



## Original article

## Consensus on the use of Rituximab in Rheumatoid Arthritis. A document with evidence based recommendations

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## ABSTRACT

**Introduction:** Rituximab has been employed successfully for the treatment of Rheumatoid Arthritis (RA). However, its particular mechanism of action, as well as a lack of concrete guidelines for its management have generated doubts on its use.

**Objective:** To establish recommendations that facilitate the use of rituximab in common clinical practice.

**Methods:** In a first Delphi round, 9 expert rheumatologists got together to develop questions on those subjects generating most doubts on the efficacy and safety of the drug. These were adapted to perform a systematic review of the evidence, which was presented in a second meeting. Nominal groups were formed to respond to each question and give a recommendation. These recommendations were presented in a second Delphi round to a larger group of experts in rheumatology. Once again recommendations were discussed, modified and voted upon. Once approved, a vote on the degree of agreement for each recommendation was carried out.

**Results:** Seventeen recommendations were established, 10 regarding efficacy and 7 safety. All of the efficacy recommendations except 3 presented a good or moderate degree of evidence. Among the safety recommendations, 3 had a good or moderate degree of evidence while in the rest it was indirect, scarce or non-existent and a product of expert recommendation. The degree of agreement between experts was elevated for most of the recommendations.

**Conclusions:** These recommendations attempt to clear doubts on the use of rituximab and establish guidelines for its use in daily practice. Efficacy recommendations have a high degree of evidence, allowing the clinician to be guided in therapeutic decisions. Safety recommendations have a lower degree of evidence.

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### Consenso de uso de rituximab en artritis reumatoide. Un documento con recomendaciones basadas en la evidencia

## RESUMEN

**Introducción:** El rituximab se ha empleado con éxito en el tratamiento de la artritis reumatoide (AR). Sin embargo, su particular mecanismo de acción, así como la ausencia de pautas concretas en su manejo, hace que se hayan generado dudas sobre su utilización.

## Palabras clave:

Artritis reumatoide

Rituximab

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<sup>o</sup>Annex 1 contains the list of researchers of the Expert Group on Rituximab.

Terapias biológicas  
Consenso

**Objetivo:** Establecer recomendaciones que faciliten el empleo de rituximab en la práctica clínica habitual.  
**Métodos:** En una primera ronda Delphi, se reunieron nueve reumatólogos expertos que desarrollaron preguntas sobre los temas con mayor duda sobre eficacia y seguridad del fármaco. Estas se adecuaron para hacer una revisión sistemática de la evidencia, que se presentó en una segunda reunión. Se formaron grupos nominales para dar respuesta a cada pregunta y emitir la recomendación. Estas recomendaciones fueron presentadas en una segunda ronda Delphi a un grupo ampliado de reumatólogos expertos. De nuevo se discutieron, se modificaron y se votaron las recomendaciones. Una vez aprobada cada recomendación, se votó el grado de acuerdo.

**Resultados:** Se establecieron 17 recomendaciones: diez de eficacia y siete de seguridad. Todas las recomendaciones de eficacia, excepto tres, presentaron un nivel de evidencia bueno o moderado. Entre las recomendaciones de seguridad, tres presentaron un nivel de evidencia bueno o moderado, mientras que para el resto la evidencia fue indirecta, escasa o nula y son producto de las recomendaciones de los expertos. El grado de acuerdo entre expertos fue elevado para la mayoría de las recomendaciones.

**Conclusiones:** Estas recomendaciones pretenden aclarar dudas sobre el uso de rituximab y establecer pautas de empleo en la práctica clínica. Las recomendaciones de eficacia tienen un nivel de evidencia alto y permiten guiar al médico en decisiones terapéuticas. Las recomendaciones de seguridad tienen un nivel de evidencia menor.

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## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease associated with disability, loss of quality of life and increased mortality. In recent years the therapeutic arsenal against RA has increased with new drugs, biological agents, which along with traditional drugs such as methotrexate (MTX) have represented a considerable progress in the treatment of this disease.

Of the new biological therapies, rituximab (RTX), a chimeric anti-CD20 monoclonal antibody which had already been marketed for the treatment of B-cell non-Hodgkin lymphoma, has been used successfully in the treatment of RA. RTX produces a deep and sustained depletion of B lymphocytes (CD20+), which covers the spectrum from pre-B cells to mature B cells without affecting stem cells or plasma cells.<sup>1,2</sup>

The first evidence of its usefulness in the treatment of RA was a pilot study which showed that depletion of B cells produced a persistent improvement in patients with RA.<sup>3</sup> Subsequently, another study conducted by the same research group confirmed the therapeutic benefit.<sup>4</sup> However, the clinical development of RTX has been different from that of other biological agents. This fact, coupled with a different mechanism of action, the absence of a specific treatment schedule and the long-term effects which persistent depletion of B cells could cause, led to some international recommendations for the use of RTX in 2007<sup>5</sup> which are being reviewed during the present year.

With regard to rheumatology in our country, the Spanish Rheumatology Society has recently published an updated consensus document on the use of biological therapies.<sup>6</sup> Since this document does not discuss the peculiarities of RTX in detail, a group of rheumatologists with experience in the use of biological agents considered it important to conduct a review which gathered recommendations to facilitate the use of RTX. This has been based on existing evidence and, in addition, some expert recommendations have also been developed for situations where evidence is weak or nonexistent.

## Methods

A modification of the RAND/UCLA methodology<sup>7</sup> was used to elaborate this consensus. Nominal groups were established and Delphi surveys and systematic reviews of the recommendations were conducted.

### *First phase: preparation of questions and first round of Delphi*

The project manager (EMM) selected 8 experienced rheumatologists, according to the following criteria: 1) at least 5 years experience in RA and biological agent consultation, including RTX; 2) articles published on biological therapies and RA in MEDLINE, Reumatología Clínica and/or Revista Española de Reumatología; 3) geographical representation of the Spanish territory. Meetings of the nominal group were held and a Delphi survey was conducted in order to decide the most controversial topics and those of greater interest to the consensus. The first meeting took place in July 2009. In it, questions were raised about the controversial points and, finally, 17 statements were developed, addressing common questions in clinical practice for the management of patients with RTX. The 17 statements contained 21 questions (some sets included more than one question), and were subjected to editorial review and reprocessing in order to perform a systematic review; the final list included 10 questions on efficacy, 12 questions on safety and 4 questions on monitoring. A first round Delphi was conducted, in which the experts scored the degree of relevance of each question.

### *Second phase: systematic review of the evidence*

Once the questions were defined and their relevance was assigned, a systematic review of the evidence was conducted (BHC, MGA), following Cochrane methodology.

The criteria to consider studies for this review were observational studies and clinical trials of RTX. The target population was composed of adult patients with RA according to the 1987 classification criteria of the American College of Rheumatology.

### *Intervention: treatment with RTX*

Outcome measures: the proposals by Outcome Measurements in Rheumatic Arthritis Clinical Trials (OMERACT) were selected.<sup>8</sup>

- Efficacy: ACR50, ACR70, DAS28, remission according to DAS28, EULAR response criteria, improvement in the HAQ.
- Radiographic outcome: percentage of patients without radiographic progression, mean change in radiographic index.
- Safety: deaths, serious infections, serious adverse events, withdrawals from the study for any reason and withdrawals from the study for serious adverse effects.

**Table 1**  
Main efficacy results of rituximab treatment versus placebo, including studies of patients with RA (failure with DMARD,<sup>11,13</sup> failure with MTX,<sup>12</sup> failure with anti-TNF<sup>19</sup> and patients without prior exposure to MTX<sup>14</sup>)

Outcome (week 24)	CCT, n	Patients, n	Frequency in RTX group, %	Frequency in PBO group, %	OR (95% CI)	NNT (95% CI)
<i>All the studies</i>						
ACR50	5	2,251	40	19	3.1 (2.5-4)	5 (4-6)
ACR70	5	2,251	24	10	3 (2.3-4)	7 (5-10)
DAS28<2.6	3	1,723	17	5	3.5 (2.4-5.2)	9 (6-15)
Good EULAR response	4	1,497	17	3	5.2 (3.2-8.7)	8 (5-15)
Improvement of HAQ>0.2	2	876	63	42	2.3 (1.7-3.1)	5 (4-8)
Patients without radiographic progression at week 52, %	2	1,179	60	50	1.5 (1.2-1.9)	10 (7-22)
Severe adverse events	5	2,327	8	9	0.94 (0.68-1.3)	<sup>a</sup>
Deaths	5	2,367	0.12	0.37	0.33 (0.08-1.37)	<sup>a</sup>
Severe infections	4	1,652	1.7	1.8	0.93 (0.45-2.05)	<sup>a</sup>
Study withdrawals	4	1,652	9	15	0.6 (0.44-0.81)	19 (13-41) <sup>b</sup>
Withdrawals due to SAEs	4	1,652	2	0.9	2.23 (0.87-5.69)	<sup>a</sup>

CCT indicates controlled clinical trials; CI, confidence interval; NNT, number of patients needed to treat; OR, odds ratio; PBO, placebo; RTX, rituximab; SAEs, severe adverse effects.

