

Guidelines

Use of rituximab for the treatment of rheumatoid arthritis: the Latin American context

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GLADAR (Grupo Latino Americano de Estudio de Artritis Reumatoide or Latin American Study Group for the Study of Rheumatoid Arthritis) is a large group of Latin American rheumatologists experienced in the diagnosis and treatment of RA. GLADAR reviews data on the efficacy and safety of rituximab in RA with the objective to produce evidence-based guidelines for use in Latin America. To prepare this document a geographically-balanced Latin American group of GLADAR rheumatologists ($n=18$) met in Panama during 12–14 April 2007. Prior to the meeting, the rheumatologists attending it were divided into working groups; each group was assigned a specific area to be reviewed in depth. These groups searched and distributed the literature on rituximab to all GLADAR centres for their formal input. Only original publications in the peer-reviewed literature were considered. During the meeting, the literature reviewed and the input from GLADAR rheumatologists were presented and discussed and this document was drafted. The document was forwarded to all GLADAR centres and presented to Latin American rheumatologists attending a meeting in Merida, Mexico in April 2007 and their input incorporated into the final document. A recent consensus publication has emanated from a group of European investigators; however, as opposed to their work, our consensus document deals with the particulars of the use of rituximab in Latin America. This document should help Latin American rheumatologist in the use of this new biological agent in treating RA patients.

KEY WORDS: Rheumatoid arthritis, Treatment guidelines, Biologic therapy, Anti-CD20 antibody, Rituximab, Latin America.

Introduction

In 2006, PANLAR (Pan American League of Associations of Rheumatology) and GLADAR (Grupo Latino Americano de Estudio de Artritis Reumatoide or Latin American Study Group for the Study of Rheumatoid Arthritis) published the first Latin American position paper on the pharmacological

treatment of RA [1]. In this publication, PANLAR and GLADAR reiterated the feeling of rheumatologists around the world that the main objective of therapy in RA is to achieve clinical remission, and when this is not possible, to minimize disease activity and its consequences. The ultimate goal is to preserve the patient's ability to function independently with an optimal quality of life [1]. Non-biological DMARD therapies fall short of these objectives in too many patients; the development of biological therapies for the treatment of RA has made these objectives closer to reality. Nevertheless, there are still patients who despite these newer therapies do not achieve the therapeutic goals noted above.

Etanercept was the first anti-TNF compound approved for the treatment of RA. It is a soluble receptor blocker that can be used as monotherapy, or preferentially, in combination with MTX. Etanercept improves the symptoms and signs of RA, prevents structural damage and improves physical function in patients with RA refractory to MTX therapy or in those who have not received MTX yet [2–4]. Long-term treatment with etanercept is generally well tolerated and the efficacy seems to be maintained. The 50-mg weekly dose is available in some but not all Latin American countries; this dose has comparable efficacy with the 25 mg twice weekly dose [3].

Infliximab is a chimeric monoclonal antibody which binds to both, the soluble and the membrane-bound forms of TNF resulting in the death of those cells expressing it either directly due to the antibody or through complement activation. The doses currently used varied from 3 to 10 mg/kg and, preferentially, are administered in conjunction with MTX every 6–8 weeks [5–8]. In general, infliximab has been shown to improve the symptoms and signs of RA, improve patients' function and their quality of life. In addition, patients treated with infliximab are less likely to experience progressive joint destruction [5–8].

Adalimumab is a fully humanized anti-TNF compound which as monotherapy or preferentially in combination with MTX has also proven to be beneficial in the management of patients with RA. It is

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currently recommended at a dose of 40 mg every 2 weeks. Its safety profile is probably comparable with other anti-TNF compounds and its efficacy includes the prevention of radiographic structural damage and improvement in patient's function [9–11].

There are limited data about the response to one anti-TNF compound after receiving another; best results are achieved when the switch is made because of the occurrence of adverse events than when the switch is done because of lack of efficacy [12].

Abatacept is a co-stimulatory blocking agent, which prevents the activation of T-cells and, which has been shown in randomized controlled trials at doses of 10 mg/kg every other 28 days, to have efficacy in the treatment of RA with inadequate response to MTX and anti-TNF compounds [13–16]. It can be used alone or with other non-biological DMARDs but its use in combination with anti-TNF therapy is not recommended because of the increased occurrence of serious infections [17].

Rituximab is a chimeric anti-CD20 monoclonal antibody approved in 1997 in the USA for the treatment of indolent CD20 non-Hodgkin B-cell lymphoma and in 2006, by the Food and Drug Administration in the USA and Europe by the Committee for Medicinal Products for Human Use of the European Agency for the Evaluation of Medicinal Products for the treatment of patients with RA who have had an inadequate response to TNF blockers; this was done on the basis of the proper double-blind controlled trials demonstrating improvement in the symptoms and signs of RA in patients with inadequate response to MTX [18] and anti-TNF [13]. It can be used as monotherapy or in combination with MTX [18]. Response occurs within 8–16 weeks and is sustained even after B cells are reconstituted [13, 19].

