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Review article

Rituximab for rheumatoid arthrits treatment: a systematic review

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ABSTRACT

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by systemic joint inflammation that often leads to significant disability. Several effective anti-TNF agents have been used, but some patients have shown an inadequate response. Rituximab is a therapeutic monoclonal antibody indicated in such cases.

Methods: We conducted a systematic review to access efficacy and safety of rituximab in patients with active RA which have or have not been treated with anti-TNF agents before, and to relate outcome with RF and anti-CCP serology. We searched major electronics databases, grey literature and searched for references manually. We used Review Manager®5.1 for meta-analysis.

Results: We included six RCTs comparing rituximab 1000 mg with placebo. Methotrexate was used by both groups. Treatment with rituximab was more effective in naïve and in anti-TNF treatment failure patients - ACR20/50/70 and EULAR response. We observed lower changes in Total Genant-modified Sharp score, erosion score and joint narrowing scores in the rituximab group, and SF-36, FACIT-T and HAQ-DI scores were also better in this group. There were no differences between groups regarding safety outcomes, with exception of acute injection reactions, which were more common on rituximab group. More RF/anti-CCP seropositive patients achieved ACR20 than RF/anti-CP negative patients in rituximab group.

Conclusion: Available data support the use of rituximab for the treatment of RA, as it is an effective and safe option for naïve and anti-TNF treatment failure patients. RF and anti-CCP seam to influence treatment results, but this inference needs further research.

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Rituximabe para o tratamento da artrite reumatoide: revisão sistemática

R E S U M O

Palavras-chave:
Artrite reumatoide
Rituximabe
Revisão sistemática
Segurança
Eficácia

Introdução: A artrite reumatoide (AR) é uma doença autoimune crônica caracterizada por inflamação articular sistêmica que, com frequência, leva a significativa incapacitação. Vários agentes anti-TNF têm sido usados efetivamente, mas alguns pacientes demonstraram resposta inadequada. Rituximabe é um anticorpo monoclonal terapêutico indicado em tais casos.

Métodos: Realizou-se uma revisão sistemática para avaliar a eficácia e a segurança de rituximabe em pacientes com AR ativa previamente tratados ou não com agentes anti-TNF e para relacionar o desfecho com a sorologia para FR e anti-CCP. Pesquisaram-se importantes bancos de dados eletrônicos e a literatura não convencional, além de se fazer uma busca manual de referências. Para a meta-análise, utilizou-se o programa Review Manager® 5.1.

Resultados: Consideramos seis ERCs comparando rituximabe 1000 mg com placebo. Em ambos os grupos usou-se Metotrexato. O tratamento com rituximabe foi mais efetivo em pacientes jamais tratados e nos que não obtiveram sucesso com a terapia anti-TNF – critérios ACR 20/50/70 e EULAR. No grupo de rituximabe, observaram-se mudanças menos expressivas nos escores de Sharp/Genant, de erosão e de estreitamento do espaço articular; nesse grupo, os escores SF-36, FACIT-T e HAQ-DI também foram melhores. Não foram notadas diferenças entre grupos com relação aos desfechos de segurança, com exceção das reações agudas à infusão, que foram mais comuns no grupo de rituximabe. Ainda no grupo de rituximabe, um número maior de pacientes soropositivos para FR/anti-CCP alcançou ACR20, em comparação com pacientes negativos para RF/anti-CCP.

Conclusão: Os dados disponíveis falam em favor do uso de rituximabe para o tratamento da AR, como opção efetiva e segura para pacientes jamais tratados ou que não obtiveram sucesso com o tratamento anti-TNF. FR e anti-CCP parecem influenciar os resultados do tratamento, mas essa inferência ainda está à espera de futuras pesquisas.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by symmetrical joint inflammation that often evolves into erosive joint damage.[1-3] Its prevalence and incidence vary among countries, affecting 2% of Argentina's population and over 10% of the U.S. population.[4] In addition to the articular manifestations, which can lead to damage and functional disability, the disease is related to systemic manifestations and an increase in cardiovascular mortality.[5]

The development of anti-TNF monoclonal antibodies shed light on the treatment of those patients who have failed the first-line therapy, in which synthetic disease modifying drugs (DMD) such as methotrexate (MTX), sulfasalazine and leflunomide are used.[6-8] However, after one year of treatment, approximately 20% of patients abandoned treatment with anti-TNF due to its ineffectiveness.[9] To work around this situation, the use of a different therapeutic target is an interesting alternative.

Rituximab is a monoclonal antibody that selectively depletes peripheral CD20+ B cells. Evidence supports its use in combination with MTX in patients who have failed anti-TNF therapy and in those naïve to treatment with these agents.[10-13] However, the patients' response may be incomplete, indicating the necessity to investigate biomarkers that have predic-

tive or prognostic value, to assist in choosing the best treatment strategy. Rheumatoid factor (RF) is an IgM antibody targeted to the constant region of IgG. The anti-cyclic citrullinated peptide (anti-CCP) antibody has more specificity for RA, relating to a more aggressive disease. Both markers are used for the diagnosis of RA and its titration corresponds to the disease activity.[14]

The objectives of this review were to evaluate the safety and efficacy data of rituximab, as well as to illustrate the influence of RF and anti-CCP in the outcome of treatment of patients with active RA.

Methods

This systematic review (SR) is part of a larger trial that also includes infliximab, adalimumab and etanercept, designed to evaluate the efficacy and safety of these agents in the treatment of RA. We conducted this trial according to the Cochrane handbook[15] and prepared the manuscript using PRISMA Statement as reporting guidance.[16]

Eligibility criteria

Randomized controlled trials (RCTs) comparing a scheme with rituximab versus without rituximab in the treatment of RA in patients over 18 years of age were eligible. We excluded

trials with less than a total of 30 participants, pilot trials and dosage comparison.

Search for trials

We investigated the databases EMBASE (until April 2012), Cochrane Register of Controlled Trials (CENTRAL; until June 2012), MEDLINE (via PubMed; until July 2012) and LILACS (until October 2012) in order to to identify potentially eligible articles in English, Spanish or Portuguese languages. For manual search we investigated meetings' annals (American College of Rheumatology, 2010 and 2011; European League Against Rheumatism, 2010, 2011 and 2012) dissertations and theses' banks (OpenThesis, National Library of Australia – Trove, Biblioteca Digital Brasileira de Teses e Dissertações from USP, Theses Database of Capes, Pro Quest Dissertation & Theses Database) and reference lists of articles included in other SRs. We searched ongoing trials and unpublished trials in the databases of ClinicalTrials.gov and EUClinical Trials Register records.

Outcome measurements

We considered as primary outcome measures: ACR20, ACR50 and ACR70.[17] The secondary outcome measures were EULAR responses,[18] individual components of ACR, disease activity measured by baseline DAS28-ESR change, SF-36 scores,[19,20] fatigue assessed by FACIT-F[21] and adverse events (AE) .

Study selection and data extraction

We performed the assessment of the eligibility of the trial and data collection, in a standard form, in duplicate and, when necessary, a third reviewer solved disagreements. Authors of the papers were contacted when there was any difficulty in extracting data. We organized the trials according to the previous use of DMD.