<sup>a</sup>Not evaluated, since the risk estimate included unit and no harmful effects with rituximab were found.

<sup>b</sup>The number of patients needed to treat with placebo versus rituximab in order to have withdrawals in the study; the majority were due to disease activity in the placebo group.

*Electronic searches:* PubMed, EMBASE, Cochrane library. Other sources of data collection: manual search of EULAR and ACR conference abstracts from 2003 to 2009. Data request from Roche Pharma. Mabthera 2009 technical data sheet.

*Search period:* from January 2003 to September 2009.

*Statistical analysis:* this was performed by calculating the number of patients needed to treat (NNT), number of patients needed to harm (NNH) and the confidence intervals (CI), using the fixed effects model, meta-analysis technique following the Cochrane methodology. Statistical analysis was performed with the STATA 10.0 and RevMan 5 programs. A non-systematic review of the literature was carried out where it was not possible to perform a systematic review. The degree of agreement among experts was defined as the percentage of consensus between the votes of each of the recommendations. The level of evidence and recommendation grade of the evidence were issued as recommended by the Oxford Centre for Evidence Based Medicine.<sup>9</sup>

*Third phase: presentation and discussion of the evidence. Development of recommendations*

The results of the evidence were presented and various points of interest were discussed at a second meeting (November 2009). The relevant recommendations were discussed and developed through nominal groups. Each expert in this initial group suggested at least 2 recommendations, one for each question, which were followed by a brief discussion expanding on the proposed recommendation. This material became the first document (draft), which was distributed to all the initial experts and to a wider group of experts (20 rheumatologists) who fulfilled similar characteristics to those of the initial experts and who attended the final consensus meeting.

*Fourth phase: second round of Delphi*

Finally, in April 2010, the last meeting of the initial group of experts and the remaining 20 experts took place. At that meeting, the evidence on RTX was presented and subsequently, in small groups, the proposed recommendations were discussed and, if

deemed necessary, modified. Later, at a joint meeting of all experts, the recommendations proposed as final were presented, but since some experts had not been present for the discussion of all the recommendations, some time was given for these, if they believed it necessary, to offer an alternative recommendation. The approval of a recommendation as final in a first vote required at least 75% of the vote, and if that was not reached, it was then discussed until it was reformulated. Approval in a second round required at least 67% of the votes and, finally, if this did not happen, a third reformulation would have required at least a simple majority. However, this situation did not arise, since most of the recommendations were adopted in a first or, in some cases, second ballot. At the same time and once the recommendation in question was approved, the degree of agreement was voted. The voting process was based on a modification of the Delphi technique.<sup>10</sup>

### Results of the systematic review of the efficacy and safety of RTX in clinical trials

Table 1 shows the main results of efficacy of RTX treatment versus placebo in various stages of RA patients, primarily in failure with disease-modifying antirheumatic drugs (DMARDs)<sup>11-13</sup> or inhibitors of tumour necrosis factor (anti-TNF)<sup>19</sup> and in patients without prior exposure to methotrexate (MTX).<sup>14</sup>

The NNT with RTX versus placebo, in order to obtain a clinical or radiographically significant response, was 5-10 (95% CI, 4-22). The NNH to obtain a serious adverse event, a severe infection, death or withdrawal from the trial by serious adverse events did not register significant differences between the groups treated with RTX and placebo. The estimated odds ratio (OR) included the unit and, therefore, it was not possible to calculate the NNH, except for withdrawal due to adverse events. There were more withdrawals in the group receiving placebo and the cause were outbreaks of RA activity (Table 1).

### Recommendations

Table 2 summarizes the recommendations with evidence level and degree of agreement of each recommendation.

**Table 2**  
Summary of the recommendations with evidence level<sup>9</sup> and degree of agreement of each recommendation

Recommendation	Level of the evidence	Category	Final agreement, %
<b>Efficacy</b>			
<i>Question 1. What is the efficacy of rituximab as a first biological agent?</i>			
Rituximab has proven effective as a first biologic agent in rheumatoid arthritis, although this indication is not currently approved. At the recommended dose, it delays structural damage in patients without prior treatment with methotrexate	1a	A	96
<i>Question 2. What is the efficacy of rituximab when administered as a second or third biological agent, after the failure of one or more anti-TNF agents, respectively? Are there differences in efficacy when it is administered as a second or third biological agent?</i>			
Rituximab is effective in patients with an inadequate response to TNF	1c	A	96
Its efficacy is lower when used in later therapeutic stages	2a	C	96
<i>Question 3. What is the efficacy of rituximab in patients with negative RF and ACPA?</i>			
The absence of RF and ACPA does not rule out the response to rituximab. If administered to this population, the therapeutic response is less than that obtained in patients with positive RF and/or ACPA	1c	B	82
<i>Question 4. What is the efficacy of rituximab monotherapy compared to rituximab plus methotrexate? What is the efficacy of rituximab plus methotrexate compared with rituximab plus another DMARD?</i>			
Treatment with rituximab seems more effective when it is combined with methotrexate or other DMARDs, especially leflunomide	2b	B	85
<i>Question 5. How does rituximab (500 mgx2) behave compared to rituximab (1 gx2)?</i>			
The effective dose of RTX in RA patients who have not responded to anti-TNF is 1,000 mgx2. A dose of 500 mgx2 cannot currently be recommended because there are no data confirming its efficacy in these patients	2b	B	100
<i>Question 6. What is the efficacy of rituximab after two or more cycles of treatment?</i>			
Patients with rheumatoid arthritis who have had a satisfactory response to a first cycle of RTX (1,000 mgx2), may benefit from new cycles of treatment	1c	B	100
<b>Following</b>			
<i>Question 7. Are there benefits from treatment with rituximab following a fixed schedule (every 6 months) with respect to treatment on demand?</i>			
Rituximab has shown effectiveness both in patients who were treated following a fixed dosing schedule (every 6 months) and in those who received it on demand. Administration following a fixed schedule could help to maintain patients with a lower level of activity	-2b	C	74
<i>Question 8. What are the efficacy data of re-treatment of patients without prior response to rituximab compared with patients who had a moderate or good response (EULAR criteria)?</i>			
The effectiveness of the administration of a new cycle of rituximab in patients without a previous response is questionable	-2b	D	89
<i>Question 9. Is it useful to monitor B lymphocytes in patients receiving rituximab?</i>			
In clinical practice, the efficacy of rituximab treatment or the need for new courses must be determined by clinical activity indices and not by the amount of B lymphocytes in peripheral blood	4	D	100
<i>Question 10. What is the optimal time to assess the response of a patient treated with rituximab (12 vs 16 weeks)?</i>			
It is considered that the most appropriate time to evaluate the response to rituximab treatment should be around week 16	1c	A	100
<b>Safety</b>			
<i>Question 11. In patients receiving rituximab, what is the rate of decrease of immunoglobulins and what is the relationship between this decline and the emergence of severe infections?</i>			
Patients treated with rituximab may present decreases in IgG and IgM at some point during the treatment	1a	A	96
A possible trend towards more severe infections after IgG decline has been observed. A periodical quantification of immunoglobulins is recommended	1c	B	96
<i>Question 12. What is the effectiveness of vaccination in patients receiving rituximab?</i>			
Patients about to be treated with rituximab should receive the same vaccines as immunocompromised patients. The response to vaccination is reduced in them. Vaccination is recommended, preferably before initiating treatment with rituximab or as far as possible from the previous cycle	-1c	B	96
<i>Question 13. Is there an increase in severe infections in patients receiving rituximab versus placebo?</i>			
The risk of severe infections in patients with rheumatoid arthritis treated with 1,000 mgx2 rituximab was increased compared with similar patients who received placebo. Repeated cycles did not increase this risk	2b	B	89
<i>Question 14. What is the risk of developing a new solid tumour in patients with prior solid neoplasm who subsequently received rituximab?</i>			
Although rituximab treatment did not appear to increase the risk of a new solid neoplasm, a close monitoring of all patients receiving this biological agent is recommended	-4	D	100
<i>Question 15. What is the risk of interstitial lung disease in patients treated with rituximab?</i>			
There is no evidence to suggest that diffuse interstitial lung disease is developed in rheumatoid arthritis with rituximab. There are insufficient safety data to support or contraindicate the administration of rituximab in patients with rheumatoid arthritis and diffuse interstitial lung disease	5	C	93
<i>Question 16. What is the risk of congestive heart failure in patients treated with rituximab?</i>			
There is no evidence that the administration of rituximab favours the development of congestive heart failure. Rituximab can be administered to patients with well-controlled heart failure. The use of rituximab is contraindicated in patients with severe congestive heart failure (class IV) or uncontrolled severe heart disease	5	D	96
<i>Question 17. What is the risk of fulminant hepatic failure in patients suffering hepatitis B virus infection and receiving rituximab?</i>			
There is a risk of reactivation of hepatitis B virus infection, including fulminant hepatitis, in patients who are chronically infected with this virus and who receive rituximab. It is recommended not to treat patients with chronic HBV infection with rituximab, except under very exceptional circumstances. The treatment must include close monitoring of the patient and appropriate antiviral treatment	-4	D	100