We will now review the data about the efficacy and safety of rituximab. We realize that a recent consensus publication has emanated from a group of European investigators [9]; however, as opposed to their work, our consensus document deals with the particulars of the use of rituximab in Latin America and it represents the work of GLADAR having been endorsed by all GLADAR centres (Appendix 1). To prepare this document a geographical balanced Latin American group of GLADAR rheumatologists ($n=18$) met in Panama during 12–14 April 2007. The meeting was sponsored by an unrestricted grant from Roche; however, Roche representatives were not present at the meeting, or had any saying on approving it. Prior to the meeting, the rheumatologists attending it were divided into working groups; each group was assigned a specific area to be reviewed in depth. These groups searched and distributed electronically the literature on rituximab to all GLADAR centres for their formal input. Only original publications in the peer-reviewed literature were considered. During the meeting in Panama the literature reviewed and the input from GLADAR rheumatologists were presented and discussed and this document was drafted. Categories of evidence according to Shekelle *et al.* [20] are indicated close to each reference and the strength of recommendations graded as follows is indicated close to each recommendation: Grade A: Category 1 evidence, Grade B: Category 2 evidence or extrapolation from Category 1 evidence, Grade C: Category 3 evidence or extrapolation from Category 1 or 2 evidence, Grade D: Category 4 evidence or extrapolation from Category 2 or 3 evidence.

The document was forwarded to all GLADAR centres and presented to Latin American rheumatologists attending a meeting in Merida, Mexico at the end of April 2007, and their input incorporated into the final document.

Review of the evidence

Rationale for the use of rituximab in RA

The stages involved in the pathogenesis of RA include a non-specific inflammatory phase, an amplification phase resulting from T-cell activation and finally a stage of chronic inflammation

and tissue injury. A variety of stimuli may initiate the non-specific inflammatory phase that may last for a protracted time period.

The rheumatoid synovium is characterized by the presence of a number of cytokines and chemokines secreted by activated lymphocytes, macrophages and fibroblasts. The cytokines IL-1 and TNF play an important role stimulating cells to produce collagenases and other neutral proteases that lead to joint destruction [21].

During the last few years, new data have emerged, stressing the leading role of B lymphocytes, as opposed to T lymphocytes in RA pathogenesis; these data include the results of experiments involving transgenic animal models of antibodies against glucose-6-phosphate isomerase-induced arthritis [22], the studies on the non-obese severely diabetic, combined immunodeficiency mice demonstrating that T-cell activation is B-cell dependent [23] and the description of a second biological biomarker, both for diagnosis and prognosis, namely the anti-citrullinated protein (CCP) antibodies [24, 25].

The promising results of Rituximab in clinical studies have challenged the traditional T-cell centred paradigm of the pathogenesis of RA with a new one emerging: B cells have a pathogenic role in antibody production, antigen presentation, cytokine production and T-cell co-stimulation [26]. CD20 is a B lymphocyte-restricted transmembrane protein expressed in pre-B and mature B lymphocytes but not haematopoietic stem cells, pro-B lymphocytes and plasma cells [27]. Antibodies to CD20 specifically eliminate pre-B and mature B cells without preventing their regeneration. Rituximab variable region is derived from a mouse antibody and contains a human IgG1- κ constant region and a variable region from a murine antibody IDEC-C2B8, which binds with high affinity to cells expressing the CD20 antigen. Its anti-inflammatory actions in rheumatic diseases are thought to be derived via five mechanisms: (i) activation of complement via lysis of the targeted cells; (ii) antibody-dependent cell-mediated cytotoxicity; (iii) impairment of the ability of B cells to respond to antigens, thus decreasing the production of B-cell derived cytokines, IL-6 and IL-10; (iv) Down-regulation of the T cell CD40L co-stimulatory pathway that results in a decreasing Th cell activation; and (v) promotion of apoptosis. New effects on different cell types and mechanisms of action are continuously being described and investigated [28, 29].

Summary of the evidence on the clinical efficacy of rituximab in RA

As shown in Table 1, three randomized double-blind clinical trials have been conducted to assess the efficacy of rituximab in RA [13, 18, 19].

In the first study [18], Edwards *et al.* reported on 161 patients with RF-positive active RA despite treatment with MTX who were randomized to receive one of the four treatments: oral MTX (control) (≥ 10 mg/week); rituximab (1000 mg on days 1 and 15); rituximab plus cyclophosphamide (750 mg on days 3 and 17); or rituximab plus MTX. All groups, including the control group, received a course of 17 days of corticosteroids for a total dose of 910 mg. The primary efficacy end-point was the proportion of patients achieving an ACR50 response at week 24. Secondary efficacy outcome measures included ACR20, ACR70, a change in the 28-joint disease activity score (DAS28) and response according to the European League Against Rheumatism (EULAR) response criteria [30]. Follow-up of patients was conducted up to 48 weeks. As noted in Table 2, a significantly greater proportion of patients in the rituximab plus cyclophosphamide and rituximab plus MTX groups achieved an ACR50 level of response at 24 weeks compared with the control group (MTX alone) (41 and 43% vs 13%). For the ACR20 and ACR70, all three rituximab groups were significantly superior to MTX alone at 24 weeks; in addition, in all groups treated with rituximab a significantly higher proportion of patients achieved a moderate or good EULAR

TABLE 1. Characteristics of randomized clinical trials of rituximab in RA

Author, reference; Trial name (total number of patients)	Mean age, yrs (s.d.)	Mean disease duration, yrs (s.d.)	Rituximab dose (mg)	Glucocorticoids	Concomitant MTX	Previous anti-TNF, <i>n</i> (%)	Seronegative patients, <i>n</i> (%)	Mean DAS28 (s.d.)	Primary end-point	Imputation method	Treatment duration (weeks)
Edwards <i>et al.</i> [18]; (161)	54.0 (11.0)	11.0 (7.0)	2 × 1000	2 × 100 mg MP + oral GC	One group	NS	No	6.9 (0.8)	ACR50	Con: LOCF Cat: LOCF	24 and 48
Emery <i>et al.</i> [19]; DANCER (465)	51.2 (NS)	10.4 (NS)	2 × 500	Not all groups	All groups	134 (29)	Yes (85)	6.8 (NS)	ACR20	Con: LOCF	24
Cohen <i>et al.</i> [13]; REFLEX (520)	52.5 (12.4)	12.0 (8.0)	2 × 1000 2 × 1000	2 × 100 mg + oral GC	All groups	520 (100)	Yes (113)	6.8 (1.0)	ACR20	Con: NS Cat: WE	24

NS: not stated; MP: methylprednisolone; GC: glucocorticoids; Con: continuous variables; Cat: categorical variables; LOCF: last observation carried forward; WS: worst scenario (premature withdrawals included in non-responders).