Quality assessment and risk of bias of included trials

We assessed the methodological quality using the modified Jadad scale[22] and the risk of bias by Cochrane Collaboration tool.[23] The trial was considered high risk if presented a possibility of high risk of bias in at least one of the criteria evaluated. We calculated the interobserver agreement using Kappa statistics[24] using SPSS® 17 software, which we considered excellent for Jadad scale; Kappa = 0.83 ± 0.60 (SD), and substantial for assessing risk bias; Kappa = 0.71 ± 0.69. We also checked conflicts of interest declared by authors of the included articles.

Statistical analysis

We used the Review Manager® 5.1 software to conduct the meta-analyses using the random effects model and considered those analyses with $I^2 > 40\%$ and P value of chi-squared test < 0.10 with substantial heterogeneity.[25] The causes of heterogeneity were investigated by the exclusion of one trial at a time and subsequent verification of the change in the values of I^2 and P. For dichotomous outcomes, we used the relative risk (RR) with confidence interval (CI) of 95% and standard deviation as a measure of association. Continuous outcomes were qualitatively evaluated and presented as mean ± SD. We planned subgroup analyses considering seropositivity for RF and anti-CCP and developed a sensitivity analysis using participant type for primary outcomes. We assessed meta-analyses' publication bias by funnel chart.

Results

Results of the Search

After review by title and abstract, 249 references for rituximab, infliximab, adalimumab and etanercept were considered eligible. Six RCTs were enrolled on rituximab, comprising 15 published articles (Fig. 1).
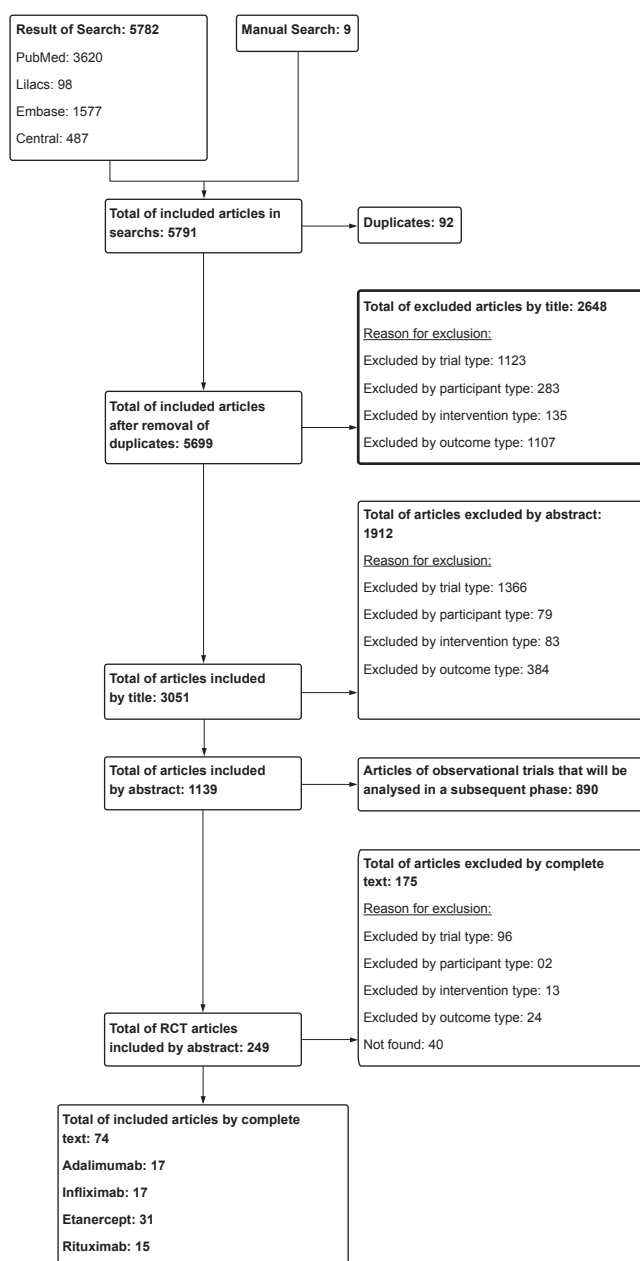

Fig. 1 – Flowchart of selection of trials.

We included 15 trials in progress, and one of them was terminated prematurely in some research centres without stated justification (2008-002381-55). A trial was completed, but we could not find the publication of the results (NCT01117129). We did not include any dissertation or thesis.

Trial characteristics

The characteristics of RCTs included are shown in Table 1. We evaluated a total of 2,139 patients with active disease, of which 1,198 used rituximab 1,000 mg twice with an interval of 15 days. MTX was used as co-treatment for all patients. The participants averaged 50 years of age, and 80% were female. The inclusion criteria of the trials were similar in terms of the diagnostic criteria – all followed the classification criteria of the American College of Rheumatology (ACR).[26]

One trial evaluated outcomes in 52 and 104 weeks of MTX naïve participants who had, on average, less than one year of diagnosis.[27-29] The baseline data of participants in this trial were similar to those in the other trials, with the exception of the radiographic score, much lower in those newly diagnosed patients. In the other five trials, the participants had active disease despite MTX use and averaged more than seven years of disease evolution. In two trials, the participants were naïve for anti-TNF, while the outcomes were presented for 24,[30] 48 and 104 weeks.[31-34] In the other three trials, the participants exhibited treatment failure with anti-TNF agent, while the outcomes were presented after 24 weeks of follow-up (Table 1).[35-41]

One trial evaluated the effectiveness of the second administration of rituximab in patients in whom the first application cycle was not sufficient to achieve remission, i.e., DAS28-ESR < 2.6.[41] In this trial, all participants received rituximab in an open phase. After 24 weeks of follow-up, those patients who did not achieve remission were randomized to receive re-treatment with rituximab or placebo and were followed for another 24 weeks. We considered the results of this part of the trial in the meta-analyses.

Assessment of methodological quality and risk of bias

All included trials had high methodological quality (Jadad score, modified = 5). The risk of bias assessment showed that the methods of generation of allocation sequence and of ensuring allocation confidentiality were considered adequate in only one RCT.[27-29] For the remaining domains, all trials had low risk of bias (Fig. 2).

Conflicts of interest and publication bias

All included trials were funded by the pharmaceutical industry and only one report[36] did not declare a conflict of interests. The funnel plot suggested publication bias, but this analysis could not be considered robust, considering that the number of included trials was small.

Primary outcomes

The meta-analyses that evaluated ACR measures after 24 weeks of treatment included studies whose participants were naïve or had failed with anti-TNF treatment (n = 1,640). In general, more patients in rituximab group achieved ACR20, ACR50 and ACR70 compared to placebo. However, these analyses showed substantial heterogeneity, and the subset of patients naïve to anti-TNF displayed a robust result. But it is notewor-