ACPA indicates anti-citrullinated protein antibodies; DMARD, disease-modifying antirheumatic drugs; RA, Rheumatoid Arthritis; RF, rheumatoid factor; RTX, rituximab; TNF, tumour necrosis factor.

As recommended by the Oxford Centre for Evidence Based Medicine,<sup>9</sup> a – sign must be added to indicate that the level of evidence is not conclusive if it is a randomized clinical trial with a large confidence interval and not statistically significant or a systematic review with statistically significant heterogeneity.

**Question 1. What is the efficacy of rituximab as a first biological agent?**

**Recommendation**

*Rituximab has proven effective as a first biologic agent in rheumatoid arthritis, although this indication is not currently approved. At the recommended dose it delays structural damage in patients without prior treatment with methotrexate.*

*a) Category of the evidence: 1a; b) strength of the recommendation: A; degree of agreement: 7.8/9 (86%).*

Votes in favour between two proposals: 73%. Votes in favour as a single option: 96%.

This is one of the recommendations with the highest level of evidence (1a), and the degree of agreement reached 86%. This recommendation had to be chosen between two options, finally reaching 96% of votes in favour of the recommendation.

*Commentary on the recommendation*

The DANCER study investigated the effect of two doses of RTX (500 mg×2 and 1,000 mg×2) and the pattern of steroids in RA patients with an inadequate response to DMARDs, which also included approximately 30% of patients previously treated with anti-TNF. Efficacy analysis was performed only on patients with positive rheumatoid factor (RF), although, as discussed in the article, the inclusion of patients with negative RF would not have altered the results. There was no difference in ACR20 and ACR50 response between the two doses of RTX at 24 weeks. Although there were no significant differences in ACR70 response, the numerical response of 1,000 mg×2 was greater. In addition, this study showed that the pattern of steroids did not influence the long-term efficacy of RTX, but that given before the infusion they reduced infusion-related reactions. This study did not provide data on structural damage.<sup>11</sup> In the SERENE study, which aimed to evaluate the efficacy of RTX in patients with RA and inadequate response to MTX who had not previously received biological agents, those patients who received both doses—500 mg×2 or 1,000 mg×2—obtained a significant improvement of all response rates: ACR20, ACR50, ACR70, EULAR and HAQ scales of disability, fatigue and quality of life. The initial response was not clearly higher in the seropositive group, although it did become so when the cycle was repeated. Neither did this study provide data on structural damage.<sup>12</sup> The MIRROR study investigated the effect of 3 RTX patterns in patients with active RA and inadequate response to DMARDs, and could include patients who had received at most one biological agent. The doses used were 500 mg×2 and re-treatment with 500 mg×2 (reduced), 500 mg×2 initial dose and re-treatment with 1,000 mg×2 (increasing) and finally 1,000 mg×2 and re-treatment with 1,000 mg×2 (approved). At week 48 there were no significant differences in ACR response, but the approved dose (1,000 mg×2) obtained numerically higher responses than the low or increasing doses. However, differences did exist in favour of the approved dose with respect to the EULAR response. The response in patients without previous biological treatment was numerically higher than that of patients who had received prior anti-TNF. This study did not provide data on structural damage.<sup>13</sup> Finally, in the IMAGE study, which included patients with RA with less than 4 years evolution, seropositive or with erosions, at doses of 1,000 mg×2 or 500 mg×2, both doses demonstrated similar efficacy with traditional measurements of response. However,

after one year of treatment, the dose of 1,000 mg×2 significantly reduced the progression of structural damage compared with the dose of 500 mg×2 or placebo.<sup>14</sup> The appearance of some cases of progressive multifocal leukoencephalopathy (PML) in different clinical situations meant that Hoffman La Roche decided not to pursue the indication for RTX in these patients: RA without prior treatment with DMARDs.

There are no clinical studies in patients with contraindications to anti-TNF, although there are observational descriptions which refer improvements similar to those described previously.<sup>15–18</sup>

**Question 2. What is the efficacy of rituximab when administered as a second or third biological agent, after the failure of one or more anti-TNF agents, respectively? Are there differences in efficacy when it is administered as a second or third biological agent?**

**Recommendation**

*Rituximab is effective in patients with an inadequate response to TNF antagonists.<sup>a</sup> Its efficacy is lower when used in later therapeutic stages.<sup>b</sup>*

*<sup>a</sup>a) Category of the evidence, 1c; b) strength of the recommendation, A; degree of agreement: 7.8/9 (86%).*

*<sup>b</sup>b) Category of the evidence, 2a; b) strength of the recommendation, C; degree of agreement: 7.8/9 (86%).*

Votes in favour between two proposals: 78%; votes in favour as a single option 96%.

*Commentary on the recommendation*

The evidence for this recommendation was divided into two parts, as it referred to slightly different aspects. Evidence was superior for the first part of the recommendation (1c) and the degree of agreement (86%) and its acceptance, once the other possibility had been eliminated, was high (96%).

RTX has proven effective and safe in RA patients with an inadequate response to anti-TNF.<sup>19,20</sup> In fact, this clinical situation is currently the only indication for RTX in the technical data sheet. In these patients, RTX is most effective when administered as a second biological agent in later therapeutic steps. This is based mostly on the results of a sub-analysis of the REFLEX study presented at the 2006 ACR,<sup>21</sup> which showed that the rate of ACR response at week 24 in patients receiving RTX was 10% better in those patients in whom only one anti-TNF had failed than in those in whom more than two had done so. These results were confirmed in studies with different designs<sup>17,22,23</sup> and reflected mainly the selection of a group of patients with a more refractory disease. However, another study found no relationship between clinical response to treatment with RTX and the number of previous anti-TNF treatments.<sup>16</sup> As in other works, in the latter the response to RTX was determined primarily by the reason of suspension of anti-TNF treatment: better response to RTX by prior ineffectiveness to anti-TNF than when this was discontinued for other reasons, e.g. safety.<sup>16</sup>

**Question 3. What is the efficacy of rituximab in patients with (both) negative RF and anti citrullinated protein antibodies (ACPA)?**

**Recommendation**

*The absence of RF and ACPA does not rule out the response to rituximab. If administered to this population, the therapeutic response is less than that obtained in patients with positive RF and/or ACPA.*

*a) Category of the evidence, 1c; b) strength of the recommendation, B; degree of agreement: 7.4/9 (82%).*

Votes in favour between two proposals: 58%; votes in favour as a single option: 96%.

**Commentary on the recommendation**

This recommendation presented a good level of evidence (1c) with a degree of agreement which was also high (82%).