TABLE 2. Main results on ACR responses in randomized clinical trials of rituximab in RA at 24 weeks

Author, reference; Trial name (total number of patients)	Rituximab doses (<i>n</i>)	Number on placebo	ACR20			ACR50			ACR70		
			Rituximab (%)	Placebo (%)	<i>P</i> -value	Rituximab (%)	Placebo (%)	<i>P</i> -value	Rituximab (%)	Placebo (%)	<i>P</i> -value
Edwards <i>et al.</i> [18]; (161)	2 × 1000 mg (40)	40	65	38	0.025	33	13	0.059	15	9	NS
	2 × 1000 mg + CTX (41)	40	76	38	0.001	41	13	0.005	15	5	NS
	2 × 1000 mg + MTX (40)	40	73	38	0.003	43	13	0.005	23	5	0.048
Emery <i>et al.</i> [19] DANCER (465)	2 × 500 mg (124)	149	55	28	0.0001	33	13	0.001	13	5	0.029
	2 × 1000 mg (192)	149	54	28	0.0001	34	13	0.001	20	5	0.001
Cohen <i>et al.</i> [13]; REFLEX (520)	2 × 1000 mg (311)	209	51	18	0.0001	27	5	0.0001	12	1	0.0001

CTX: cyclophosphamide.

response at 24 weeks (83–85% vs 50%). All ACR responses were maintained at week 48 in the rituximab–MTX group.

In the second trial (DANCER) [19], 465 patients with moderate or severe RA despite ongoing treatment with MTX were randomized into nine treatment groups: three initial rituximab groups: rituximab placebo (*n* = 149); rituximab 500 mg (2 × 500, *n* = 124); and rituximab 1000 mg (2 × 1000, *n* = 192) on days 1 and 15 [19]. Each group was in turn randomized to receive intravenously placebo glucocorticoids, methylprednisolone pre-medication or methylprednisolone pre-medication plus oral prednisolone for 2 weeks. All patients received MTX (10–25 mg/week). Patients must have failed prior treatment with at least one but not more than five DMARDs (other than MTX) and/or biologic response modifiers. The primary efficacy analysis included only the RF-positive patients (*n* = 380). A limited number of RF-negative patients (*n* = 85) were included for a safety exploratory analysis. The primary trial end-point was the proportion of RF-positive patients achieving an ACR20 response at week 24. Secondary outcome measures were the proportion of patients achieving an ACR50 and ACR70 response, DAS28 assessment, EULAR responses, fatigue and the effect on individual parameters of the ACR improvement criteria. As shown in Table 2, significantly more patients who received 2 × 500 mg or the 2 × 1000 mg infusions of rituximab met the ACR20 response criteria at week 24 compared with the placebo-treated patients (55 and 54% vs 28%). Although ACR70 responses were numerically more frequent in the rituximab 2 × 1000 mg infusion group than in the 2 × 500 mg, the difference was very small and did not reach statistical significance. Otherwise, there were no differences between the two rituximab groups. Furthermore, glucocorticoids did not contribute significantly to the primary efficacy end-point. Secondary end-points were also significantly more frequently achieved by the Rituximab groups than by the control group. The exploratory analysis of RF-negative patients alone proved inconclusive and was confounded by an unusually high placebo response and a relatively small sample size.

The third trial (REFLEX) [13] was performed to determine the efficacy and safety of treatment with rituximab plus MTX in patients with active RA who had an inadequate response to anti-TNF therapies; 517 patients with active RA and an inadequate response to one or more anti-TNF agents were randomized to receive intravenous rituximab (2 × 1000 mg) or placebo, both with MTX. The primary efficacy end-point was the proportion of patients achieving an ACR20 response at 24 weeks. Secondary end-points were responses on the ACR50, ACR70, DAS28 and EULAR response criteria at 24 weeks. Additional end-points included scores on functional assessment including fatigue, the HAQ and the Short Form-36 (SF-36) instruments. Radiographic progression was also assessed using the Genant-modified Sharp radiographic scores at 24 weeks. As noted in Table 2, at week 24, significantly more rituximab-treated patients than placebo-treated patients demonstrated ACR20 (51 vs 18%), ACR50 (27 vs 5%) and ACR70 (12 vs 1%) responses and moderate-to-good EULAR responses (65 vs 22%). Favourable and significant differences were also observed for fatigue and SF-36 summary measures whereas radiographic progression was less evident in the rituximab-treated patients. Furthermore, fewer RF-negative than RF-positive patients achieved an ACR20 response at week 24 (41 vs 54%).

The long-term impact on physical function of a single course of rituximab in RF-positive patients with active RA despite ongoing MTX treatment was assessed [31] at 2 yrs in the subset of patients who demonstrated sustained clinical benefit following the single course of rituximab in the Edwards *et al.*'s study [18]. Although at week 104 more patients treated with rituximab plus MTX achieved ACR20, ACR50 and ACR70 responses compared with the other groups, the differences did not reach statistical significance, and the numbers in each group were very small. Continued protocol participation was highest at 48 weeks in the rituximab plus MTX group. At 2 yrs rituximab plus MTX provided higher rates of clinical improvement at each level of ACR response than the other groups, suggesting that background therapy resulted in more sustained clinical responses following treatment with rituximab. Standard effect sizes (SES) were

calculated for physician- and patient-reported measures as well as ESR and CRP at 24, 48 and 72 weeks. Overall, SES with active treatment were larger.