Table 1 – Summary of characteristics of included trials							
Study	N	Women (%)	Age (years ± DP)	Disease duration (years ± DP)	Previous use of MMCD (others than MTX; no. ± DP)	Previous use of anti-TNF	
						N (%)	No. (DP)
MTX virgins IMAGE [29-31]							
placebo	249	77	48,1 (12,7)	0,91 (1,1)	30	-	
rituximab	250	85	47,9 (13,3)	0,92 (1,3)	31	-	
Anti-TNF virgins Edwards [33-36]							
placebo	40	80	54 (11)	11 (7)	2,6 (1,3)	-	
rituximab	40	75	54 (12)	12 (7)	2,5 (1,4)	-	
SERENE [32]							
placebo	172	85,5	52,16 (12,390)	7,48 (7,642)	1,1 (1,10)	-	
rituximab	170	81,2	51,30 (12,644)	6,61 (7,294)	1,1 (1,11)	-	
Failure with Anti-TNF DANCER [37,38]							
placebo	122	79,5	50,8 (11,7)	9,6 (7,7)	2,2	27	
rituximab	122	76,2	52,1 (10,9)	11,3 (8,5)	2,5	31,1	
REFLEX [39-42]							
placebo	201	82	52,89 (12,31)	11,74 (7,68)	2,4 (1,8)	IFX: 81; ADA: 18; ETA: 50	
rituximab	298	81	52,24 (12,20)	12,15 (8,4)	2,6 (1,8)	IFX: 71; ADA: 23; ETA: 55	
SUNRISE [43]							
placebo	157	79	54 (11)	11 (8,5)	4,1 (1,9)*	1: 53; 2: 35; 3: 12†	
rituximab	318	81	54 (11)	12 (9,2)	4,1 (2,0)*	1: 57; 2: 32; 3: 11	

ADA adalimumab, *ETA* etanercepte, *IFX* infliximab
* Including anti-TNF, † 1, 2, 3 mean one, two and three agents anti-TNF, respectively.
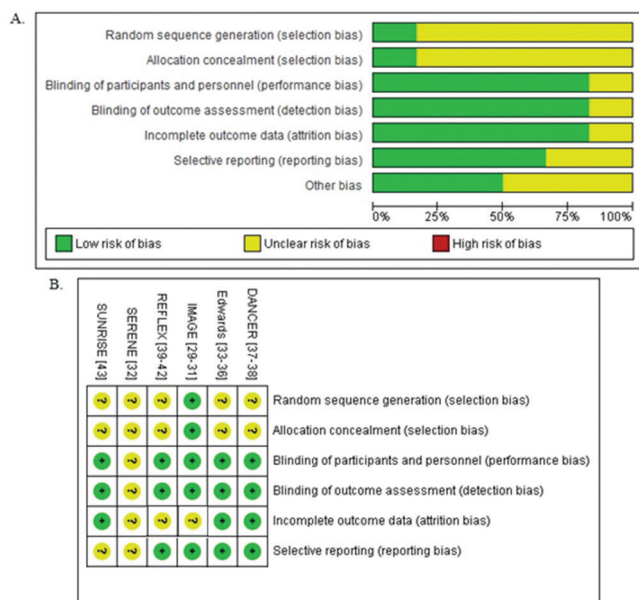
Fig. 2 – Assessment of risk of bias using the Cochrane Collaboration tool. A. Graph of risk of bias of all trials included in this review, presented by author names of each trial and their respective percentages in each item of the assessment. B. Summary of risk of bias of the trials (represented by trial names) with their respective result in each item of assessment.

thy that this subgroup is small, n = 22; then, more studies are needed to confirm the result (Fig. 3). In the analyses of heterogeneity, it was noted that one trial reported favourable results with the use of rituximab, a statistically significant result, but less expressive than the other RCTs.[41] After its exclusion of the meta-analyses, the results favouring the use of rituximab persisted, and the heterogeneity decreased to ACR20, ACR50 and ACR70, respectively RR (95% IC) = 2.24 (1.86-2.69; I^2 = 15 %; P = 0.32) , RR = 2.86 (2.07-3.94; I^2 = 0%; P = 0.90) and RR = 3.91 (1.84-8.31; I^2 = 50%; P = 0.11).

In the pooled analysis of two trials (n = 579), we did not perceive any benefits from the use of the biological agent compared to placebo for ACR20 until 48-52 weeks and 104 weeks of follow-up.[27-29,31-34] The ACR50 and ACR70 results did not favour the use of rituximab until 48-52 weeks, although they have favoured its use till 104 weeks. This fluctuation of the presence or absence of benefit may be related to the small number of participants. Furthermore, the type of patients in these two trials was different: one trial evaluated MTX-naïve patients with less than one year of disease evolution,[29-31] and the other evaluated patients naïve to anti-TNF with more than ten years of diagnosis.[31-34]

Secondary outcomes

In general, the group of patients who used rituximab achieved a statistically significant improvement compared to placebo in all individual components of the ACR, including in relation to the average change in HAQ-DI score. The meta-analysis of the number of participants who showed a change in HAQ-DI

score ≥ 0.22 after 24 weeks from baseline (n = 1,161) pointed to the benefit of rituximab use with substantial heterogeneity, probably due to the SERENE trial.[30] The joint analysis of two trials (n = 562) showed no statistically significant difference between groups after 48-52 weeks. After 72 weeks, there was no difference between intervention and control groups of patients with more than ten years of diagnosis.[31] But after 104 weeks there was a difference which benefited the use of rituximab in patients with less than one year of disease progression (Table 2).[27-29]

After 24 weeks of follow-up, more patients in rituximab group compared to placebo achieved good (n = 1,637) and moderate (n = 1,393) EULAR responses, but with substantial heterogeneity (data not shown). Regarding good EULAR response, in the analysis of heterogeneity (and after removal of the SERENE trial)[30] the outcome continued favouring rituximab. The analysis of the trial that evaluated recently diagnosed patients showed that the benefit of rituximab remained after 52 and 104 weeks of follow up.[27-29] The heterogeneity of good and moderate EULAR responses diminished with the exclusion of those participants with therapeutic failure with anti-TNF,[35,39] and with the exclusion of participants naïve to anti-TNF, respectively.[30-34] The change of baseline DAS28-ESR was generally higher in rituximab group compared to placebo after 24, 52 and 104 weeks of follow-up. A pooled analysis of two trials showed no difference between groups in relation to the outcomes of low activity of the disease and remission till 24 weeks of follow-up;[30,41] however, more patients in rituximab group compared to placebo achieved these targets after 52 and 104 weeks in the trial that evaluated patients with less diagnosis time (Table 2).[27-29]

The summarized physical component (SPC) change of SF-36 was superior and statistically significant in rituximab group compared to placebo after 24 and 52 weeks of follow-up. On the other hand, the results of the summarized mental component (SMC) change were divergent: two trials showed no difference between groups and other two showed a statistically significant difference. In joint analyses, the chances of achieving a mean change of SPC > approx. 5 and SMC > approx. 5 after 24 weeks of treatment were higher and statistically significant in participants who used rituximab. The heterogeneity of the first analysis was substantial, but the individual reports favoured rituximab (Table 2).

The group using rituximab had benefits with respect to the fatigue measured by FACIT-F, as compared to placebo after 24 and 52 weeks of treatment. Likewise, the chance of achieving a clinically significant lower change after 24 weeks of treatment, i.e., a mean change in FACIT-F score ≥ approx. 3.5, was higher in participants who used the biological agent (Table 2).

Two trials reported that the participants using rituximab achieved better results in radiological outcomes than those in placebo.[35-40] A joint analysis (n = 934) showed that the participants treated with the biological agent had lower probability of progression by the Sharp score (modified) compared to placebo + MTX after 104 weeks of treatment (Table 2).

Regarding safety, there was no difference between intervention and control groups regarding the incidence of severe AEs, malignancies and death. Infection was the most common AE in the trials. In any case, the rate of occurrence of serious infections was low, about 2% after 24 months of treatment in both groups, increasing to approximately 6% after this pe-

riod. Acute reaction to the first infusion was more common in rituximab group compared to placebo. In the second infusion, we could observe an opposite association; more patients in placebo group exhibited a reaction. There were no deaths related to this outcome in the RCTs included (Table 2).