There are no studies specifically aimed at observing whether RTX is effective in the subgroup of patients with RA and negative for both antibodies, RF and ACPA. Randomized controlled studies of RTX versus placebo, such as the REFLEX<sup>19</sup> or DANCER<sup>11</sup> studies, included a relatively small number of seronegative patients. In the DANCER study, the ACR20 response rate in the group of patients with negative RF was similar to that of the placebo group (48% vs 52%). The number of seronegative patients in this study was very small (n=63 in the RTX group and n=21 in the placebo group) and the high response rate with placebo was surprising.<sup>11</sup> In the REFLEX study, the ACR responses were higher in patients with positive RF than in those with negative RF. The ACR20 response rates at week 24 in patients treated with RTX were 54% in patients with positive RF and 41% in patients with negative RF.<sup>19</sup> A sub-analysis of this study, which analyzed the RTX response rate versus placebo in the small subgroup (29 with RTX and 16 with placebo) of patients who were seronegative for both antibodies, showed that the ACR20 response, but not the ACR50 or ACR70, was superior with RTX than with placebo (28% vs 6%), as was the EULAR response (44% vs 14%).<sup>24,25</sup> The statistical analysis was not completed due to the small size of the sample.

Isaacs et al<sup>26</sup> analyzed combined data from the MIRROR and SERENE phase III RTX studies and compared the rates of response to RTX in patients who were seropositive for RF and/or ACPA compared to patients without the antibodies mentioned. The ACR20, 50 and 70 response rates at week 48 were significantly higher in seropositive patients. In addition, the decrease of DAS28 was higher in the seropositive group than in the seronegative (-2.48 vs -1.72). The study concluded that the probability of response in seropositive patients with respect to seronegative ones was 2-3 times higher.<sup>26</sup>

A sub-analysis of the IMAGE study carried out in patients with initial RA not previously treated with MTX, analyzed the clinical and radiological response to RTX (+MTX) versus placebo (+MTX) and compared the results between seropositive patients (RF and/or ACPA positive) and seronegative patients (RF and ACPA negative). The ACR50 response at one year of treatment in the seropositive group was higher in those patients who received RTX (+MTX) (66% vs 46%), while there were no differences in the seronegative group (54% of responses in both groups). With regard to radiographic progression, there were significant differences in favour of RTX among the seropositive, but not among the seronegative.<sup>27</sup>

**Question 4. What is the efficacy of rituximab monotherapy compared to rituximab plus methotrexate? What is the efficacy**

**of rituximab plus methotrexate compared with rituximab plus another DMARD?****Recommendation**

*Treatment with rituximab seems more effective when it is combined with methotrexate or other DMARDs, especially leflunomide.*

*a) Category of the evidence, 2b; b) strength of the recommendation, B; degree of agreement: 6.9/9 (77%).*

Votes in favour between two proposals: not done, due to lack of other proposals; votes as a single option: 85%.

**Commentary on the recommendation**

This recommendation provided acceptable evidence (2b), with a degree of agreement which exceeded 75%.

There is only one randomized study comparing RTX monotherapy with RTX plus MTX, although the number of patients studied was only 404. A numerically higher response was found in the group who received RTX+MTX compared to those treated with RTX monotherapy, but it lacked statistical significance. However, in an open prospective study with 107 patients, 19 were treated with RTX alone, as they had not tolerated MTX previously. The response was compared with that of other patients who received RTX and MTX. After 6 months, the DAS28 of patients receiving the combination was significantly lower than that of patients treated in monotherapy.<sup>28</sup> In an open observational study of cases and controls with 20 patients in each group, the efficacy measured by DAS28 was similar in both groups at week 16.<sup>29</sup> A record of 50 patients treated with RTX established a superior response in patients treated with RTX+MTX (88%) with respect to those treated with RTX alone (53%).<sup>30</sup> However, this difference was not seen in other records of 108 patients, of whom 95 were assessable, since the EULAR response was similar in patients receiving RTX, with or without MTX.<sup>31</sup> These discrepancies may be based on the differences existing between the different populations studied, as they were not obtained from controlled studies.

Regarding the effect on depletion of B cells, the original study by Edwards showed no differences between RTX as monotherapy or in combination.<sup>4</sup> However, a subsequent study, in which B lymphocytes were determined by high sensitivity flow cytometry, showed evidence of B lymphocytes values which were significantly lower in patients treated with the combination of RTX and MTX.<sup>28</sup>

Fundamental studies have been conducted with MTX, either as a comparator drug or associated with RTX. In a German multicentre study, prospective and without intervention, which included 2,400 patients with RA, an interim analysis was performed with the data from 995 patients from 124 centres. After 4 months of treatment, a numerically superior response was observed ( $P>.05$ ) in patients treated with RTX+LFN versus RTX+MTX versus RTX in monotherapy. There was no evidence of a different rate of adverse events. However, this study did not clarify the characteristics of the patients.<sup>32</sup> Other studies also support the use of leflunomide associated with RTX as an alternative to MTX when this is contraindicated. Thus, in a retrospective study of 10 patients by Henes et al,<sup>33</sup> 7 achieved a good or moderate EULAR response at 6 months of combination therapy. Similarly, another recent study<sup>34</sup> treated 15 patients (5 of them previously treated with anti-TNF) with active RA who

had presented resistance to leflunomide monotherapy. The combination of RTX and leflunomide induced an EULAR response in 80% of patients treated with the combination, without a significant increase in adverse events.

**Question 5: How does rituximab (500 mg×2) behave compared to rituximab (1 g×2)?**

**Recommendation**

*The effective dose of RTX in RA patients who have not responded to anti-TNF is 1,000 mg×2. A dose of 500 mg×2 cannot currently be recommended because there are no data confirming its efficacy in these patients.*

*a) Category of the evidence, 1b; b) strength of the recommendation, A; degree of agreement: 8/9 (89%).*

Votes in favour between two proposals: 85%; votes as a single option: 100%.

*Commentary on the recommendation*

This recommendation is one of those providing better evidence (1a) and degree of agreement (89%). Also, once chosen between two proposals, 100% of the experts voted in favour.

RTX has been approved for use after failure of DMARD, of which at least one must be an anti-TNF. The REFLEX study,<sup>19</sup> on which this indication is supported, was conducted among patients with active RA in whom at least one anti-TNF had failed. The study had two branches; in one, patients received MTX plus placebo and in the other, MTX plus 1,000 mg×2 RTX. All efficacy measurements were higher in the active branch. There was no branch with a lower dose.

However, other studies with different populations have used RTX at doses of 500 and 1,000 mg. Thus, the IMAGE study<sup>14,35</sup> compared 500 mg×2 and 1,000 mg×2 of RTX in RA patients who had not received MTX. In this study, the results of improved function measured by SF-36 and radiographic progression of joint damage after one year of treatment were significantly more favourable with a dose of 1,000 mg×2 than with 500 mg×2. However, the improvement of signs and symptoms and HAQ were not different with either dose. In the DANCER study,<sup>11</sup> the percentages of patients achieving ACR20/50/70 responses were not different at 24 weeks in patients treated with 500mg×2 than in those treated with 1,000mg×2. The DANCER study was not designed to compare the two doses and included patients who had responded incompletely to non-biological or biological DMARDs. The MIRROR study<sup>13</sup> in patients with RA who had not responded to MTX (some of them had also been treated with anti-TNF), compared the efficacy of three different RTX regimens: two courses of RTX 500 mg×2, two courses of RTX 1,000 mg×2 and one course of 500 mg×2 followed by a course of 1,000 mg×2. At 48 weeks, the percentages of patients achieving ACR20/50/70 responses were not significantly different. The collective data indicate that the dose of RTX which has proven to be effective in patients with RA who have incompletely responded to anti-TNF is 1,000 mg×2. However, in other RA populations the doses of 500 mg×2 could be as effective as 1,000 mg×2.

**Question 6. What is the efficacy of rituximab after two or more cycles of treatment?**

**Recommendation**

*Patients with RA who have had a satisfactory response to a first cycle of RTX (1,000 mg×2), may benefit from new cycles of treatment.*

*a) Category of the evidence, 1C; b) strength of the recommendation, B; degree of agreement: 8/9 (89%).*

Votes in favour between two proposals: 93%; votes as a single option: 100%.

*Commentary on the recommendation*

This recommendation also presents a high level of evidence (1c) and a high degree of agreement (89%).