Table 1 summarizes the main characteristics of these randomized clinical trials whereas Table 2 summarizes the ACR responses on each of them.

In summary, there is evidence on the efficacy of rituximab on RF-positive RA patients [13] (Evidence Ib). In the DANCER study [19], where RF-negative patients were not part of the primary endpoint analyses, the exploratory analysis proved inconclusive; This is in contrast with the data for RF-negative RA patients in the REFLEX study, limited to anti-TNF non-responders; although fewer RF-negative patients than RF-positive patients achieved an ACR20 response, this response rate was still significantly better than the response in the placebo-treated patients [13].

The data from these trials indicate that rituximab is efficacious in patients with long-standing RA and high disease activity who have failed previous DMARDs, especially anti-TNF compounds (Evidence Ib). A superior response is attained if rituximab is administered in combination with MTX than if administered alone. Also there is some evidence (Category IIb) that patients receiving this combination therapy have a more sustained clinical response [31]. Methylprednisolone and oral glucocorticoids are not needed for clinical efficacy [13] (Evidence Ib); however, the administration of intravenous methylprednisolone as pre-medication is needed to reduce the frequency and severity of infusion reactions (Evidence Ib).

Most patients who received a simple treatment of rituximab relapse over time (ACR50) [31] (Evidence IIb). The only evidence of efficacy of repeated treatment in patients who have lost the effect after an initial response comes also from this study [31].

Summary of the evidence on the toxicity of rituximab in RA

There is enough accumulated evidence to evaluate the short-term (<5 yrs) toxicity and safety profile of rituximab [13, 18, 19, 31–33]; however, there is not enough evidence in the literature to evaluate it in studies longer than 5 yrs [33].

In the DANCER study [19], 70% of placebo-treated patients reported at least one adverse event at any time during the study, compared with 81 and 85% of rituximab-treated patients (2 × 500 mg and 2 × 1000 mg infusion groups), respectively. The majority (82%) of the events in each group were mild to moderate in severity. Similar proportions of patients reported severe events in each group: 18% of placebo-treated patients and 17 and 18% of rituximab-treated patients, 2 × 500-mg and 2 × 1000-mg infusion groups, respectively. The most frequently reported adverse events in each treatment group occurred with the first infusion. RA exacerbation, reported as an adverse event, distinguished rituximab–placebo from both rituximab doses, probably reflecting the efficacy of rituximab relative to placebo (30, 17 and 14%, placebo, 2 × 500 mg, 2 × 1000 mg, respectively).

The most frequent adverse events reported are infusion reactions (30–35% with the first infusion) [19]. Acute infusion reactions were more frequently reported in the rituximab-treated group (23%) than in the placebo-treated group (18%) of patients; these reactions were mainly associated with the first than with the second infusion (23 vs 8%, respectively) [34]. The most frequently reported infusion reactions are shown in Table 3.

Low incidences of human anti-chimeric antibody (HACA) responses (<1%) have been reported in patients with B-cell malignancies but they have rarely been associated with any clinical symptom [34]. Significant HACA responses have been reported in 4.3–9.2% in RA patients to date [13].

Infections have been reported in 28% of the placebo-treated and in 35% of each of the rituximab-treated patients in the DANCER study [19]. The type and severity of infections were similar across the placebo and active rituximab groups, the most common being respiratory tract infections (including

TABLE 3. Infusion-associated adverse events^a

Mild and moderate reactions	Severe reactions
<ul style="list-style-type: none"> • Fever, chills • Headache • Pruritus • Fatigue • Nausea, vomiting • Tachycardia • Flushing and rash 	<ul style="list-style-type: none"> • Anaphylaxis • Circulatory collapse • Angioedema • Respiratory distress • Bronchospasm • Thrombocytopenia

^aTime of presentation: 30–120 min (24 h).

nasopharyngitis) and urinary tract infections. No serious infections occurred in the rituximab 2 × 500 mg infusion group. The rate of serious infections was slightly higher; however, in patients receiving rituximab 2 × 1000 mg (3.19/100 patient-yr for the rituximab–placebo group, and 4.74 for the 2 × 1000 mg rituximab group).

In the REFLEX study [13], the incidence of infections was also slightly higher in patients treated with rituximab (41%) than in patients who received placebo (38.5%). The most common infections in both groups were upper respiratory tract infections including nasopharyngitis and sinusitis followed by urinary tract infections and bronchitis. In the same study, the rate of serious infections was again higher in the rituximab group (3.7/100 patient-yr in the placebo vs 5.2/100 patient-yr in the rituximab-treated patients). No cases of tuberculosis or opportunistic infections occurred in this study.

To date there are no data suggesting an increase risk of malignancies in patients receiving rituximab; however, continued vigilance is warranted.

Other adverse reactions reported are RA exacerbations [13, 19] and some reactions mainly reported in patients with lymphoma treated with rituximab such as: tumour lysis syndrome, severe mucocutaneous eruptions (including Stevens–Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis and toxic epidermal necrolysis) [34, 35], severe congestive heart failure including death in patients with pre-existent cardiopulmonary disease [13] and acute intracerebral haemorrhage [36].