The loss for total follow-up was higher in placebo group compared to rituximab. Individually, the trials were different as the magnitude of the loss, ranging from 2.5% to 14% in rituximab group and from 5% to 35% in placebo group. The losses due to lack of efficacy were more frequent in placebo group and the rates of loss due to AEs were not different between groups (Table 2).

Subgroup analysis – RF and anti-CCP

With the exception of one trial that included only rheumatoid factor-positive (RF+) participants, the groups of other trials were balanced with regard to the inclusion of positive and negative participants.[31-34] These latter were always minority and were not included in the overall analysis of a trial.[35,36] The distribution of patients in relation to anti-CCP was reported by a trial, with homogeneity between groups.[41]

With respect to ACR20, we could observe a smaller proportion of responders in the FR- group when compared to FR+. We could also observe that in the group FR+ the number

A.

Study or subgroup	Rituximabe Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
Anti-TNF virgins								
Edwards [33]	29	40	15	40	17.4%	1.93 [1.24, 3.01]	2004	
SERENE [32]	86	170	40	172	20.3%	2.18 [1.60, 2.96]	2010	
Subtotal (95% CI)		210		212	37.7%	2.09 [1.62, 2.70]		
Total events	115		55					
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.67); I² = 0%								
Test for overall effect Z = 5.70 (P < 0.00001)								
Failure with Anti-TNF								
DANCER [37]	66	122	34	122	19.9%	1.94 [1.40, 2.70]	2006	
REFLEX [39]	152	298	36	201	20.1%	2.85 [2.08, 3.91]	2006	
SUNRISE [43]	172	318	71	157	22.3%	1.20 [0.98, 1.46]	2010	
Subtotal (95% CI)		738		480	62.3%	1.86 [1.07, 3.22]		
Total events	390		141					
Heterogeneity: Tau² = 0.22; Chi² = 23.54, df = 2 (P = 0.00001); I² = 92%								
Test for overall effect Z = 2.20 (P = 0.03)								
Total (95% CI)		948		692	100.0%	1.92 [1.36, 2.73]		
Total events	505		196					
Heterogeneity: Tau² = 0.13; Chi² = 26.49, df = 4 (P = 0.00001); I² = 85%								
Test for overall effect Z = 3.66 (P = 0.0003)								
Teste for subgroup differences: Chi² = 0.15, de = 1 (P = 0.70). I² = 0%								

0.1 0.2 0.5 1 2 5 10
Favours placebo Favours Rituximab

B.

Study or subgroup	Rituximabe Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
Anti-TNF virgins								
Edwards [33]	17	40	5	40	15,8%	3.40 [1.39, 8.33]	2004	
SERENE [32]	44	170	16	172	21,8%	2.78 [1.64, 4.73]	2010	
Subtotal (95% CI)		210		212	37,6%	2.93 [1.86, 4.63]		
Total events	61		21					
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%								
Test for overall effect Z = 4.61 (P < 0.00001)								
Anti-TNF failure								
REFLEX [39]	27	298	5	201	15.1%	3.64 [1.43, 9.30]	2006	
DANCER [37]	41	122	16	122	22.0%	2.56 [1.52, 4.31]	2006	
SUNRISE [43]	92	318	41	157	25.3%	1.11 [0.81, 1.52]	2010	
Subtotal (95% CI)		738		480	62.4%	2.01 [0.95, 4.26]		
Total events	160		62					
Heterogeneity: Tau² = 0.34; Chi² = 11.39, df = 2 (P = 0.003); I² = 82%								
Test for overall effect Z = 1.83 (P = 0.07)								
Total (95% CI)		948		692	100.0%	2.33 [1.35, 4.01]		
Total events	221		83					
Heterogeneity: Tau² = 0.28; Chi² = 17.97, df = 4 (P = 0.001); I² = 78%								
Test for overall effect Z = 3.05 (P = 0.002)								
Test for subgroup differences: Chi² = 0.70, de = 1 (P = 0.40). I² = 0%								

0.1 0.2 0.5 1 2 5 10
Favours placebo Favours Rituximab

C.

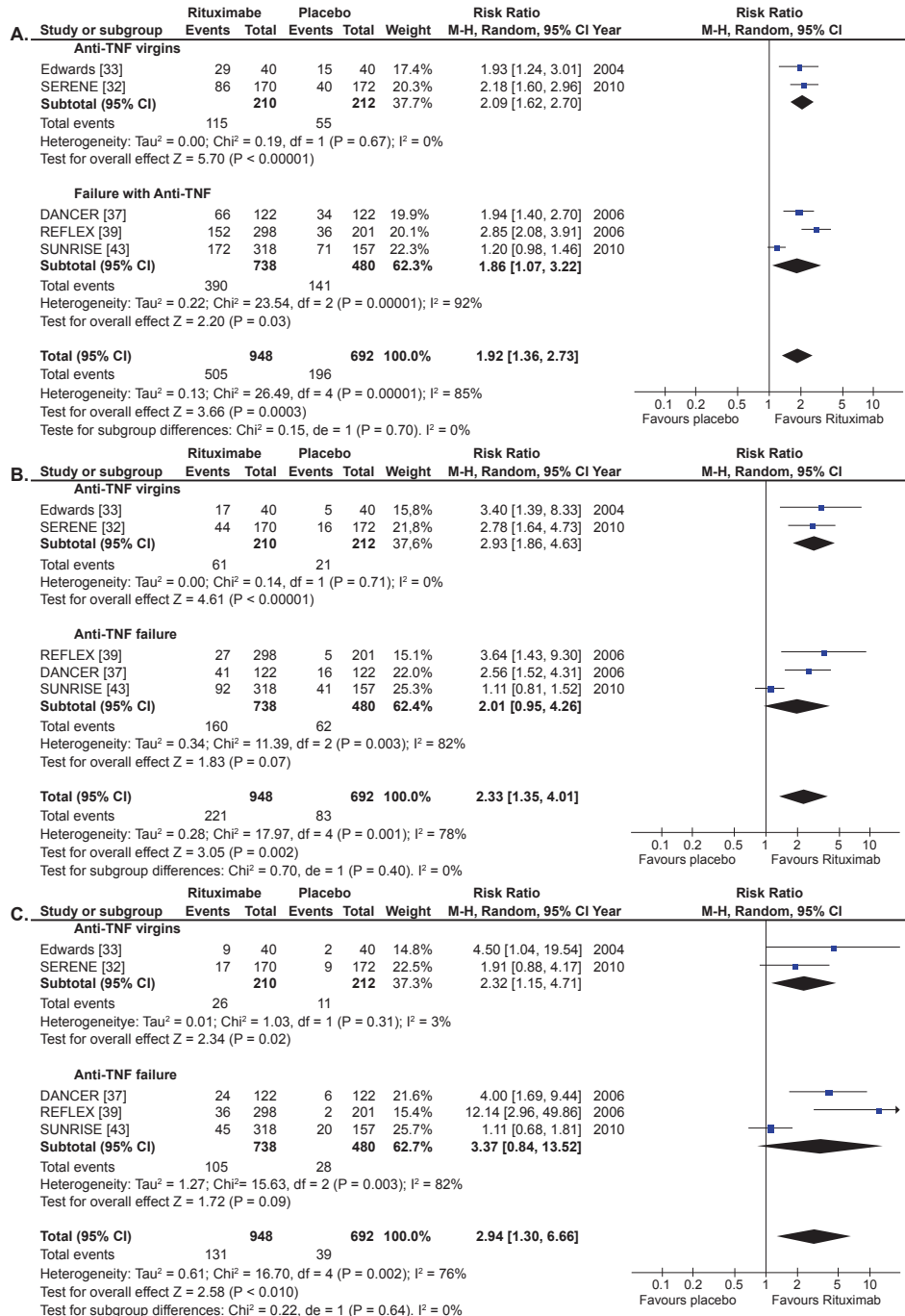| Study or subgroup	Rituximabe Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
Anti-TNF virgins								
Edwards [33]	9	40	2	40	14.8%	4.50 [1.04, 19.54]	2004	
SERENE [32]	17	170	9	172	22.5%	1.91 [0.88, 4.17]	2010	
Subtotal (95% CI)		210		212	37.3%	2.32 [1.15, 4.71]		
Total events	26		11					
Heterogeneitye: Tau² = 0.01; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%								
Test for overall effect Z = 2.34 (P = 0.02)								
Anti-TNF failure								
DANCER [37]	24	122	6	122	21.6%	4.00 [1.69, 9.44]	2006	
REFLEX [39]	36	298	2	201	15.4%	12.14 [2.96, 49.86]	2006	
SUNRISE [43]	45	318	20	157	25.7%	1.11 [0.68, 1.81]	2010	
Subtotal (95% CI)		738		480	62.7%	3.37 [0.84, 13.52]		
Total events	105		28					
Heterogeneity: Tau² = 1.27; Chi² = 15.63, df = 2 (P = 0.003); I² = 82%								
Test for overall effect Z = 1.72 (P = 0.09)								
Total (95% CI)		948		692	100.0%	2.94 [1.30, 6.66]		
Total events	131		39					
Heterogeneity: Tau² = 0.61; Chi² = 16.70, df = 4 (P = 0.002); I² = 76%								
Test for overall effect Z = 2.58 (P < 0.010)								
Test for subgroup differences: Chi² = 0.22, de = 1 (P = 0.64). I² = 0%								

