, we must bear in mind that, due to the effects of IL-6 blockade, the clinical symptoms of diverticulitis can be masked.^{101,102}

Furthermore, we should point out that thrombocytopenia is rare and, from a clinical point of view, is usually of little relevance (see the technical datasheets for monitoring of thrombocytopenia).^{101,102}

Recommendation 8: IL-6 blockage in RA is not associated with an increased risk of cardiovascular disease, and therefore no special action other than the usual are required (LE 5; GR D; GA 100%).

In terms of general mortality rate, there are no data to indicate that this increases with any drug that blocks IL-6, or that it is different to that recorded with other biological therapies.^{24,103,104}

Therefore, in relation to cardiovascular mortality, different RCT and observational studies have shown that TCZ does not increase the incidence of cardiovascular disease (acute myocardial infarction [AMI] or acute cerebrovascular accident [ACVA]) either in the short or long term, and this is not associated with time of exposure or route of administration and dose, and that the rates recorded are similar to those expected in the population of patients with RA.^{7,18,38,86} On the other hand, with regard to SAR, in the published RCTs (up to 52 weeks) only one case of ACVA resulting in death has been described with SAR 200 mg, in a total of almost 2800 patients.⁶² We have little evidence for the rest of the drugs.

The panel advises following the recommendations of the principal scientific societies on cardiovascular risk prevention and management.^{93,94}

In RCTs and their extensions (short and long term), and in observational studies (close, or routine clinical practice) on TCZ^{103,105} heart failure has not been reported as either a frequent adverse event or one associated with use of the drug. Similarly, in short and medium term RCTs with SAR,^{10,62,106–109} it has not been found to be a frequent adverse event or one associated with use of the drug. Finally, with regard to the remaining IL-6 inhibitors, in short- to medium-term (12–54 weeks depending on the drug) RCTs of olokizumab,^{21,22} sirukumab,^{25,110,111} and clazakizumab,²³ the results have been similar.

The TCZ datasheet,¹⁰¹ in the section on special warnings and precautions for use, states the following: “Physicians should be vigilant for symptoms potentially indicative of new-onset central demyelinating disorders. The potential for central demyelination with TCZ is currently unknown”. The datasheet for SAR does not indicate anything in this regard.¹⁰²

In RCTs, in extension studies (short and long term) and in observational studies (close or routine clinical practice), there are no events that indicate that the use of TCZ is associated with demyelinating disorders.⁷ There are isolated cases of patients with RA and multiple sclerosis who have been prescribed TCZ for RA without it having worsened their multiple sclerosis.¹¹² At present there is no data relating to other IL-6 inhibitors. On the other hand, there are observational studies where patients with demyelinating diseases, such as neuromyelitis optica, have been treated with TCZ with good results.¹¹³

Regarding cancer, with the use of IL-6 inhibitors, TCZ has not been associated with greater development of neoplasia^{86,114–116} and the rate found is comparable to that detected in patients under treatment with synthetic DMARDs, and does not increase with exposure time or administration route or dose. The data for SAR,⁶² point in the same direction.

The panel advises following the recommendations on the technical datasheets and consensus on risk management when using these therapies.^{89,101,102}

Finally, to date it has not been clinically demonstrated that the use of IL-6 blockade causes a specific lung disease in subjects with RA. The use of TCZ has not been associated with the development or exacerbation of any lung disease, such as interstitial lung disease (in either RCTs or observational studies).^{70–73} Although there is insufficient data, the rest of the IL-6 inhibitors point in the same direction.

Discussion

We present a series of recommendations in this paper on the use of IL-6 inhibitors in RA, focussing on the aspects considered to contribute most in daily practice, based on the best available evidence. In addition, we synthesised all the evidence gathered, in terms of efficacy and risk management.

For this purpose we followed the nominal group and Delphi techniques, widely used in these types of documents.⁸⁹ We also selected a group of nationally recognised experts, supported by a systematic review with the help of an expert methodologist.