Recommendations (graded from A–D)

Indications for rituximab

Rituximab may be used in patients with active (DAS28 > 3.2) [37, 38] RF-positive RA who have had an inadequate response or intolerance to an adequate course as previously defined with TNF inhibitors (recommendation grade A). In patients with an inadequate response or intolerance to more than one conventional DMARD who cannot receive TNF inhibitors (because of contraindications, or unavailability), rituximab may also be used. As of date, there is no strong evidence to recommend rituximab to RF-negative RA patients; GLADAR, however, recommends that RF-negative patients be considered for treatment if they fulfil the conventional treatment failure criteria (Grade B).

Who should administer rituximab?

A rheumatologist with experience in the diagnosis, evaluation and treatment of patients with RA should be the one managing this treatment (Grade D). Treatment should be administered in an experienced infusion unit, with immediately available emergency care. Disease activity should be assessed before treatment and every 3 months thereafter, using the composite score DAS28, or any other composite activity index available.

How should the patients be screened before initiating rituximab?

As in most patients initiating a new therapy, a complete physical examination and detailed history searching especially for comorbid conditions and recurrent infections should be performed. A chest radiograph is not mandatory but it is advisable (Grade D). Routine laboratory testing including complete blood count with differential should be included in the initial screening.

Baseline immunoglobulin levels (IgA, G, M) and before each re-treatment should be determined; if decreased levels are observed, it is advisable to infuse patients with immunoglobulins before initiating rituximab [35, 39].

Hepatitis B, C and HIV serologies are recommended prior to treatment initiation. Patients with hepatitis B should not be treated with rituximab, as cases of reactivated, fulminant hepatitis B have been reported [40–42] (Grade D). Patients with hepatitis C could be treated with rituximab, as it has been successfully used to treat patients with diverse manifestations due to this viral infection [43–46] (Grade D); however, before this is done viral load should be obtained and proper anti-viral treatment be given [47] (Grade D).

Vaccines with inactivated pathogens (hepatitis B, pneumococcus, influenza) should be administered prior to rituximab therapy as in patients already receiving rituximab, response is ineffective to these vaccines [35, 48] (Grade D).

Vaccination against influenza virus and pneumococcus is recommended at least 4 weeks prior to the administration of rituximab (Grade D).

How should the patients be treated?

A treatment algorithm is summarized in Fig. 1. For patients who have already received anti-TNF therapy the data indicate that a starting dose of 1000 mg per infusion on days 1 and 15 [13] should be given (Grade A). In the DANCER study, 41 patients with prior TNF-blocker treatment were included in the 2×500 mg group; however, the results on this subgroup were not reported [19]. Overall, however, the 2×500 mg per infusion dose showed similar efficacy than the 2×1000 mg dose in all outcomes measured except for the ACR70 response at 24 weeks, and the EULAR good response (Table 2). Taking this evidence into account, GLADAR recommends that a dose of 2×1000 mg should be considered initially in most cases (left side of the algorithm) (Grade A), but a 2×500 mg could be considered particularly in patients with prior inadequate response to traditional DMARDs who have not received anti-TNF therapy (right side of the algorithm) (Grade A). GLADAR has discussed this recommendation; however, it has not formally been approved by the regulatory agencies of the countries of the region. This dose could be used since clinical information was obtained in a randomized clinical trial and no important differences were detected between rituximab 500 mg $2 \times$ or 1000 mg $2 \times$ [2] (Table 1). Monetary implications using a small dose are particularly important in Latin America and should be formally tested in an economic analysis.

Rituximab should be administered in conjunction with MTX, as the only trial that compared rituximab alone with placebo failed to show significant differences on the ACR50 and ACR70 responses [18] (Grade A). However, rituximab monotherapy was shown to be more effective than placebo on the ACR20 response [18]. MTX should be administered at adequate doses: that is between 15 and 25 mg/week. There is no evidence to recommend another DMARD, so the decision to use other DMARD, such as LEF or SSZ, or rituximab monotherapy for those patients who cannot tolerate MTX, should be left to the treating rheumatologist. Although concomitant treatment with cyclophosphamide [18] has proven to be efficacious, given its potential side-effects, its use is not recommended (Grade D). The use of intravenous methylprednisolone (100 mg) prior to each Rituximab