The SUNRISE study<sup>36</sup> was a randomized, double-blind, placebo-controlled study designed to evaluate the effect of a second course of RTX versus placebo in a group of patients in whom at least one anti-TNF had previously failed. Patients received a first cycle of RTX, and after 24 weeks, those who were not in remission received placebo or a new infusion of RTX. A total of 475 patients were randomized from an initial 559, and a persistent clinical response was observed, even greater than initially observed in patients who received a second course of RTX. In fact, those patients who achieved a major response (ACR 70) in the first cycle were more likely to benefit from a second cycle (OR=4.5; P=.037).

In an open study of patients in whom at least one anti-TNF had failed, derived from an extension of clinical trials in phases II and III with RTX, those who had presented a clinical response to a first cycle of RTX received new cycles at least every 4 months if they presented clinical activity (more than 8 swollen and painful joints or DAS 28>2.6). Patients presented a superior clinical response than that observed after the first cycle; in fact, the results of low activity or remission achieved (DAS 28) doubled those observed after the first cycle. However, one of the inclusion criteria for a new cycle was having shown a clinical response to the first, which means that this group of patients responded to RTX.<sup>37</sup>

The results obtained in the two previous studies were observed in RA patients with treatment failure after at least one anti-TNF. However, there is information from an open study in 570 patients with active RA after a period of clinical response; up to 41% of the total were patients with failure of DMARDs who had never received biological therapy. A similar efficacy was observed in this population as in the studies mentioned previously. There were no differences in response depending on whether they had previously received anti-TNF or not.<sup>38</sup>

**Question 7. Are there benefits from treatment with rituximab following a fixed schedule (every 6 months) with respect to treatment on demand?**

**Recommendation**

RTX has shown effectiveness both in patients who were treated following a fixed dosing schedule (every 6 months) and in those who received it on demand. Administration following a fixed schedule could help to maintain patients with a lower level of activity. However, this strategy involves administering more cycles of RTX, which must be taken into account in the risk/benefit balance.

a) Category of the evidence, -2b; b) strength of the recommendation, C; degree of agreement: 6.7/9 (74%).

Votes in favour between two proposals: 70%; votes as a single option: 93%.

**Commentary on the recommendation**

This recommendation has a discrete degree of evidence (-2b), with an acceptable degree of agreement (74%).

No controlled study has compared the administration of RTX on demand with fixed administration every 6 months. Therefore, there is no established recommendation for the use of RTX in RA. In fact, the technical data sheet of the product<sup>39</sup> only indicates what should be the dose of the treatment cycle (1 g with 15 day intervals up to a total of 2 g), but does not indicate when patients should be re-treated. Establishing a defined dosing schedule would have the advantage for the rheumatologist of facilitating the service structural organization. The problem with treating on demand is that it depends heavily on patient access and organizational possibilities of the service to administer RTX promptly.

During the clinical development of the drug, patients were re-treated using two different therapeutic regimens: 1) on demand, and 2) with a fixed therapeutic regimen every 6 months. In any case, with both regimens those patients who received further cycles of RTX were, in general, those who had initially responded to RTX. In the on-demand treatment, RTX was administered at the discretion of the physician from week 16 of the last treatment, while patients who received RTX with a fixed schedule took it every 6 months as long as they were not in remission (DAS28<2.6).<sup>11-13,19,36</sup>

An open prospective study conducted at two centres in two different countries (United Kingdom and the Netherlands) with a total of 48 patients for 1 year of treatment, did not demonstrate the superior efficacy of one therapeutic regimen over another. There were no differences with respect to safety.<sup>40</sup> Later, the same authors presented the results at 2 years of treatment, and confirmed the results from the previous study.<sup>41</sup> Interestingly, being two populations from two different hospitals, the baseline characteristics were slightly different. The population treated on demand had a significantly higher baseline DAS28 (6.1 vs 5.1;  $P=.03$ ) and mean anti-TNF received previously was numerically higher (2.05 vs 1.54;  $P=.33$ ), indirectly suggesting that these patients had a more severe disease.<sup>41</sup>

Recently, results have been presented from a sub-analysis of patients treated on demand and with a fixed schedule (every 6 months) from phase II and III trials of the drug. With the fixed scheme patients were treated every 6 months provided they did not have a DAS28<2.6. This fixed regimen kept the patients with persistently low DAS28 and HAQ. As was logical, the incidence of outbreaks was lower with the fixed schedule (19% vs 42%). The median re-treatment

was clearly superior with the fixed regimen (25 vs 62 weeks), although the administration of further cycles of RTX did not increase the secondary effects.<sup>42</sup>

**Question 8. What are the efficacy data of re-treatment of patients without prior response to rituximab compared with patients who had a moderate or good response (EULAR criteria)?****Recommendation**

The effectiveness of the administration of a new cycle of RTX in patients without a previous response is questionable.

a) Category of the evidence, -2b; b) strength of the recommendation D; level of agreement: 6.3/9 (70%).

Votes in favour between two proposals (in second round): 68%; votes as a single option: 89%.

**Commentary on the recommendation**

This recommendation has a discrete degree of evidence and was one of the recommendations with a lower degree of agreement (70%); moreover, the strength of the recommendation was only grade D. Information on the effectiveness of a second course of RTX in patients who did not respond to a first cycle was contradictory. Patients who had not responded to a first cycle of RTX were usually excluded from additional cycles in the main clinical trials.<sup>11,19</sup> In a small, open study, 7 patients who had not responded to a first cycle of RTX received one or two additional cycles and no clinically significant response was observed.<sup>43</sup> However, in another study, also open, 25 patients with no response to a first cycle of RTX received a second course of treatment and EULAR response was observed in 71% of cases.<sup>44</sup> In this second study, the greater efficacy of re-treatment in these patients appeared to be related to a more profound depletion of B lymphocytes in peripheral blood, assessed by high sensitivity flow cytometry techniques.<sup>45</sup>

**Question 9. Is it useful to monitor B lymphocytes in patients receiving rituximab?****Recommendation**

In clinical practice, the efficacy of RTX treatment or the need for new courses must be determined by clinical activity indices and not by the amount of B lymphocytes in peripheral blood.

a) Category of the evidence, 4; b) strength of the recommendation D; level of agreement: 8.5/9 (94%).

Votes in favour between two proposals: not done because there was only one proposal; votes as a single option: 100%.

**Commentary on the recommendation**

This recommendation had grade 4 evidence, although the degree of agreement was one of the highest (94%).

B lymphocyte depletion caused by RTX is more intense in peripheral blood than in the bone marrow or other lymphoid organs.<sup>46,47</sup> No clear relationship has been found between the depletion of circulating B cells measured by conventional flow cytometry<sup>48</sup> and response or relapse of symptoms, but there seems to be a relationship between the persistence of B lymphocytes in peripheral blood at 2 weeks of administration and the absence of clinical response when using high sensitivity flow cytometry.<sup>49</sup> The problem is that high sensitivity flow cytometry is not available in most hospitals for its use in everyday clinical practice.

While the depletion is almost total in peripheral blood, in rheumatoid synovial blood the depletion is mild or moderate, but is always greater in responders, so that the more B cells persist in the synovium, the lesser is the response or its persistence.<sup>50</sup>

The clinical significance of B lymphocytes partial depletion in sites of inflammation (synovial) or of cell maturation (bone marrow) is not known. It is also unknown whether RTX eliminates one cell subtype more than another, but the response has been associated with a higher number of plasma precursor cells in the synovial and/or peripheral blood which are CD20-.<sup>47</sup>

It is likely that the total B cell population is more important than cell subtypes, such as activated B cells (expressing HLA DR) or memory B cells (IgD-CD27+). It has been reported that both activated and memory B cells are the most commonly depleted in patients who respond to treatment with RTX, but these data are obtained from observational studies conducted on a relatively small number of patients.<sup>51</sup>

**Question 10. What is the optimal time to assess the response of a patient treated with rituximab (12 vs 16 weeks)?**

**Recommendation**

*It is considered that the most appropriate time to evaluate the response to RTX treatment should be around week 16.*  
*a) Category of the evidence, 1c; b) strength of the recommendation, A; degree of agreement: 8/9 (89%).*

Votes in favour between two proposals: not done because there was no second proposal; votes as a single option: 100%.