0.1 0.2 0.5 1 2 5 10
Favours placebo Favours Rituximab

Fig. 3 – Forest plot depicting the statistically significant difference between rituximab and placebo in response criteria of the American College of Rheumatology (ACR) after 24 weeks of treatment. A. ACR20 (20% of improvement). B. ACR50. C. ACR70.

Table 2 – Joint analysis of the secondary outcomes of efficacy, adverse events e loss of follow-up

Outcome	Rituximab n	Placebo n	RR (95% IC)	P Value	I² (%)
HAQ-DI < 0,22					
24 weeks [32, 36, 37, 40]	629	532	1,61 (1,22, 2,12)	0,004	77
48-52 weeks [29, 36]	288	274	1,57 (0,71, 3,44)	0,02	82
72 weeks [36]	40	40	4,33 (1,34, 14,05)	-	-
104 weeks [31]	250	249	1,12 (1,03, 1,21)	-	-
Good EULAR response					
24 weeks [32, 35, 37, 39, 43]	946	619	3,37 (1,35, 8,43)	<0,0001	84
52 weeks [29]	250	249	2,32 (1,72, 3,14)	-	-
104 weeks [31]	250	249	2,10 (1,61, 2,72)	-	-
Moderate EULAR response					
24 weeks [32, 33, 39, 43]	824	569	1,62 (1,10, 2,37)	0,0001	86
Low DAS 28 activity					
24 weeks [32, 43]	488	329	1,61 (0,70, 3,72)	0,05	73
52 weeks [29]	250	249	2,13 (1,60, 2,84)	-	-
104 weeks [31]	250	249	1,93 (1,50, 2,48)	-	-
DAS 28 remission					
24 weeks [32, 43]	488	329	2,05 (0,64, 6,53)	0,06	73
52 weeks [29]	250	249	2,40 (1,65, 3,48)	-	-
104 weeks [31]	250	249	2,49 (1,72, 3,61)	-	-
PCS (SF-36) ≥ ~5					
24 weeks [32, 40]	468	373	2.48 (1.13, 5.46)	0,0009	91
52 weeks [29]	250	249	1.21 (1.08, 1.36)	-	-
MCS (SF-36) ≥ ~5					
24 weeks [32, 40]	468	373	1,71 (1,36, 2,16)	0,53	0
52 weeks [29]	250	249	1,16 (0,98, 1,37)	-	-
FACIT-F ≥ ~3.5					
24 weeks [37, 40]	420	322	1,90 (1,60, 2,25)	0,41	0
52 weeks [29]	250	249	1,11 (1,00, 1,25)	-	-
No progression at mTSS					
24 weeks [29]	244	232	1,19 (1,04, 1,36)	-	-
52 weeks [29]	244	232	1,21 (1,03, 1,41)	-	-
96-104 weeks [31,42]	252	420	1,53 (1,29, 1,81)	0,84	0
No progression at erosion score					
24 weeks [40]	268	177	1,10 (0,95, 1,28)		
96-104 weeks [31,42]	514	420	1,50 (1,26, 1,78)	0,20	39
Serious adverse events					
24 weeks [32, 33, 37, 39, 43]	1028	727	0,98 (0,70, 1,38)	0,44	0
48-52 weeks [29, 33]	290	289	0,93 (0,57, 1,52)	0,91	0
104 weeks [31]	250	249	0,78 (0,51, 1,19)	-	-
Serious infections					
24 weeks [32, 33, 37, 43]	720	518	0,86 (0,36, 2,04)	0,74	0
48-52 weeks [29, 33]	290	289	0,68 (0,30, 1,57)	0,34	0
104 weeks [31]	250	249	0,63 (0,31, 1,27)	-	-
Reaction at the infusion site					
1° infusion [29, 32, 33, 37, 39, 43]	1280	976	1,55 (1,30, 1,86)	0,42	0
2° infusion [29, 32, 37, 39, 43]	1238	936	0,79 (0,63, 0,99)	0,83	0
Losses of follow-up					
24 weeks [32, 33, 37, 39, 43]	1030	727	0,47 (0,29, 0,76)	0,18	36
48-52 weeks [29, 33]	290	289	0,54 (0,04, 7,56)	0,0004	92
72 weeks [36]	40	40	0,48 (0,28, 0,82)	-	-
104 weeks [31, 36]	290	289	0,48 (0,28, 0,82)	-	-
Losses by lack of efficacy					
24 weeks [33, 37]	232	189	0,27 (0,16, 0,45)	0,85	0
48-52 weeks [29, 33]	290	289	0,19 (0,08, 0,50)	0,74	0
72 weeks [37]	40	40	0,44 (0,15, 1,33)	-	-
104 weeks [36]	40	40	0,24 (0,09, 0,64)	-	-
Losses by AE					
24 weeks [32, 33, 37, 39, 43]	1028	727	1,47 (0,53, 4,09)	0,15	41
48-52 weeks [29, 33]	290	289	0,95 (0,17, 5,34)	0,21	37
72 weeks [36]	40	40	0,33 (0,04, 3,07)	-	-
104 weeks [31, 36]	290	289	0,38 (0,17, 0,85)	0,67	0

AE Adverse events, DAS 28 Disease Activity Score 28-joint assessment for swelling and tenderness, EULAR European league Against Rheumatism, FACIT-F Functional Assessment of Chronic Illness Therapy – Fatigue, HAQ-DI Health Assessment Questionnaire – Disability Index, MCS Mental Component Summary, mTSS Mean change in Genant-modified Sharp radiographic score, PCS Physical Component Summary, SF-36 Medical Study Short-Form Health Survey.

of participants treated with rituximab achieved ACR20 that was statistically significant compared to placebo, but with substantial heterogeneity; RR = 1.71 (1.19-2.48), I^2 = 90%; P < 0.00001), and this was explained by the exclusion of any trial. In FR- group, there was no difference between experimental and control groups; however, the analysis also showed substantial heterogeneity; RR = 1.16 (0.73-1.85; I^2 = 71%; P = 0.02), with no explanation (Fig. 4).