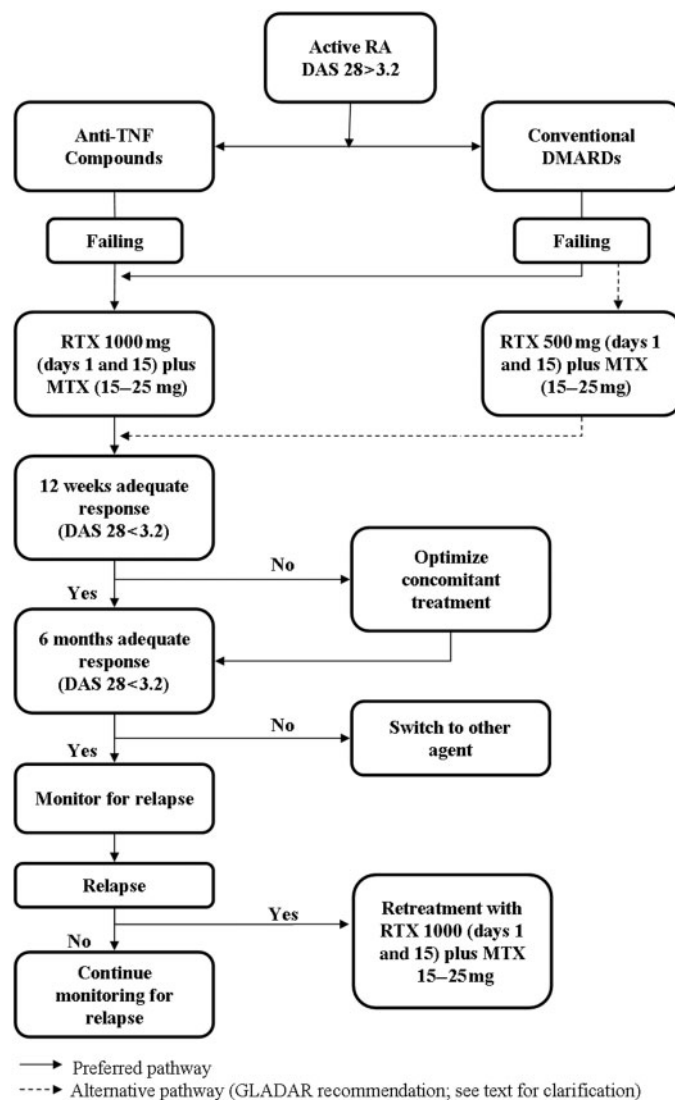


FIG. 1. Algorithm for the use of rituximab in patients with RA. Broken line represents an alternative pathway, while continuous line represents the recommended pathway; RTX: rituximab.

infusion is recommended to reduce the frequency and severity of infusion reactions (Grade A).

Repeated treatment should be considered in those patients who relapse after initial response only after 6 months have elapsed (recommendation Grade C). Relapse is defined as a DAS28 ≥ 3.2 . Those patients who remain with a good clinical response as per the defined criteria, do not need to receive repeated treatment until they relapse, as there is evidence that 20% of patients had persistent ACR50 response 2 yrs after the first infusion [49] (Grade C).

How should the patients be evaluated?

All medical decisions should be primarily based on objective measures. Patients should be assessed before treatment initiation and at least every 3 months thereafter.

Although any composite activity index could be used, GLADAR strongly recommends the use of the DAS28 because of its simplicity, friendliness and feasibility in daily clinical practice. A patient should be considered a responder if she/he achieves a DAS28 score < 3.2 at week 24 (6 months). For patients who do not experience clinical improvement by week 12, GLADAR recommends optimizing the doses of concomitant

therapies (e.g. increasing MTX or prednisolone doses, or administering IA glucocorticoid injections) (Grade D).

Individualized responses should be carefully evaluated by the treating rheumatologist in order to take further therapeutic decisions (for example, patients with very high initial DAS28 score, who failed multiple previous treatments and achieve a reduction of DAS28 score ≥ 1.2 , yet this score is >3.2 , may not be considered failures) (Grade D).

Measurement of HACAs is not required in the follow-up of patients treated with rituximab (Grade A). Measurement of immunoglobulins is recommended prior to any new infusion (Grade D).

Contraindications

Rituximab should not be administered to children, pregnant women and during lactation, to patients allergic or hypersensitive to rituximab or any other chimerical and/or humanized antibodies. Rituximab is also contraindicated in the presence of active and recurrent infections, and severe heart failure (New York Heart Association Class IV) (Grade A).

Switching anti-TNF or giving rituximab?

A practical question faced by clinicians and patients is whether to switch TNF blockers or to start other biologic agents, such as rituximab, when a clinical response to anti-TNF agents is not achieved. There are data indicating that switching among the three available TNF antagonists (adalimumab, etanercept and infliximab) is safe and effective, with few withdrawals because of intolerance or lack of efficacy [12, 13, 50–54]. A recent observational study suggested, however, that treatment with rituximab may be more effective than switching to an alternative anti-TNF agent in patients with RA in whom active disease persists despite anti-TNF therapy [55]. As there are no head-to-head studies comparing the efficacy and tolerance of the diverse biologic treatments available, whether to switch to another TNF inhibitor or start a new biologic agent is a decision best left to the experience of the treating rheumatologist and to the patient's preference.

Special issues in the Latin American context

Certain circumstances affect the implementation of early and effective treatment in patients with RA, including the lack of definite diagnostic criteria for early RA, delays in obtaining qualified medical care and difficulties in identifying patients likely to develop persistent disease or with risk factors for severe or erosive disease [1]. Additionally, there is in general an absence of governmental programmes for the rheumatic diseases and public educational programmes about RA are lacking (second Latin American Consensus on Education and Treatment of RA, in preparation).

It is usually considered that in Latin America there are deficiencies in drug availability and in access to treatments, especially biological DMARDs; in addition, there is an insufficient number of rheumatologists, and adequate medical records and clinical information are sub optimal [1]. However, rituximab is available in the majority of countries in the region, and in some countries such as Cuba, it is the only biological DMARD available (only approved for lymphoma). Furthermore, there is consensus on the need to consider RA as a public health priority, to promote access to specialized diagnosis and treatment, to implement algorithms suitable to the Latin American reality, to establish routine epidemiological surveillance and to conduct adequate educational programmes for both, patients and physicians [56].

Healthcare in most Latin American countries is insufficient because there is less governmental investment as a percentage of the gross domestic product (GDP); furthermore, and as noted in

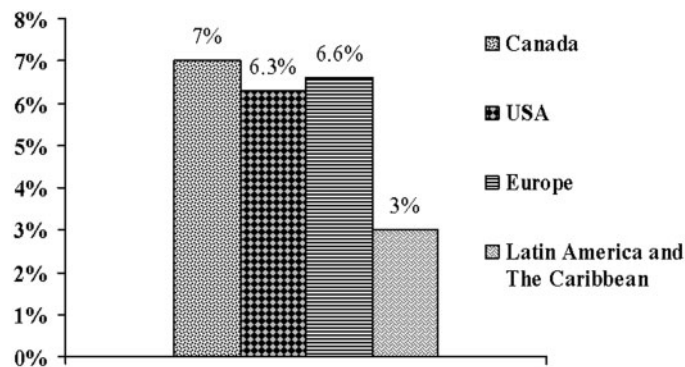


FIG. 2. Investment in health care as a percentage of the GDP in different regions of the world. Adapted from Londoño and Szekely [57].