The important changes that have appeared in recent years in the treatment of RA^{1–4} are well known. One of these changes has been the incorporation of the biological therapies. These were initially the TNF inhibitors, after which drugs with different mechanisms of action have been emerging, which include those that block IL-6, both the receptor and the cytokine itself, although only the former have been approved for use in RA (TCZ and SAR).^{6–18}

In this context, national and international organisations are trying to issue and update recommendations on the treatment of RA.^{1,117} However, bearing in mind that we have a very wide therapeutic arsenal and a great deal of scientific evidence, it is not always possible to delve deeper into the fine management of these therapies. For this reason, there are also documents by experts that focus on the use of a specific therapeutic target. A document was published 5 years ago on the use of IL-6 inhibitors.⁷⁹

However, since then new drugs have emerged and there is much new evidence, which justifies a new recommendation document on these drugs, as in this paper. In addition, and to avoid repetition, the panel decided to address the most clinically relevant aspects of the use of these therapies.

Thus, from the point of view of efficacy and indication, we approached the use of these drugs in monotherapy and combined therapy, and in patient profiles of clinical interest, such as those for whom TNF inhibitors have failed, and those with an important systemic component. The latter, due to the potent effect at this level of these drugs' mechanism of action. This systemic effect also includes a very marked decrease in acute phase reactants, usually included in many compound disease activity indices, which has led to specific recommendations on how to assess treatment response more accurately and reliably.

Also, because of its mechanism of action, the panel considered it clinically important to be aware of certain adverse events. Although many of them are known and therefore monitoring is similar to that of other biological therapies, the panel considered it very important to emphasise those that are characteristic of IL-6 blockade such as neutropenia, risk of bowel perforation, dyslipidaemia and cardiovascular prevention.

Furthermore, although the systematic review of the literature was very extensive, the main limitation is the difficulty in establishing very specific recommendations in the different lines of treatment in relation to other biological therapies, since there are practically no data in this regard. Nor do we currently have studies comparing the different IL-6 inhibitors.

In summary, in order to improve clinical practice, it is essential to have explicit recommendations on the role of IL-6 inhibitors in RA. Although evidence is still scarce in some areas, this document presents a number of recommendations that we believe could be relevant and useful for clinicians. In addition, everyday aspects related to their use are referred to, which means that the recommendations can be implemented without difficulties in daily practice. The panel is convinced that monitoring will contribute to more rational use of the drug, with the consequent improvement in management, prognosis and quality of life.

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Conflict of interests

HC reports having received honoraria for talks, collaborations and courses from Sanofi, Lilly, MSD, Abbvie, Gebro. JTM has received funds for research or training from Gebro Pharma, Janssen, Lilly, Novartis, Pfizer and Sanofi. The remaining authors have no conflicts of interest to declare.