**Commentary on the recommendation**

This recommendation has an acceptable level of evidence (1c) and a degree of agreement of 100%.

In all patients receiving RTX, the response must be assessed within a specified period after drug administration. This is critical, considering that most re-treated patients were those who presented a clinical response to the drug. There are no studies specifically aimed at trying to determine the optimal timing of RTX response; however, published data from the DANCER and REFLEX studies,<sup>11,19</sup> enabled several conclusions to be drawn. In the first, the ACR20 response was clearly defined from week 12 (30% in ACR20 with placebo compared with 55% in ACR20 with RTX). This was also true of ACR50 and 70, although the ACR70 response in the group treated with 1,000 mg×2 increased more slowly and reached its highest level in week 24.<sup>11</sup> In the REFLEX study,<sup>19</sup> the first significant difference with respect to placebo in ACR20 appeared at week 8. Subsequently, patients were evaluated at weeks 12, 16, 20, and 24

and showed a similar response profile with no differences in the different evaluation time points although the ACR70 was only significant after week 16.

The recommendation to clinically evaluate patients at week 16 would have the advantage of collecting the vast majority of patients who manifested a response. Doing it later, especially at week 24 in patients with a fixed therapeutic regimen, might involve assessing patients in the outbreak stage, without knowing the degree of response for certain.

**Question 11. In patients receiving rituximab, what is the rate of decrease of immunoglobulins and what is the relationship between this decline and the emergence of severe infections?**

**Recommendation**

*Patients treated with rituximab may present decreases in IgG and IgM at some point during the treatment.<sup>a</sup> A possible trend towards more severe infections after IgG decline has been observed.<sup>b</sup> A periodical quantification of immunoglobulins is recommended.*

*<sup>a</sup>a) Category of the evidence, 1a; b) strength of the recommendation, A; degree of agreement: 7.6/9 (84%).*

*<sup>b</sup>a) Category of the evidence, -1c; b) strength of the recommendation, B; degree of agreement: 7.6/9 (84%).*

Votes in favour between two proposals: 82%; votes as a single option: 96%.

**Commentary on the recommendation**

This recommendation was analyzed by its evidence in two parts: first, the relationship between RTX treatment and decrease in immunoglobulins, and second, the possible relationship between this decrease and infections. Both have a high level of evidence and degree of agreement.

Patients treated with RTX showed an overall decrease in the concentration of IgM and, to a lesser extent, of IgG. Still, both averages remained above the normal lower limits.<sup>11,19</sup> In a general analysis of safety in 2,578 patients included in clinical trials (5,013 patients-year follow-up) it was observed that 5% and 23% of patients presented IgG and IgM plasma levels, respectively, below normal.<sup>38,52</sup> While the proportion of patients with decreases in IgG became stable with repeated cycles of treatment, that of patients who experienced decreases in IgM at some point increased with the number of cycles received. These data referred to reductions which occurred at any point during treatment. About 1% of patients showed a persistent decrease of IgG.<sup>52</sup> There were cases of patients with undetectable immunoglobulin.<sup>39</sup>

Regarding the clinical impact of these immunoglobulin declines, it was observed that the frequency of serious infections was similar in patients with and without them. However, when analyzing the frequency of serious infections in patients before and after IgG declines, there was a trend towards more serious infections after the decrease, without this increase reaching statistical significance.<sup>52</sup> IgM decline did not appear to be associated with increased risk of adverse effects.<sup>38,52</sup> Recent, unpublished data from

Roche mention that repeated treatment with RTX may cause low levels of IgM with no increase in infection, while persistently low IgG values (4 months or more) may be associated with an increase in severe infections.

A subsequent publication to the systematic review indicates that low levels of IgG (<6 g/l) prior to administration of RTX are an independent risk factor for severe infections.<sup>53</sup> This would reinforce the need to monitor and to determine baseline immunoglobulin values before starting treatment with RTX.

**Question 12. What is the effectiveness of vaccination in patients receiving rituximab?**

**Recommendation**

*Patients about to be treated with RTX should receive the same vaccines as immunocompromised patients. The response to vaccination is reduced in them. Vaccination is recommended, preferably before initiating treatment with RTX or as far as possible from the previous cycle.*

*a) Category of the evidence, -1c; b) strength of the recommendation, B; degree of agreement: 7.8/9 (87%).*

Votes in favour between two proposals: 82%; votes as a single option: 96%.

*Commentary on the recommendation*

This is a recommendation with a high degree of evidence (-1c) and agreement (86%).

An open study compared the formation of antibodies against seasonal flu virus and H1N1 in 20 patients treated with MTX, 23 with RTX and 29 healthy controls. Patients treated with RTX received the vaccine early, at 4-8 weeks of administering RTX, or late, 6-10 months after the cycle of RTX. Antibody formation was lower in patients treated with RTX compared with controls or those receiving MTX. No response was observed in the early group, while the late vaccinees showed a moderate increase in antibodies, even in the absence of CD19 cells.<sup>54</sup> The response was higher in patients who had been vaccinated in previous years. The safety of vaccination was similar in the different groups of RTX. Similar data were found in a previous, more limited study.<sup>55</sup>

The formation of antibodies after vaccination was compared in patients treated with MTX or RTX in an open, randomized, placebo-controlled study (RTX 1,000x2+MTX vs placebo+MTX). The response to tetanus toxoid (four-fold increase in antibody titers) and the response to other neo-antigens, between weeks 24 and 36 after administration of RTX, were measured. The response to vaccination with tetanus toxoid was similar in both groups. Delayed hypersensitivity to cutaneous stimulation with *Candida* was preserved in a similar manner in both groups. The response to pneumococcal polysaccharide and neo-antigen vaccine (KLH), measured as an increase in specific antibody titers, was lower in the group treated with RTX.<sup>56</sup> The authors noted the need to complete a vaccination program before treating with RTX.

**Question 13. Is there an increase in severe infections in patients receiving rituximab versus placebo?**

**Recommendation**

*The risk of severe infections in patients with RA treated with 1,000mgx2 RTX was increased compared with similar patients who received placebo. Repeated cycles did not increase this risk.*

*a) Category of the evidence, 2b; b) strength of the recommendation, B; degree of agreement: 7.6/9 (84%).*

Votes in favour between two proposals: not performed because there was only one proposal; votes as a single option: 89%.

*Commentary on the recommendation*

This recommendation had a moderate level of evidence with a very high degree of agreement (89%).

Data on the risk of infections in patients treated with RTX come from controlled clinical trials and extension trials. The conclusion that can be obtained from the studies is that the risk of severe infections is increased in patients treated with 1,000mgx2 compared with lower doses or placebo. In the REFLEX study,<sup>19</sup> the rate of severe infections in patients treated with 1,000 mgx2 was 5.2/100 patients-year, while in those treated with placebo the rate was 3.7/100 patients-year. In the IMAGE study,<sup>14</sup> the rates of severe infections were 6.09, 4.61, and 3.73/100 patients-year with doses of 1,000 mgx2, 500 mgx2 and placebo, respectively. In a study involving all patients treated with RTX in the pre-registry trials, the rates of severe infection in patients who received RTX was 4.25 (3.8-4.7), similar to that obtained with placebo, 4.33 (3.21-6), with no changes observed in the rate after re-treatment.<sup>52</sup> Similar data were obtained from a systematic review (Table 1). The results of this study were difficult to interpret, taking into account the following aspects: 1) patients received different doses of RTX; 2) the frequency of severe infections was low, a fact which require a large sample size in order to accept or reject the hypothesis, and 3) a high rate of infections was found in the placebo group. In another study<sup>57</sup> with a small sample and limited follow-up, biological treatment after RTX did not increase the risk of severe infections. The rates of severe infection were 6.99/100 patients-year during treatment with RTX and 5.49/100 patients-year with the introduction of another biological agent after RTX. In the TAME safety study,<sup>58</sup> carried out with RA patients on stable doses of etanercept or adalimumab, severe infection rates at 24 weeks in 33 patients who had received one or two courses of 500 mgx2 RTX were 6.43 (0.91-45.6)/100 patients-year and 0 in 13 patients in the placebo group. The small number of patients and the infection rate in the group receiving RTX are arguments which contraindicate the combined use of RTX and anti-TNF until more safety data are available. Despite this increase in severe infections, the number of patients with opportunistic infections and tuberculosis was low or nil. When analyzing the rates of severe infections in different cohorts of patients treated with rituximab, the figures were similar to those of patients treated with anti-TNF or other biological agents.<sup>59</sup> These data must be supplemented with real-life data obtained from records.