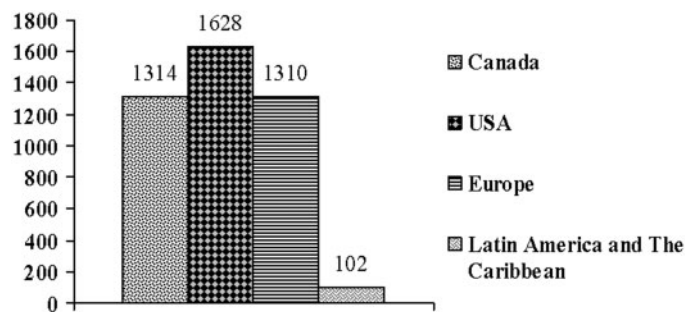


FIG. 3. Per capita spent on health in US dollars in different regions of the world. Adapted from Londoño and Szekely [57].

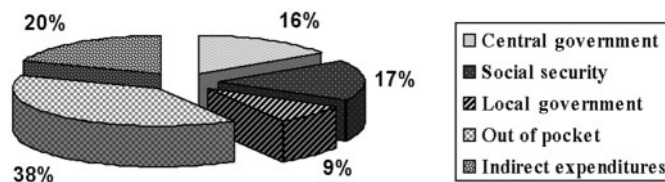


FIG. 4. Mean health care expenditures composition as a function of payer in Latin America. Adapted from Londoño and Szekely [45].

Figs 2 and 3, the per capita spending on health is less than that in developed countries [57]. Finally, a sizeable proportion of Latin Americans (39%) pay out of pocket for their health care, particularly their medications, as the health care systems may not cover these costs [57] (Fig. 4).

After searching the medical Latin American databases including Scielo, Lilacs and Imbiomed, only one open prospective controlled study [58] and several descriptive studies were identified [58–63]. The majority of these Latin American publications include small series and case reports. Rituximab has been used for RA and SLE, but also for difficult cases in a variety of disorders including scleroderma, thrombocytopenic purpura and other autoimmune diseases [58–63]. These cases only represent a small fraction of the total number of patients treated with rituximab in Latin America as more and more rheumatologists are becoming familiar with the use of this compound.

The cost of a treatment is an important issue for all Latin American governments. There is some variation on the price of different biologic compounds among the various Latin American countries. However, while the price of biologics in Latin America is closer to that in the USA and Europe, the price of other health care services in most of our countries is much cheaper. Thus, in

Latin America, the price of biologic compounds represents a larger proportion of direct costs than in developed countries. Also indirect costs in underdeveloped countries constitute a smaller percentage of total costs (due to cheaper salaries), making cost-effectiveness of biologics more difficult to achieve.

Unresolved issues and research agenda

- There are still no data on the long-term efficacy and safety of rituximab, as it is not always appropriate to extrapolate data from the haematology/oncology literature.
- There is much to be learned about the best regimen for RA patients, including dose, retreatment and concomitant medications. It would be useful to identify serological markers preceding clinical relapse in order to begin retreatment before it occurs.
- The concomitant use of DMARDs other than MTX may prove to be efficacious and safe and it is worth exploring.
- The efficacy of rituximab on seronegative RA patients seems to be less impressive and deserves further investigation.
- The role of rituximab as a true DMARD, that is halting or retarding the radiographic progression of the disease is uncertain at this time. A trend was observed; thus follow-up data on those patients who participated in clinical trials are urgently needed.
- Rituximab has only been tested in severe long-standing RA; whether it is also useful in early RA and even to induce remission should be explored.
- Information about the cost-effectiveness of rituximab is needed, as it is a very important part of the decision process for governments, payors, physicians and patients.

Conclusions

- The use of rituximab in RA has re-opened the debate on the role of B cells in the pathogenesis of this disease and has provided new insights into it.
- Rituximab is a new therapeutic option for patients with active RA who have not responded to more than one DMARD. It is especially useful in those RF-positive patients that have failed one or more anti-TNF compounds.
- Rituximab has proven to be safe and effective in the short-term. Long-term safety data are only available in the haematological literature. Long-term efficacy and safety data in RA are not yet available.
- Rituximab, as all the other treatments available for RA, does not cure RA; most patients relapse months to years after treatment, requiring retreatment.
- All new treatments for RA are expensive; that is much more relevant in the developing countries of Latin America. The rational use of these compounds by Latin American rheumatologists may help balance the inherent inequalities in health care across populations with many other urgent and unsolved needs.
- Because Rituximab is generally available in Latin America, it constitutes a valuable option for the treatment of patients with RA, many of whom are running out of therapeutic alternatives.
- As always, these recommendations and guidelines are intended to help rheumatologists on the use of rituximab, but the ultimate decision of what is best for the individual patient should rest with the patient and his/her treating physician.

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clinical trials with rituximab as a principal investigator. L.M.H.M. has been a co-investigator in rituximab clinical trials for Roche and has received financial support for Medical Congress from Roche. C.G.-M. has been a principle investigator in biologic products clinical trials for Roche and Abbott. He has also received honoraria as an Advisory Board Member from Wyeth. All other authors have declared no conflicts of interest.