References

- Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis.* 2017;76:960–77.
- 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.
- Versteeg GA, Steunebrink LMM, Vonkeman HE, Ten Klooster PM, van der Bijl AE, van de Laar M. Long-term disease and patient-reported outcomes of a continuous treat-to-target approach in patients with early rheumatoid arthritis in daily clinical practice. *Clin Rheumatol.* 2018;37:1189–97. <http://dx.doi.org/10.1007/s10067-017-3962-5>.
- De Andrade NPB, da Silva Chakr RM, Xavier RM, Viaceli D, Correa RHB, de Oliveira Filho CM, et al. Long-term outcomes of treat-to-target strategy in established rheumatoid arthritis: a daily practice prospective cohort study. *Rheumatol Int.* 2017;37:993–7.
- Takeuchi T. Revolutionary change in rheumatoid arthritis management with biological therapy. *Keio J Med.* 2011;60:75–81.
- Tanaka Y, Martin Mola E. IL-6 targeting compared to TNF targeting in rheumatoid arthritis: studies of olokizumab, sarilumab and sirukumab. *Ann Rheum Dis.* 2014;73:1595–7.
- Navarro-Millan I, Singh JA, Curtis JR. Systematic review of tocilizumab for rheumatoid arthritis: a new biologic agent targeting the interleukin-6 receptor. *Clin Ther.* 2012;34:788–802, e3.
- Blanco Alonso R, Agudo Bilbao M. Inhibition of interleukin 6, a new therapeutic option in rheumatoid arthritis [artículo en español]. *Reumatol Clin.* 2009;5:121–7.
- Boyapati A, Msihid J, Fiore S, van Adelsberg J, Graham NM, Hamilton JD. Sarilumab plus methotrexate suppresses circulating biomarkers of bone resorption and synovial damage in patients with rheumatoid arthritis and inadequate response to methotrexate: a biomarker study of MOBILITY. *Arthritis Res Ther.* 2016;18:225.
- 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.
- Fleischmann R, van Adelsberg J, Lin Y, Castelar-Pinheiro GD, Brzezicki J, Hrycaj P, et al. Sarilumab and nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. *Arthritis Rheumatol.* 2017;69:277–90.
- Genovese MC, Fleischmann R, Kivitz AJ, Rell-Bakalarska M, Martincova R, Fiore S, et al. Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. *Arthritis Rheumatol.* 2015;67:1424–37.
- Huizinga TW, Fleischmann RM, Jasson M, Radin AR, van Adelsberg J, Fiore S, et al. Sarilumab, a fully human monoclonal antibody against IL-6R α in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. *Ann Rheum Dis.* 2014;73:1626–34.
- Burmester GR, Choy E, Kivitz A, Ogata A, Bao M, Nomura A, et al. Low immunogenicity of tocilizumab in patients with rheumatoid arthritis. *Ann Rheum Dis.* 2017;76:1078–85.
- Burmester GR, Feist E, Kellner H, Braun J, Iking-Konert C, Rubbert-Roth A. Effectiveness and safety of the interleukin 6-receptor antagonist tocilizumab after 4 and 24 weeks in patients with active rheumatoid arthritis: the first phase IIIb real-life study (TAMARA). *Ann Rheum Dis.* 2011;70:755–9.
- Burmester GR, Rigby WF, van Vollenhoven RF, Kay J, Rubbert-Roth A, Blanco R, et al. Tocilizumab combination therapy or monotherapy or methotrexate monotherapy in methotrexate-naïve patients with early rheumatoid arthritis: 2-year clinical and radiographic results from the randomised, placebo-controlled FUNCTION trial. *Ann Rheum Dis.* 2017;76:1279–84.
- 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.
- Burmester GR, Rubbert-Roth A, Cantagrel A, Hall S, Leszczynski P, Feldman D, et al. Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMATA). *Ann Rheum Dis.* 2016;75:68–74.
- Choy E. Clinical experience with inhibition of interleukin-6. *Rheum Dis Clin North Am.* 2004;30:405–15, viii.