**Question 14. What is the risk of developing a new solid tumour in patients with prior solid neoplasm who subsequently received rituximab?**

**Recommendation**

*Although RTX treatment did not appear to increase the risk of a new solid neoplasm, a close monitoring of all patients receiving this biological agent is recommended.*

*a) Category of the evidence, -4; b) strength of the recommendation D; level of agreement: 8.1/9 (90%).*

Votes in favour between two proposals: not available; votes as a single option: 100%.

*Commentary on the recommendation*

There is currently no data in the literature review that enables the question to be answered (level of evidence -4). The rate of solid tumours in patients with RA who received RTX in both controlled clinical trials and in observational cohorts was similar to that of the population with RA.<sup>52</sup>

The possibility of developing tumours has been examined in other biological agents for which there is more available experience in RA. The result of a meta-analysis of randomized clinical trials with anti-TNF (only adalimumab and infliximab were included) showed an increased risk of neoplasms in patients treated with them.<sup>60</sup> However, the results of other studies indicated that treatment with biological agents, mainly anti-TNF, did not increase the risk of solid neoplasms, with the exception of cutaneous neoplasms.<sup>61–64</sup> Neither was a higher mortality rate found in patients treated with anti-TNF in whom a tumour developed.<sup>65,66</sup> In two series with a small number of cases in which patients were treated with RTX instead of an anti-TNF, due to already having a tumour among other reasons, the authors described an increase in tumours. However, follow-up was short and in no case was it the main reason for the study.<sup>18,67</sup> It is likely that a previous history of neoplasm may have affected the medical decision regarding the prescription of a biological agent (confusion by indication), and in this sense, the possibility of being treated with a biological agent may be lower in patients with a history of cancer. However, a study conducted in the United States found that, in patients with previous cancer, the probability of being treated with a biological agent was reduced only by 29%.<sup>68</sup> Furthermore, it was not observed that the incidence of cancer was higher in patients who had suffered a tumour.<sup>63</sup> Notwithstanding the above, the technical specifications and recommendations for the use of biological agents should always be taken into account before prescribing these drugs.<sup>6</sup>

**Question 15. What is the risk of interstitial lung disease in patients treated with rituximab?**

**Recommendation**

*There is no evidence to suggest that diffuse interstitial lung disease is developed in RA with RTX. There are insufficient safety data to support or contraindicate the administration of RTX in patients with RA and diffuse interstitial lung disease.*

*a) Category of the evidence, 5; b) strength of the recommendation, C; degree of agreement: 7.2/9 (80%).*

Votes in favour between two proposals: 83%; votes as a single option: 93%.

*Commentary on the recommendation*

This recommendation has no supporting evidence, so it can be seen in its entirety as an expert recommendation. Isolated cases of interstitial pneumonitis plus respiratory failure after administration of RTX have been described, but these are generally patients with haematologic malignancies.<sup>69,70</sup> On the other hand, RTX has also been used successfully for the treatment of interstitial pneumonitis resistant to conventional therapy in patients with systemic lupus erythematosus and systemic sclerosis.<sup>71–73</sup> Furthermore, isolated cases of interstitial pneumonitis, some of them fatal, have also been described in patients treated with anti-TNF (infliximab, etanercept and adalimumab).<sup>74,75</sup>

**Question 16. What is the risk of congestive heart failure in patients treated with rituximab?**

**Recommendation**

*There is no evidence indicating that the administration of RTX favours the development of congestive heart failure. RTX can be administered to patients with well-controlled heart failure. The use of RTX is contraindicated in patients with severe congestive heart failure (class IV) or uncontrolled severe heart disease.*

*a) Category of the evidence, 5; b) strength of the recommendation D; level of agreement: 7.5/9 (83%).*

Votes in favour between two proposals: 76%; votes as a single option: 96%.

*Commentary on the recommendation*

Like the previous recommendation and due to the total absence of evidence, this should be considered in its entirety as an expert recommendation. Unlike the case with anti-TNF, there is no information available on cardiac function deterioration in patients with RA and without previous heart disease when treated with RTX. In placebo-controlled clinical trials, severe cardiac events were reported in a similar proportion to that of the placebo group.<sup>39</sup>

Since there are some reports of isolated heart failure cases associated with infusion, if patients report a history of heart disease, it is advisable to weigh the risk of cardiovascular complications arising from peri-infusional reactions before administering RTX and to carry out close monitoring during the treatment.<sup>39</sup> Treatment with RTX is contraindicated in the case of RA patients suffering from severe heart failure (NYHA class IV) or uncontrolled severe heart disease.<sup>39</sup>

**Question 17. What is the risk of fulminant hepatic failure in patients suffering hepatitis B virus infection and receiving rituximab?**

**Recommendation**

*There is a risk of reactivation of hepatitis B virus infection, including fulminant hepatitis, in patients who are chronically infected with this virus and who receive RTX. It is recommended not to treat patients with chronic HBV infection with RTX, except under very exceptional circumstances. The treatment must include close monitoring of the patient and appropriate antiviral treatment.*

*a) Category of the evidence, -4; b) strength of the recommendation D; level of agreement: 8.5/9 (94%).*

Votes in favour of two proposals: not done because there was only one proposal; votes as a single option: 100%.

#### Commentary on the recommendation

There are no controlled studies to support this recommendation, so that its inclusion is based on data from uncontrolled studies in patients with blood diseases and the experience of experts.

The reactivation of hepatitis B is well known in oncohaematological patients treated with cytotoxic agents. Most of the experience has been accumulated in patients with non-Hodgkin lymphoma or bone marrow transplant.<sup>76</sup> This reactivation can cause asymptomatic hepatitis, clinical hepatitis and even fulminant hepatitis resulting in death. Lymphoma patients treated with RTX may have an additional risk of developing this complication.<sup>77</sup> In a retrospective study of 115 cases of non-Hodgkin lymphoma treated with RTX (plus chemotherapy), of whom 15 were carriers of HBsAg, it was found that 8 of the 10 who did not receive lamivudine prophylaxis suffered a reactivation of hepatitis B, including fulminant hepatitis resulting in death.<sup>78</sup> None of the 5 patients who received lamivudine presented this complication. However, hepatitis B was detected *de novo* in 4 HBsAg negative patients, of whom 2 died from fulminant hepatitis.<sup>78</sup> A systematic literature review published in 2007 identified 64 cases of viral infections associated with RTX in patients with lymphoma; it was observed that 40% were by hepatitis B. Half of these infections by hepatitis B virus resulted in death by fulminant hepatitis.<sup>79</sup>

The risk of reactivation of hepatitis B in patients with RA is unknown. It is also unknown if this risk is lower than in the case of haematological diseases, for which RTX is used in combination with chemotherapy. In clinical trials with RTX in RA, patients with positive serology for hepatitis B virus were excluded. No evidence of cases of hepatitis B reactivation were found in a recently reported safety analysis in 3,095 patients (7,198 patients/year) with RA treated with RTX.<sup>52</sup> However, there have been isolated reports on hepatitis B reactivation<sup>80</sup> or *de novo* hepatitis B<sup>39</sup> in RA patients treated with RTX.

#### Discussion

The recommendations presented are based on a systematic literature review and expert opinion when scientific evidence was scarce or nonexistent. A scientific methodology was followed which was established *a priori*, based on a modification of the Delphi technique. This included a systematic review of the evidence where possible, or not systematic in other cases and the participation of a large group of Spanish rheumatologists.

Certain aspects of the recommendations developed may generate more controversy or be more problematic and are discussed below.

Recommendation number 1, one of those with the greatest degree of evidence (1a), addresses the efficacy of RTX as a first biological agent. The efficacy of RTX as first biological agent has been demonstrated. The level of evidence for this recommendation is high. The findings on radiographic progression are based primarily on the IMAGE study.<sup>14</sup> In this study the radiographic benefit was only observed clearly with a dose of 1,000 mg $\times$ 2. The appearance of some cases of progressive multifocal leukoencephalopathy (PML) in different clinical situations has meant that Hoffman La Roche has decided not to pursue the indication for RTX in these patients: RA without prior treatment with DMARDs.