The IMAGE trial also assessed ACR50, ACR70, good EULAR response, low activity, and remission of disease according to DAS28-ESR, percentage of participants without radiological progression and mean change in modified Sharp score in relation to seropositivity for RF and anti-CCP.[27] After 52 weeks of follow-up, only the mean change in modified Sharp score was statistically different between rituximab and placebo in the analysis of participants FR+. In this trial, all participants FR- were anti-CCP-.

According to Tak et al.,[29] after 104 weeks of follow-up the participants FR+ and/or anti-CCP+ in rituximab group had a higher probability of not showing radiological progression compared to placebo; odds ratio (OR, 95% CI) = 2.228 (1.513-3.281).[29] In the analyses of the participants FR- and anti-CCP-, rituximab group showed a tendency to higher probability of non-progression compared to placebo, but without statistical significance; OD = 1.833 (0.558-6.027). Regarding ACR50, the group differences were statistically significant in the subgroup FR+ and/or anti-CCP+. The participants FR- and anti-CCP- that used placebo achieved ACR50 in greater proportion

versus intervention group; however, these analyses were not statistically significant.

In SERENE trial,[30] after 24 weeks of treatment (the controlled trial phase) there was no difference in relation to the change in DAS28-ESR among patients FR+ and FR- who used rituximab. In the open phase of the trial (24 to 48 weeks of treatment), the patients who had not achieved remission were re-treated with the biological agent; more patients FR+ achieved ACR50 and ACR70, compared to patients FR-.

Discussion

The results of efficacy and safety of this RS point to the benefit of rituximab 1000 mg applied twice at 15-day intervals associated with weekly MTX for the treatment of RA. Regarding the primary outcomes, greater number of patients achieved ACR20, ACR50 and ACR70 in rituximab group versus placebo. This result was obtained for up to 24 weeks of follow-up in patients naïve and in those patients who have failed with anti-TNF and with more than seven years of the disease; and for up to 52 weeks for patients naïve to MTX and anti-TNF and newly diagnosed. These results can also be applied to good and moderate EULAR responses.

In comparison to individual components of ACR response criteria, summarized physical and mental components of SF-36, fatigue measured by FACIT-F and in relation to the change in baseline DAS28-ESR, we noted better results with ritux-
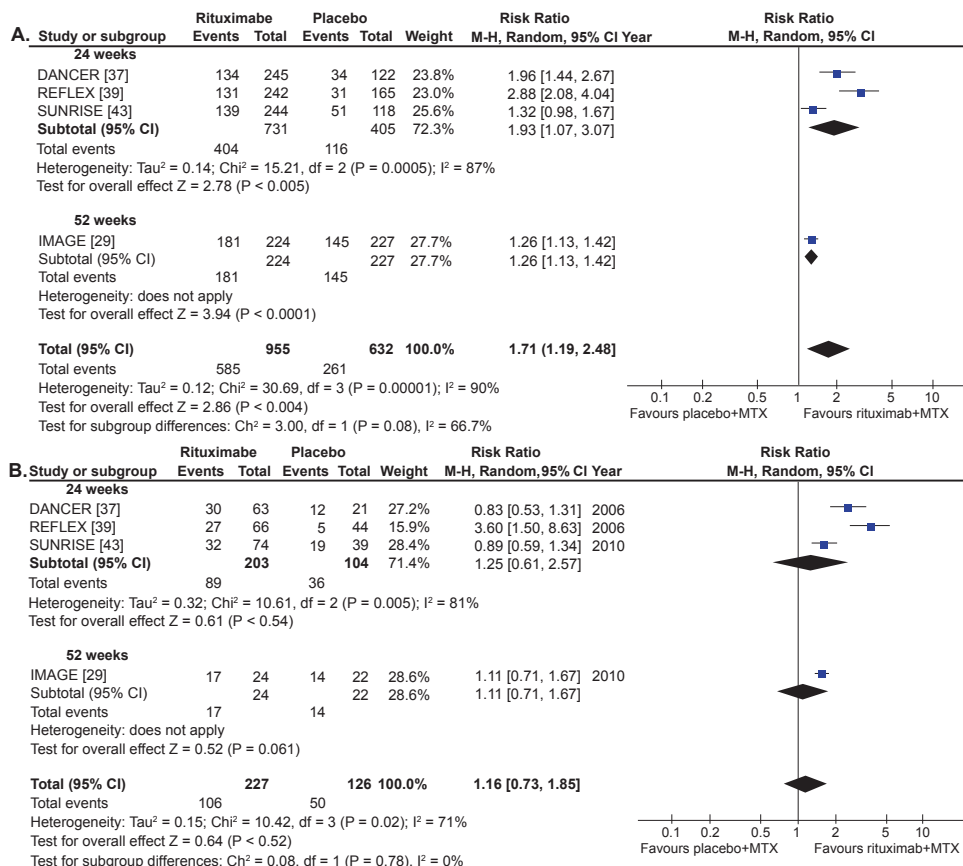

Fig. 4 – Forest-plot depicting the responses of the American College of Rheumatology ACR20 (20% improvement) of rituximab versus placebo. A. RF-positive patients. B. RF-negative patients.

imab. Remission and low disease activity were reported by three trials, despite all other trials also measured disease activity by DAS28-ESR.[27,30,41] These measures were achieved after 52 weeks of treatment for newly diagnosed patients.[27]

The prevention or minimization of the progression of joint damage is a mainstay RA treatment; however, only IMAGE[27] and REFLEX[39] performed an analysis of radiographic progression, and in both trials the participants who used rituximab achieved better results versus placebo after 104 weeks. We need more trials to strengthen the results of radiographic progression.

In this review we observed that the favourable results with rituximab according to ACR were more expressive in the trial that studied patients with less than one year of diagnosis,[27] which confirms the recommendations of ACR[7] and EULAR[8] current guidelines, pointing to the fact that the treatment of RA will be more effective if started early.

SUNRISE[41] was responsible for high heterogeneity in various analyses. In this trial, patients who did not achieve remission with an application of rituximab were randomized to re-treatment from 24th week. This trial showed benefits of rituximab versus placebo in all parameters measured, but the results were less significant than those shown by the other included trials. The authors reported that patients who achieved ACR20, ACR50 and ACR70 after the first application of rituximab were more likely to maintain its gains or improve with re-treatment with rituximab. On the other hand, patients who did not achieve such measures were not benefited with the second drug application.