20. Straub RH, Cutolo M. Circadian rhythms in rheumatoid arthritis: implications for pathophysiology and therapeutic management. *Arthritis Rheum*. 2007;56:399–408.
21. Genovese MC, Fleischmann R, Furst D, Janssen N, Carter J, Dasgupta B, et al. Efficacy and safety of olokizumab in patients with rheumatoid arthritis with an inadequate response to TNF inhibitor therapy: outcomes of a randomised Phase IIb study. *Ann Rheum Dis*. 2014;73:1607–15.
22. Takeuchi T, Tanaka Y, Yamanaka H, Amano K, Nagamine R, Park W, et al. Efficacy and safety of olokizumab in Asian patients with moderate-to-severe rheumatoid arthritis, previously exposed to anti-TNF therapy: results from a randomized phase II trial. *Mod Rheumatol*. 2016;26:15–23.
23. Weinblatt ME, Mease P, Mysler E, Takeuchi T, Drescher E, Berman A, et al. The efficacy and safety of subcutaneous clazakizumab in patients with moderate-to-severe rheumatoid arthritis and an inadequate response to methotrexate: results from a multinational, phase IIb, randomized, double-blind, placebo/active-controlled, dose-ranging study. *Arthritis Rheumatol*. 2015;67:2591–600.
24. Aletaha D, Bingham CO 3rd, Tanaka Y, Agarwal P, Kurrasch R, Tak PP, et al. Efficacy and safety of sirukumab in patients with active rheumatoid arthritis refractory to anti-TNF therapy (SIRROUND-T): a randomised, double-blind, placebo-controlled, parallel-group, multinational, phase 3 study. *Lancet*. 2017;389:1206–17.
25. Smolen JS, Weinblatt ME, Sheng S, Zhuang Y, Hsu B. Sirukumab, a human anti-interleukin-6 monoclonal antibody: a randomised, 2-part (proof-of-concept and dose-finding), phase II study in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis*. 2014;73:1616–25.
26. Black N, Murphy M, Lamping D, McKee M, Sanderson C, Askham J, et al. Consensus development methods: a review of best practice in creating clinical guidelines. *J Health Serv Res Policy*. 1999;4:236–48.
27. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1–12.
28. CEBM. *Medicine*. CfEB 2011; Pages. Available from: <http://www.cebm.net/index.aspx?o=1025> [accessed 11.04.13].
29. 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.
30. Ogata A, Tanimura K, Sugimoto T, Inoue H, Urata Y, Matsubara T, et al. Phase III study of the efficacy and safety of subcutaneous versus intravenous tocilizumab monotherapy in patients with rheumatoid arthritis. *Arthritis Care Res*. 2014;66:344–54.
31. Conaghan PG, Peterfy C, Olech E, Kaine J, Ridley D, Dicarolo J, et al. The effects of tocilizumab on osteitis, synovitis and erosion progression in rheumatoid arthritis: results from the ACT-RAY MRI substudy. *Ann Rheum Dis*. 2014;73:810–6.
32. 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.
33. Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). *Ann Rheum Dis*. 2013;72:43–50.
34. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATOR): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Mod Rheumatol*. 2009;19:12–9.
35. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis*. 2010;69:88–96.
36. Weinblatt ME, Kremer J, Cush J, Rigby W, Teng LL, Devenport J, et al. Tocilizumab as monotherapy or in combination with nonbiologic disease-modifying antirheumatic drugs: twenty-four-week results of an open-label, clinical practice study. *Arthritis Care Res (Hoboken)*. 2013;65:362–71.
37. Yabe Y, Kojima T, Kaneko A, Asai N, Kobayakawa T, Ishiguro N. A review of tocilizumab treatment in 122 rheumatoid arthritis patients included in the Tsurumi Biologics Communication Registry (TBCR) Study. *Mod Rheumatol*. 2013;23:245–53.
38. Burmester GR, Rubbert-Roth A, Cantagrel A, Hall S, Leszczynski P, Feldman D, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). *Ann Rheum Dis*. 2014;73:69–74.
39. Nishimoto N, Amano K, Hirabayashi Y, Horiuchi T, Ishii T, Iwahashi M, et al. Drug free REmission/low disease activity after cessation of tocilizumab (Actemra) Monotherapy (DREAM) study. *Mod Rheumatol*. 2014;24:17–25.