Recommendation number 3, which refers to the efficacy of RTX in patients with negative RF and/or ACPA, resulted from the discussion of sub-analysis from RTX studies in RA. There were no studies aimed at assessing whether RTX was effective in patients with negative RF and/or ACPA. The systematic review in this context was impossible and the data from the non-systematic review were not clear, as

they only led to confusion. Since there was evidence of the benefit of RTX in this subgroup of patients and in the absence of variables which could predict response, the recommendation was based on the work by Isaacs et al,<sup>26</sup> reinforced by expert opinion. The use of RTX in patients with negative RF and ACPA should be reserved for cases where the physician deems it appropriate, after an individual analysis of each case.

Recommendation number 5 discussed whether a dose of 500 mg $\times$ 2 is as effective as a dose of 1,000 mg $\times$ 2. In the subgroup of patients who had suffered failure with one or more anti-TNF, the studied and effective dose of the drug was 1,000 mg $\times$ 2. According to radiographic progression, the benefits of the drug included patients in the REFLEX study<sup>19</sup> who were treated with 1,000 mg $\times$ 2, while in patients from the IMAGE study<sup>14</sup> suffering arthritis of less than 4 years evolution without previous exposure to MTX, the effective dose in this outcome was 1,000 mg $\times$ 2 and higher than 500 mg $\times$ 2. Controlled clinical trials designed to evaluate efficacy in variables other than radiographic outcome (DAS, EULAR response, physical function, quality of life, etc.) showed no differences between the two doses, with a tendency towards better outcomes in patients with doses of 1,000 mg $\times$ 2, with no differences in adverse events between the two groups (quoted from the systematic review). Due to these findings, the panel decided, with high levels of evidence and agreement, that the RTX dose should be that mentioned in the technical specifications and that, currently, a dose of 500 mg $\times$ 2 cannot be recommended as equivalent in the context of treatment for patients with RA and anti-TNF failure. Similarly, in cases where the indication to administer RTX is accelerated progression of structural damage, the recommended dose is 1000 mg $\times$ 2.

Recommendation number 7 deals with the administration of RTX following a fixed schedule or on demand. The level of evidence is low, since there are no controlled studies in this regard. The data available from prospective studies and sub-analysis concluded that RTX was as effective in patients who were treated following a fixed dosing schedule as in those who received it on demand. However, patients treated with a fixed schedule showed a better clinical response and fewer outbreaks, with no differences in other events. These patients received a greater number of cycles. Administration following a fixed schedule could help to maintain patients at a lower activity level. However, this strategy would involve administering more cycles of RTX, which must be taken into account in the risk/benefit balance.

Recommendations 8 and 9, on re-treatment and monitoring aspects, had a very low level of evidence and an acceptable level of agreement among the panellists. This was due to the limited literature on the subject and the contradiction in the results from studies of low methodological quality, which are problems inherent to the development of clinical practice guidelines. Until the end of the review, recommendation 8 stated that the effectiveness of administering a new RTX cycle in patients who had not shown a response previously was questionable. Recommendation 9 concluded that in clinical practice, the efficacy of RTX or the need for new cycles should be determined based on clinical activity indices and not according to the concentration of B lymphocytes in peripheral blood. These recommendations could be amended in the near future with the introduction of advanced laboratory techniques for the identification of B cell depletion.

Recommendation 11 included a very important clinical aspect, given that the monitoring of immunoglobulins is a relatively simple and straightforward test. Patients with RA from clinical trials who are candidates for RTX have a baseline rate of IgG decline below the values considered as clinically significant (<6 g/l), 1.7%. This percentage increased to 4.7% after four cycles of RTX. In the French cohort of biological therapies, it was reported that 4.6% of patients presented

IgG values below this figure at baseline, that is, before treatment.<sup>53</sup> In other diseases such as primary immunodeficiencies, leukaemia or organ transplant patients, the decline in IgG values is associated with clinically relevant infections. A very recent work, published after the systematic review conducted for this article, noted that a low IgG value before RTX administration was an independent risk factor for severe infections.<sup>53</sup> After discussion by the group of panellists, it was decided to issue the recommendation for greater patient safety, as it would reinforce the need not only to monitor but also to determine baseline immunoglobulin values before starting treatment with RTX.

Recommendation 13 (“The risk of severe infections in patients with RA treated with 1,000mg×2 RTX is increasing compared with similar patients who received placebo. Repeated cycles do not increase this risk”) was one of the most difficult to address. It was not possible to conclude whether the lack of association between the use of RTX and severe infections identified in the systematic review was real or whether it could not be demonstrated due to methodological problems (type II error). The clinical impression was that the number and type of severe infections in patients treated with RTX was similar to that observed with other anti-TNF and more so in other targets such as those of abatacept.<sup>59</sup> Discussion in this respect could be extended in the systematic review.<sup>81</sup> The authors assume the responsibility of recommending that “the rate of severe infections in patients treated with RTX is similar to that of other biological processes”.

Recommendation number 14 presented a low level of evidence, since there was no data in the literature to help answer the question of: what is the risk of developing a new solid tumour in patients with a prior history of neoplasm? Indirect evidence available from other biological agents, mainly anti-TNF, presented some controversy. The results of a meta-analysis of randomized clinical trials demonstrated that anti-TNF increased the risk of neoplasm, especially when administered at high doses.<sup>60</sup> However, most medical records could not show an increased risk of neoplasm, except for cutaneous neoplasms other than melanoma.<sup>61–64</sup> No increase in the number of malignancies was described in two small series of patients treated with RTX, among other causes because some of them had already suffered malignancy.<sup>18,67</sup> Nevertheless, the sample size of the works did not enable major conclusions to be drawn.

Recommendations 15 and 16, based on the risk that RTX may increase the likelihood of suffering interstitial lung disease or congestive heart failure, were established based on expert opinion because the only evidence available was a very small number of reports from isolated cases, from which it was impossible to establish causality. Therefore, they should be considered in their entirety as expert recommendations, with a high level of agreement among experts.

Finally, recommendation 17, focused on the risk that RTX may favour liver failure in patients previously infected with hepatitis B virus, is also the result of uncontrolled studies conducted mainly in oncohematological patients. Given that the recommendations are focused on patient safety, it was decided to maintain a recommendation in which the level of agreement among experts was one of the highest.

The creation of a consensus document aimed at enhancing clinical practice required considerable effort, particularly when it came to resolving management questions about a subgroup of patients with RA treated with RTX. The authors of this consensus were rheumatologists with experience in handling biological agents, with consultation in different areas. The main strengths are based on a systematic review whenever possible and in the opinion of experts issued on a systematic basis. The main weaknesses are those related to the systematic review: the inability to answer many questions due to insufficient scientific

evidence, as was the case with most safety recommendations. In some areas the evidence was so weak that it often created confusion rather than resolve doubts (doses of 1,000 mg×2 vs 500 mg×2 or efficacy in patients with negative RF and/or ACPA). A third problem was that the sample size was insufficient to reach a conclusion about the development of rare events. Neither was it possible to obtain the necessary evidence, due to the nature of the disease, as in the case of severe infections and their possible association with RTX. The amount of possible bias due to a systematic review which includes the best available evidence, only that from controlled clinical trials, but which does not consider observational studies, limits the external validity of its conclusions. This is added to possible undetected biases in the methodology. Finally, the reviews were limited to a date, and while the consensus was being developed, new evidence became available after the cut-off date which, in some cases, could not be taken into account.

Thus, some of these recommendations continue to generate doubts which are difficult to resolve in clinical practice. In this regard, more studies would be necessary which attempted to answer these pending questions, particularly in the case of recommendations based solely on expert opinion. However, the objectives of the present Consensus Document have been met, and 17 recommendations have been established, based on the best available evidence, which facilitate the use of RTX in patients with RA in clinical practice.

### Conflict of interest

This document has been funded through an unrestricted donation made to the Rheumatology Service at Hospital Universitario La Paz (AREPAZ) by Roche Farma Spain. The choice of the experts was the sole responsibility of the project coordinator (EMM). No employee of Roche Pharma participated in scientific meetings or had knowledge of its development until the project was completed. The organization of meetings and payment of fees to the experts was the sole responsibility of the Rheumatology Service at Hospital Universitario La Paz (AREPAZ).

### Annex 1.

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