Emery et al.[42] conducted a joint analysis of three RCTs and its extensions – SERENE[30] and MIRROR,[43] with 43 participants re-treated to achieve clinical remission (Treat to Target – TT) (n = 236), and DANCER,[35] and patients re-treated when necessary (RWN) (n = 257). The groups were homogeneous with respect to basal data, with the exception of disease duration, that was 3.6 and 8.5 years, respectively. Both groups have evolved to improve at every application of rituximab; however, patients in TT group achieved better results than participants RWN, regarding HAQ-DI and DAS-28. In addition, during the first four applications of rituximab, more patients discontinued the trial in RWN group compared to TT group, mainly due to an insufficient therapeutic response.

In general, rituximab in association with MTX proved to be as safe as MTX. Acute infusion reaction was the most common event and was more frequent in rituximab group compared to placebo, but only in the first infusion. Van Vollenhoven et al.[44] conducted a joint analysis of six RCTs (SERENE,[30] DANCER,[35] REFLEX,[37] SUNRISE,[41] MIRROR[43] and SIERRA[45]), including extensions of open phase DANCER and REFLEX trials, and demonstrated that the overall incidence was 359.6 adverse events per 100 patients-year (95% CI 354.4-364.9). The AE rate was higher after the first application, falling to 329.44 events per 100 patient-years (320.59-338.53) after the second application, remaining stable until the subsequent five years of monitoring. The most common event detected was an acute infusion reaction, occurring in 25% of participants. Other AEs occurring in ≥ 10 % of the assessed population were infections, not including RA exacerbations. In this review, the mortality rate was 0.6 per 100 patient-years, and there were no deaths due to infusion reactions.

Loss of participants is critical in epidemiological trials, since the analysis, even if done by intention to treat, may be compromised. In the included RCTs, generally the losses did not exceed 20% and total loss and loss due to lack of efficacy were higher in placebo group compared to rituximab. The loss rates for EA were not different between groups.

Finckh et al.[46] conducted a prospective cohort trial to assess which subset of patients with RA and with anti-TNF failure obtain benefit with the exchange for rituximab versus exchange for another anti-TNF agent. Blom et al.[47] evaluated a retrospective cohort of patients who had failed with two anti-TNF agents and who were treated with a third anti-TNF drug (n = 64), or with rituximab (n = 90). These authors concluded that patients using rituximab obtained better results with respect to disease activity versus patients using anti-TNF agent.[46,47] Both trials concluded that in case of failure with an anti-TNF treatment, the introduction of a biological agent with different mechanism of action, such as rituximab, would be the best conduct, increasing the efficacy of rituximab as third-line treatment.

Current guidelines from ACR for RA have established, as an alternative, the use of rituximab if the patient exhibits low activity associated with a poor prognosis, or moderate/high activity.[7] Current guidelines from EULAR recommend the use of rituximab only after a failure with anti-TNF, despite reiterating that the approval of rituximab for use as a second line option has been discussed in Europe.[8] The results of this trial point to a possible benefit of rituximab for patients naïve to anti-TNF. However, these findings should be evaluated with caution, since we could not find any RCT to evaluate the exchange by an anti-TNF, after failure of rituximab. The possibility of use of rituximab as a second line drug and of an anti-TNF as a third drug needs to be more deeply evaluated.

Data from IMAGE,[27] DANCER,[35] REFLEX,[37] and SUNRISE[41] were used in subgroup analysis for seropositivity; we observed a trend towards greater efficacy of rituximab, compared to placebo, in the subgroup FR+ and/or anti-CCP+; however, the observed heterogeneity was high. In any case, we used the method of random effects, which may have underestimated differences between groups. The predictive value of assessment of seropositivity needs to be further explored in future clinical trials, as well as the role of other biomarkers that may be useful for deciding on the best treatment to be used for each specific type of patient.

This RS has some limitations. The possibility of selection bias could not be excluded from most trials. Moreover, all included trials were funded by pharmaceutical industry, which may have led to an overestimation of the results. Systematic reviews showed that industry-funded trials tend to show favourable results for its products, compared to not funded trials.[48,49]

An inherent limitation of clinical trials, which is reflected in this RS, is the fact that they were conducted in carefully selected populations. Thus, the profile of patients does not reflect the reality, especially in relation to treatment adherence (since these patients are followed more strictly) and to comorbidities, since they exclude patients with multiple comorbidities. Depression, hypertension and diabetes, for example, negatively influence the quality of life, functionality, results and prognosis of subjects with RA.[50]

Moreover, the analysis of which type of participant would be more benefited with the use of rituximab is not conclusive, since few trials within each group (MTX-naïve and anti-NPT-naïve) were included. In general, the efficacy analyses were heterogeneous. Nevertheless, it was possible to assess the direction of the effect that showed benefit with the use of rituximab in all outcomes assessed.

Conclusion

The trials included in this RS showed that rituximab is effective and safe compared to placebo for the treatment of RA, particularly in patients with a recent diagnosis. The effectiveness was also observed both in naïve patients to anti-TNF as in those whose treatment with these agents had failed. The use of rituximab was well tolerated by all patient subtypes. More trials are needed to evaluate the role of RF and anti-CCP antibody in predicting success in the treatment of RA with rituximab, but there is indication that RF+ and anti-CCP+ patients exhibit a better response to this biological agent.

Conflicts of Interest

Coauthor Adriana Maria Kakehasi declares conflict of interest, as she received education grant from Abbott.

REFERENCES

1. McInnes IB and Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365:2205-2219.
2. Minaur NJ, Jacoby RK, Cosh JA, Taylor G, Rasker JJ. Outcome after 40 years with rheumatoid arthritis: A prospective study of function, disease activity, and mortality. J Rheumatol. 2004;31; Suppl 69:3-8.
3. Scott DL, Pugner K, Kaarela K, Doyle DV, Woolf A, Holmes J, Hiek K. The links between joint damage and disability in rheumatoid arthritis. Rheumatology. 2000;39:122-132.
4. Alamanos Y, Voulgari PV, Drosos AA. Incidence and Prevalence of Rheumatoid Arthritis, Based on the 1987 American College of Rheumatology Criteria: A Systematic Review. Semin Arthritis Rheum. 2006;36:182-188.
5. Gonzalez A, Kremers HM, Crowson CS, Nicola PJ, Davis JM, Therneau TM, Roger VL, Gabriel SE. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum. 2007;56:3583-3587.
6. Aaltonen KJ, Virkki LM, Malmivaara A, Konttinen YT, Nordstro DC, Blom M. Systematic review and meta-analysis of the efficacy and safety of existing tnf blocking agents in treatment of rheumatoid arthritis. PLoS ONE. 2012; : e30275. doi:10.1371/journal.pone.0030275.
7. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM *et al*. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Rheum. 2012;64:625-639.
8. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2010;69:964-975.
9. Gómez-Reino JJ, Rodríguez-Lozano C, Campos-Fernández C, Montoro M, Descalzo MA, Carmona L, on behalf of the BIOBADASER 2.0 Study Group Change in the discontinuation pattern of tumour necrosis factor antagonists in rheumatoid arthritis over 10 years: data from the Spanish registry BIOBADASER 2.0 Ann Rheum Dis. 2012;71:382-385.
10. Volkmann ER, Agrawal H, Maranian P and Furst DE. Rituximab for rheumatoid arthritis: A meta-analysis and systematic review. Clinical Medicine Insights: Therapeutics. 2010;749-760.
11. Hernández-Cruz B, García-Arias M, Ariza RA, Molab EM. Rituximab in rheumatoid arthritis: A systematic review of efficacy and safety. Reumatol Clin. 2011;7:314-322.
12. Lee YH, Bae S-C, Song GG. The efficacy and safety of rituximab for the treatment of active rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. Rheumatol Int. 2011;31:1493-1499.
13. Malottki K, Barton P, Tsourapas A, Uthman AO, Liu Z, Routh K *et al*. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. Health Technology Assessment. 2011;15:1-278.
14. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO *et al*. Rheumatoid Arthritis Classification Criteria. Arthritis Rheum. 2010;62:2569-2581.
15. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updatet in mar. 2011]. The Cochrane Collaboration, 2011. Available from: www.cochrane-handbook.org.
16. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Brit Med J. 2009;339:b2700.
17. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C *et al*. American-College-of-Rheumatology preliminary definition of improvement in rheumatoid-arthritis. Arthritis Rheum. 1995;38:727-735.
18. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Clin Exp Rheumatol. 2005;23(5 Suppl 39):S93-99.
19. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey: I. Conceptual framework and item selection. Med Care. 1992;30:473-483.
20. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993;31:247-263.
21. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005;32:811-819.
22. Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J *et al*. Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. Health Technology Assessment. 2005; 9:1-+. PubMed PMID: WOS:000229604400001.
23. Higgins JPT, Altman AD, Sterne JAC. Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Altman DG, Sterne JAC, eds. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated in mar. 2011]. Disponível em: www.cochrane-handbook.org, 2012.
24. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1997;33:159-174.
25. Deeks JJ HJ, altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: HIGGINS JPT, GREEN S.

Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated in mar. 2011]. Disponível em: www. cochrane-handbook.org; 2012.

26. Arnett FC, Edworthy SM, Bloch DA, Mcshane DJ, Mcshane JF, Cooper NS et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-324

27. Tak PP, Rigby WF, Rubbert-Roth A, Peterfy CG, van Vollenhoven RF, Stohl W et al for the IMAGE Investigators. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. Ann Rheum Dis. 2010;7:39-46.

28. Rigby W, Ferraccioli G, Greenwald M, Zazueta-Montiel B, Fleischmann R, Wassenberg S, Ogale S et al. Effect of rituximab on physical function and quality of life in patients with rheumatoid arthritis previously untreated with methotrexate. Arthritis Rheum. 2011;63:711-720.

29. Tak PP, Rigby W, Rubbert-Roth A, Peterfy C, van Vollenhoven RF, Stohl W et al. Sustained inhibition of progressive joint damage with rituximab plus methotrexate in early active rheumatoid arthritis: 2-year results from the randomised controlled trial IMAGE. Ann Rheum Dis. 2012;71:351-357.

30. Emery P, Deodhar A, Rigby WF, Isaacs JD, CombeB, Racewicz AJ et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trialin patients who are biological naïve with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequater Esponders (SERENE)). Ann Rheum Dis. 2010;69:1629-1635.

31. Edwards JCW, Szczepański L, Szechiński J, Filipowicz-Sosnowska A, Emery P, Close DR et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthiritis. N Engl J Med. 2004;350:2578-2581.

32. Emery P, Sheeran T, Lehane PB, Saiedabadi N, Shaw TM. Efficacy and safety of rituximab at 2 years following a single treatment in patients with active rheumatoid arthritis. Arthritis Rheum. 2004;50:1344-50.

33. Keystone EC. B cells in rheumatoid arthritis: from hypothesis to the clinic. Rheumatology. 2005; 44(Suppl. 2):ii8-ii12.

34. Strand V, Balbir-Gurman A, Pavelka K, Emery P, Li N, Yin M et al. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. Rheumatology. 2006;45:1505-1513.

35. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechetman J, Szczepanski L, Kavanaugh A et al for the DANCER Study Group. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment. Arthritis Rheum. 2006;54:1390-1400.

36. Mease PJ, Revicki DA, Szczepanski J, Greenwald M, KIvitz A, Barile-Fabris L et al. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab – results of the dose-ranging assessment: international clinical evaluation of rituximab in rheumatoid arthritis (DANCER) trial. J Rheumatol. 2008;35:20-30.

37. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC et al for the REFLEX Trial Group. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum. 2006;54:2793-2806.

38. Keystone E, Burmester GR, Furie R, Loveless JE, Emery P, Kremer J et al. Improvement in patient-reposted outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum. 2008;59:785-93.

39. Keystone E, Emery P, Peterfy CG, Tak PP, Cohen S, Genovese MC et al. Rituximab inhibits structural joint damage in rheumatoid arthritis patients with an inadequate response to tumor necrosis factor inhibitor therapies. Ann Rheum Dis. 2009;68:216-221.

40. Cohen SB, Keystone E, Genovese MC, Emery P, Peterfy C, Tak PP et al. Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximabin combination with methotrexate. Ann Rheum Dis. 2010;59:1158-1161.

41. Mease PJ, Cohen S, Gaylis NB, Chubick A, Kaell AT, Greenwald M et al. Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: results from the SUNRISE trial. J Rheumatol. 2010; 37:917-927.

42. Emery P, Mease PJ, Rubbert-Roth A, Curtis JR, Muller-Ladner U, Gaylis NB et al. Retreatment with rituximab based on a treatment-to-target approach provides better disease control than treatment as needed in patients with rheumatoid arthritis: a retrospective pooled analysis. Rheumatology. 2011;50:2223-2232.

43. Rubbert-Roth A, Tak PP, Zerbini C, Tremblay J-L, Carreno L, Armstrong G et al. Shaw TM on behalf of the MIRROR Trial Investigators. Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a Phase III randomized study (MIRROR). Rheumatology. 2010;49:1683-1693.

44. Van Vollenhoven RF, Emery P, Bingham III CO, Keystone EC, Fleischmann R, Furst DE et al. Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. J Rheumatol. 2010;37:558-567.

45. Bingham C, Looney R, Deodhar A, Halsey N, Greenwald M, Codding C et al. Results from a controlled clinical trial (SIERRA) to evaluate primary and recall responses to immunizations in RA patients treated with rituximab [abstract]. Arthritis Rheum Suppl. 2008;58:S900.

46. Finckh A, Ciurea A, Brulhart L, Moller B, Walker UA, Courvoisier D, Kyburz D, Dudler J, Gabay C, on the behalf of the doctors of the Swiss Clinical Management Programme for Rheumatoid Arthritis. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumor necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis. 2010;69:387-393.

47. Blom M, Kievit W, Donders AR, den Broeder AA, Straten VH, Kuper I et al. Effectiveness of a third tumor necrosis factor-α-blocking agent compared with rituximab after failure of 2 TNF-blocking agents in rheumatoid arthritis. J Rheumatol. 2011;38:2355-2361.

48. Bero L, Oostvogel F, Bacchetti P, Lee K (2007) Factors associated with findings of published trials of drug–drug comparisons: why some statins appear more efficacious than others. PLoS Med. 2007; 4:e184. doi:10.1371/journal.pmed.0040184.

49. Lexchin J, Bero LA, Djulbegovic B, Clark O (2003) Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ. 2003;326:1167. doi:10.1136/bmj.326.7400.1167.

50. Michaud K and Wolfe F. Comorbidities in rheumatoid arthritis. Best Pract. Res. Clin. Rheumatol. 2007;21:885-906.