40. Nishimoto N, Amano K, Hirabayashi Y, Horiuchi T, Ishii T, Iwahashi M, et al. Retreatment efficacy and safety of tocilizumab in patients with rheumatoid arthritis in recurrence (RESTORE) study. *Mod Rheumatol*. 2014;24:26–32.
41. Maini RN, Taylor PC, Szechinski J, Pavelka K, Broll J, Balint G, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum*. 2006;54:2817–29.
42. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. *Ann Rheum Dis*. 2007;66:1162–7.
43. Hashimoto J, Garnero P, van der Heijde D, Miyasaka N, Yamamoto K, Kawai S, et al. Humanized anti-interleukin-6-receptor antibody (tocilizumab) monotherapy is more effective in slowing radiographic progression in patients with rheumatoid arthritis at high baseline risk for structural damage evaluated with levels of biomarkers, radiography, and BMI: data from the SAMURAI study. *Mod Rheumatol*. 2011;21:10–5.
44. Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2004;50:1761–9.
45. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. *Ann Rheum Dis*. 2009;68:1580–4.
46. Strand V, Kosinski M, Chen CI, Joseph G, Rendas-Baum R, Graham NM, et al. Sarilumab plus methotrexate improves patient-reported outcomes in patients with active rheumatoid arthritis and inadequate responses to methotrexate: results of a phase III trial. *Arthritis Res Ther*. 2016;18:198.
47. Strand V, Reaney M, Chen CI, Proudfoot CW, Guilloinneau S, Bauer D, et al. Sarilumab improves patient-reported outcomes in rheumatoid arthritis patients with inadequate response/intolerance to tumour necrosis factor inhibitors. *RMD Open*. 2017;3:e000416.
48. Genovese MC, Fleischmann R, Hagino O, Hu C, Pena-Rossi C, Sadeh J, et al. The effect of sarilumab in combination with dmards on fasting glucose and glycosylated hemoglobin in patients with rheumatoid arthritis with and without diabetes. *Arthritis Rheum*. 2017;69 Suppl. 10.
49. Van der Heijde D, van Adelsber J, Fay J, van Hoogstraten H, Mangan E, Graham N, et al. Clinical and radiographic outcomes after two years of sarilumab in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2016;75:724.
50. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum*. 2008;58:2968–80.
51. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet*. 2008;371:987–97.
52. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis*. 2008;67:1516–23.
53. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum*. 2011;63:609–21.
54. Bijlsma JWJ, Welsing PMJ, Woodworth TG, Middelink LM, Petho-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.
55. Smolen JS, Avila JC, Aletaha D. Tocilizumab inhibits progression of joint damage in rheumatoid arthritis irrespective of its anti-inflammatory effects: disassociation of the link between inflammation and destruction. *Ann Rheum Dis*. 2012;71:687–93.
56. Gaubitz M, Gottl KH, Behmer O, Lippe R, Meng T, Loschmann PA. Etanercept is effective as monotherapy or in combination with methotrexate in rheumatoid arthritis: subanalysis of an observational study. *Clin Rheumatol*. 2017;36:1989–96.
57. Singh JA, Hossain A, Tanjong Ghogomu E, Mudano AS, Tugwell P, Wells GA. Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane systematic review and network meta-analysis (NMA). *Cochrane Database Syst Rev*. 2016;11. CD012437.
58. Kuriya B, Cohen MD, Keystone E. Baricitinib in rheumatoid arthritis: evidence-to-date and clinical potential. *Ther Adv Musculoskelet Dis*. 2017;9:37–44.
59. Gabay C, McInnes IB, Kavanaugh A, Tuckwell K, Clearman M, Pulley J, et al. Comparison of lipid and lipid-associated cardiovascular risk marker changes after treatment with tocilizumab or adalimumab in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2016;75:1806–12.
60. Ogata A, Tanimura K, Sugimoto T, Inoue H, Urata Y, Matsubara T, et al. Phase III study of the efficacy and safety of subcutaneous versus intravenous tocilizumab monotherapy in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2014;66:344–54.

61. Ogata A, Amano K, Dobashi H, Inoo M, Ishii T, Kasama T, et al. Longterm safety and efficacy of subcutaneous tocilizumab monotherapy: results from the 2-year open-label extension of the MUSASHI Study. *J Rheumatol*. 2015;42:799–809.
62. Aly AM, Furst DE, Author A. Update of sarilumab to treat rheumatoid arthritis based on randomized clinical trials: a systematic review. *Expert Rev Clin Immunol*. 2017;13:741–52.
63. Lindegaard HM, Johansen P, Grondal G, Jensen EC, Juul L, Schlemmer AM, et al. Doubling the single-dose infusion rate of tocilizumab in rheumatoid arthritis is safe and efficacious. *Scand J Rheumatol*. 2016;45:262–6.
64. Sun Y, Wang D, Salvadore G, Hsu B, Curran M, Casper C, et al. The effects of interleukin-6 neutralizing antibodies on symptoms of depressed mood and anhedonia in patients with rheumatoid arthritis and multicentric Castleman's disease. *Brain Behav Immun*. 2017;66:156–64.
65. Strand V, Burmester GR, Ogale S, Devenport J, John A, Emery P. Improvements in health-related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. *Rheumatology (Oxford)*. 2012;51:1860–9.
66. Harrold LR, John A, Reed GW, Haselkorn T, Karki C, Li Y, et al. Impact of tocilizumab monotherapy on clinical and patient-reported quality-of-life outcomes in patients with rheumatoid arthritis. *Rheumatol Ther*. 2017;4:405–17.
67. Yazici Y, Curtis JR, Ince A, Baraf H, Malamet RL, Teng LL, et al. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. *Ann Rheum Dis*. 2012;71:198–205.
68. Yazici Y, Curtis JR, Ince A, Baraf HS, Lepley DM, Devenport JN, et al. Early effects of tocilizumab in the treatment of moderate to severe active rheumatoid arthritis: a one-week sub-study of a randomised controlled trial (Rapid Onset and Systemic Efficacy [ROSE] Study). *Clin Exp Rheumatol*. 2013;31:358–64.
69. Yamada S, Tsuchimoto A, Kaizu Y, Taniguchi M, Masutani K, Tsukamoto H, et al. Tocilizumab-induced remission of nephrotic syndrome accompanied by secondary amyloidosis and glomerulonephritis in a patient with rheumatoid arthritis. *CEN Case Rep*. 2014;3:237–43.
70. Akiyama M, Kaneko Y, Yamaoka K, Kondo H, Takeuchi T. Association of disease activity with acute exacerbation of interstitial lung disease during tocilizumab treatment in patients with rheumatoid arthritis: a retrospective, case-control study. *Rheumatol Int*. 2016;36:881–9.
71. Wendling D, Vidon C, Godfrin-Valnet M, Rival G, Guillot X, Prati C. Exacerbation of combined pulmonary fibrosis and emphysema syndrome during tocilizumab therapy for rheumatoid arthritis. *Joint Bone Spine*. 2013;80:670–1.
72. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Postmarketing surveillance of tocilizumab for rheumatoid arthritis in Japan: interim analysis of 3881 patients. *Ann Rheum Dis*. 2011;70:2148–51.
73. 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.
74. Gabay C, Msihid J, Zilberstein M, Paccard C, Lin Y, Graham NMH, et al. Identification of sarilumab pharmacodynamic and predictive markers in patients with inadequate response to TNF inhibition: a biomarker substudy of the phase 3 TARGET study. *RMD Open*. 2018;4:e000607.
75. Schultz O, Oberhauser F, Saech J, Rubbert-Roth A, Hahn M, Krone W, et al. Effects of inhibition of interleukin-6 signalling on insulin sensitivity and lipoprotein (a) levels in human subjects with rheumatoid diseases. *PLoS ONE*. 2010;5:e14328.
76. 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.
77. Inciarte-Mundo J, Ruiz-Esquivel V, Hernandez MV, Canete JD, Cabrera-Villalba SR, Ramirez J, et al. Calprotectin more accurately discriminates the disease status of rheumatoid arthritis patients receiving tocilizumab than acute phase reactants. *Rheumatology (Oxford)*. 2015;54:2239–43.
78. Schoels M, Alasti F, Smolen JS, Aletaha D. Evaluation of newly proposed remission cut-points for disease activity score in 28 joints (DAS28) in rheumatoid arthritis patients upon IL-6 pathway inhibition. *Arthritis Res Ther*. 2017;19:155.
79. Smolen JS, Schoels MM, Nishimoto N, Breedveld FC, Burmester GR, Dougados M, et al. Consensus statement on blocking the effects of interleukin-6 and in particular by interleukin-6 receptor inhibition in rheumatoid arthritis and other inflammatory conditions. *Ann Rheum Dis*. 2013;72:482–92.
80. Lau CS, Gibofsky A, Damjanov N, Lusa S, Marshall L, Jones H, et al. Down-titration of biologics for the treatment of rheumatoid arthritis: a systematic literature review. *Rheumatol Int*. 2017;37:1789–98.
81. Cantini F, Niccoli L, Nannini C, Cassara E, Kaloudi O, Giulio Favalli E, et al. Second-line biologic therapy optimization in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *Semin Arthritis Rheum*. 2017;47:183–92.
82. Mena-Vazquez N, Manrique-Ariza S, Rojas-Gimenez M, Urena-Garnica I, Jimenez-Nunez FG, Fernandez-Nebro A. Analysis of effectiveness, safety and optimization of tocilizumab in a cohort of patients with rheumatoid arthritis in clinical practice. *Reumatol Clin*. 2017. <http://dx.doi.org/10.1016/j.reuma.2017.05.012>, pii:S1699-258X(17)30130-4 [Epub ahead of print].
83. Sanmartí R, Martín-Mola E, Fonseca JE, Douglas JV, Escudero-Contreras A, Gonzalez CM. Clinical remission in subjects with rheumatoid arthritis treated with subcutaneous tocilizumab as monotherapy or in combination with methotrexate or other synthetic dmards: a real-world clinical trial. In: ACR/ARHP Annual Meeting. 2017. p. 3553.
84. Genovesi MC, Fay J, Parrino J, Beyer D, Iglesias-Rodriguez M, Graham N, et al. Sarilumab dose reduction in an open-label extension study in RA patients. *Arthritis Rheumatol*. 2016;68 Suppl. 10.
85. Font P, Castro MC, Romero M, Ortega R, Calvo L, Ruiz D, et al. Results at 3 years of an optimization guideline of biological therapies in rheumatoid arthritis. Create record results, Annual European Congress of Rheumatology, Madrid. *Ann Rheum Dis*. 2017;1184.
86. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther*. 2011;13:R141.
87. Bykerk VP, Ostor AJ, Alvaro-Gracia J, Pavelka K, Ivorra JA, Graninger W, et al. Tocilizumab in patients with active rheumatoid arthritis and inadequate responses to DMARDs and/or TNF inhibitors: a large, open-label study close to clinical practice. *Ann Rheum Dis*. 2012;71:1950–4.
88. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum*. 2006;54:2368–76.
89. Gomez Reino J, Loza E, Andreu JL, Balsa A, Batlle E, Canete JD, et al. Consensus statement of the Spanish Society of Rheumatology on risk management of biologic therapy in rheumatic patients [artículo en español]. *Reumatol Clin*. 2011;7:284–98.
90. Kishimoto T. IL-6: from its discovery to clinical applications. *Int Immunol*. 2010;22:347–52.
91. McInnes IB, Thompson L, Giles JT, Bathon JM, Salmon JE, Beaulieu AD, et al. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. *Ann Rheum Dis*. 2015;74:694–702.
92. Kume K, Amano K, Yamada S, Hatta K, Ohta H, Kuwaba N. Tocilizumab monotherapy reduces arterial stiffness as effectively as etanercept or adalimumab monotherapy in rheumatoid arthritis: an open-label randomized controlled trial. *J Rheumatol*. 2011;38:2169–71.
93. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis*. 2010;69:325–31.
94. Martín-Martínez MA, Gonzalez-Juanatey C, Castaneda S, Llorca J, Ferraz-Amaro I, Fernandez-Gutierrez B, et al. Recommendations for the management of cardiovascular risk in patients with rheumatoid arthritis: scientific evidence and expert opinion. *Semin Arthritis Rheum*. 2014;44:1–8.
95. Ramiro S, Gaujoux-Viala C, Nam JL, Smolen JS, Buch M, Gossec L, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis*. 2014;73:529–35.
96. Bykerk VP, Kstr AJ, Alvaro-Gracia J, Pavelka K, Ivorra JAR, Graninger W, et al. Tocilizumab in patients with active rheumatoid arthritis and inadequate responses to DMARDs and/or TNF inhibitors: a large, open-label study close to clinical practice. *Ann Rheum Dis*. 2012;71:1950–4.
97. Gout T, Ostor AJ, Nisar MK. Lower gastrointestinal perforation in rheumatoid arthritis patients treated with conventional DMARDs or tocilizumab: a systematic literature review. *Clin Rheumatol*. 2011;30:1471–4.
98. Xie F, Yun H, Bernatsky S, Curtis JR. Brief report: risk of gastrointestinal perforation among rheumatoid arthritis patients receiving tofacitinib, tocilizumab, or other biologic treatments. *Arthritis Rheumatol*. 2016;68:2612–7.
99. Monemi S, Berber E, Sarsour K, Wang J, Lampl K, Bharucha K, et al. Incidence of gastrointestinal perforations in patients with rheumatoid arthritis treated with tocilizumab from clinical trial, Postmarketing, and real-world data sources. *Rheumatol Ther*. 2016;3:337–52.
100. Strangfeld A, Richter A, Siegmund B, Herzer P, Rockwitz K, Demary W, et al. Risk for lower intestinal perforations in patients with rheumatoid arthritis treated with tocilizumab in comparison to treatment with other biologic or conventional synthetic DMARDs. *Ann Rheum Dis*. 2017;76:504–10.
101. AEMPS2018. Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000955/WC500054890.pdf [accessed 5.04.18].
102. EMA 2018. Available from: https://ec.europa.eu/health/documents/community-register/2017/20170623138002/anx_138002.es.pdf [accessed 5.04.18].
103. Tarp S, Eric Furst D, Boers M, Luta G, Bliddal H, Tarp U, et al. Risk of serious adverse effects of biological and targeted drugs in patients with rheumatoid arthritis: a systematic review meta-analysis. *Rheumatology (Oxford)*. 2017;56:417–25.
104. Desai RJ, Thaler KJ, Mahlknecht P, Gartlehner G, McDonagh MS, Messergour B, et al. Comparative risk of harm associated with the use of targeted immunomodulators: a systematic review. *Arthritis Care Res*. 2016;68:1078–88.
105. Singh JA, Hossain A, Tanjong Ghogomu E, Mudano AS, Maxwell LJ, Buchbinder R, et al. Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics: a systematic review and network meta-analysis. *Cochrane Database Syst Rev*. 2017;3:CD012591.
106. Bae SC, Lee YH. Comparative efficacy and tolerability of sarilumab 150 and 200mg in patients with active rheumatoid arthritis: A Bayesian network

- meta-analysis of randomized controlled trials [artículo en alemán]. *Z Rheumatol.* 2018;77:421–8. doi:10.1007/s00393-017-0292-6.
107. Boyapati A, Msihid J, Fiore S, van Adelsberg J, Graham NM, Hamilton JD, et al. Sarilumab plus methotrexate suppresses circulating biomarkers of bone resorption and synovial damage in patients with rheumatoid arthritis and inadequate response to methotrexate: a biomarker study of MOBILITY. *Arthritis Res Therapy.* 2016;18:225.
 108. 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.
 109. Strand V, Kosinski M, Chen CI, Joseph G, Rendas-Baum R, Graham NM, et al. Sarilumab plus methotrexate improves patient-reported outcomes in patients with active rheumatoid arthritis and inadequate responses to methotrexate: results of a phase III trial. *Arthritis Res Ther.* 2016;18:198.
 110. Aletaha D, Bingham CO, Tanaka Y, Agarwal P, Kurrasch R, Tak PP, et al. Efficacy and safety of sirukumab in patients with active rheumatoid arthritis refractory to anti-TNF therapy (SIRROUND-T): a randomised, double-blind, placebo-controlled, parallel-group, multinational, phase 3 study. *Lancet.* 2017;389:1206–17.
 111. Sun Y, Wang D, Salvatore G, Hsu B, Curran M, Casper C, et al. The effects of interleukin-6 neutralizing antibodies on symptoms of depressed mood and anhedonia in patients with rheumatoid arthritis and multicentric Castleman's disease. *Brain Behav Immun.* 2017.
 112. Sato H, Kobayashi D, Abe A, Ito S, Ishikawa H, Nakazono K, et al. Tocilizumab treatment safety in rheumatoid arthritis in a patient with multiple sclerosis: a case report. *BMC Res Notes.* 2014;7:641.
 113. Ringelstein M, Ayzenberg I, Harmel J, Lauenstein AS, Lensch E, Stogbauer F, et al. Long-term therapy with interleukin 6 receptor blockade in highly active neuromyelitis optica spectrum disorder. *JAMA Neurol.* 2015;72:756–63.
 114. Genovese MC, Rubbert-Roth A, Smolen JS, Kremer J, Khraishi M, Gomez-Reino J, et al. Long term safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of up to 4.6 years of exposure. *J Rheumatol.* 2013;40:768–80.
 115. Wadstrom H, Frisell T, Askling J, Anti-rheumatic therapy in Sweden Study G. 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.
 116. Van Vollenhoven RF, Rubbert-Roth A, Sebba A, Porter-Brown B, Rowell L, Napalkov P, et al. Tocilizumab in patients with rheumatoid arthritis and rates of malignancy: results from long-term extension clinical trials. *Rheumatology.* 2014;53:i91–2.
 117. Sanmarti R, Garcia-Rodriguez S, Alvaro-Gracia JM, Andreu JL, Balsa A, Caliz R, et al. 2014 update of the Consensus Statement of the Spanish Society of Rheumatology on the use of biological therapies in rheumatoid arthritis. *Reumatol Clin.* 2015;11:279–94.