References

- 1 Cardiel MH. First Latin American position paper on the pharmacological treatment of rheumatoid arthritis. *Rheumatology* 2006;45(Suppl 2):ii7–22.
- 2 Bathon JM, Martin RW, Fleischmann RM *et al.* A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586–93.
- 3 Keystone EC, Schiff MH, Kremer JM *et al.* Once-weekly administration of 50 mg etanercept in patients with active RA: results of a multicentre, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2004;50:353–63.
- 4 Weinblatt ME, Kremer JM, Bankhurst AD *et al.* A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;340:253–9.
- 5 Lipsky PE, van der Heijde DM, St Clair EW *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-tumor necrosis factor trial in rheumatoid arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;343:1594–602.
- 6 Maini R, St Clair EW, Breedveld F *et al.* Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;354:1932–9.
- 7 Maini RN, Breedveld FC, Kalden JR *et al.* Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41:1552–63.
- 8 Scallon BJ, Moore MA, Trinh H, Knight DM, Ghraeyeb J. Chimeric anti-TNF-alpha monoclonal antibody cA2 binds recombinant transmembrane TNF-alpha and activates immune effector functions. *Cytokine* 1995;7:251–9.
- 9 Smolen JS, Keystone EC, Emery P *et al.* Consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;66:143–50.
- 10 Furst DE, Schiff MH, Fleischmann RM *et al.* Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003;30:2563–71.
- 11 van de Putte LB, Atkins C, Malaise M *et al.* Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004;63:508–16.
- 12 Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum* 2007;56:13–20.
- 13 Cohen SB, Emery P, Greenwald MW *et al.* Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicentre, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006;54:2793–806.
- 14 Kremer JM, Genant HK, Moreland LW *et al.* Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006;144:865–76.
- 15 Kremer JM, Westhovens R, Leon M *et al.* Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4lg. *N Engl J Med* 2003;349:1907–15.
- 16 Moreland LW, Alten R, Van den Bosch F *et al.* Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4lg and LEA29Y eighty-five days after the first infusion. *Arthritis Rheum* 2002;46:1470–9.
- 17 Weinblatt M, Combe B, Covicucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. *Arthritis Rheum* 2006;54:2807–16.
- 18 Edwards JC, Szczepanski L, Szechinski J *et al.* Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;350:2572–81.
- 19 Emery P, Fleischmann R, Filipowicz-Sosnowska A *et al.* The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006;54:1390–400.
- 20 Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *Br Med J* 1999;318:593–6.
- 21 Dorer T, Burmester GR. The role of B cells in rheumatoid arthritis: mechanisms and therapeutic targets. *Curr Opin Rheumatol* 2003;15:246–52.
- 22 Schubert D, Maier B, Morawietz L, Krenn V, Kamradt T. Immunization with glucose-6-phosphate isomerase induces T cell-dependent peripheral polyarthritis in genetically unaltered mice. *J Immunol* 2004;172:4503–9.
- 23 Takemura S, Klimiuk PA, Braun A, Goronzy JJ, Weyand CM. T cell activation in rheumatoid synovium is B cell dependent. *J Immunol* 2001;167:4710–8.

- 24 Correa PA, Tobon GJ, Citera G *et al.* [Anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis: relation with clinical features, cytokines and HLA-DRB1]. *Biomedica* 2004;24:140–52.
- 25 Quinn MA, Gough AK, Green MJ *et al.* Anti-CCP antibodies measured at disease onset help identify seronegative rheumatoid arthritis and predict radiological and functional outcome. *Rheumatology* 2006;45:478–80.
- 26 Dornier T. Crossroads of B cell activation in autoimmunity: rationale of targeting B cells. *J Rheumatol* 2006;33(Suppl 77):3–11.
- 27 Dass S, Vital EM, Emery P. Rituximab: novel B-cell depletion therapy for the treatment of rheumatoid arthritis. *Expert Opin Pharmacother* 2006;7:2559–70.
- 28 Bonavida B. Rituximab-induced inhibition of antiapoptotic cell survival pathways: implications in chemo/immunosensitivity, rituximab unresponsiveness, prognostic and novel therapeutic interventions. *Oncogene* 2007;26:3629–36.
- 29 Stasi R, Del Poeta G, Stipa E *et al.* Response to B-cell depleting therapy with rituximab reverts the abnormalities of T cell subsets in patients with idiopathic thrombocytopenic purpura. *Blood* 2007;110:2924–30.
- 30 van Gestel AM, Anderson JJ, van Riel PL *et al.* ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American College of Rheumatology European League of Associations for Rheumatology. *J Rheumatol* 1999;26:705–11.
- 31 Strand V, Balbir-Gurman A, Pavelka K *et al.* Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. *Rheumatology* 2006;45:1505–13.
- 32 Cambridge G, Leandro MJ, Edwards JC *et al.* Serologic changes following B lymphocyte depletion therapy for rheumatoid arthritis. *Arthritis Rheum* 2003;48:2146–54.
- 33 Popa C, Leandro MJ, Cambridge G, Edwards JC. Repeated B lymphocyte depletion with rituximab in rheumatoid arthritis over 7 yrs. *Rheumatology* 2007;46:626–30.
- 34 Hainsworth JD. Safety of rituximab in the treatment of B cell malignancies: implications for rheumatoid arthritis. *Arthritis Res Ther* 2003;5(Suppl 4):S12–6.
- 35 Panayi GS, Hainsworth JD, Looney RJ, Keystone EC. Panel discussion on B cells and rituximab: mechanistic aspects, efficacy and safety in rheumatoid arthritis and non-Hodgkin's lymphoma. *Rheumatology* 2005;44(Suppl 2):ii18–20.
- 36 Ganguly S. Acute intracerebral hemorrhage in intravascular lymphoma: a serious infusion related adverse event of rituximab. *Am J Clin Oncol* 2007;30:211–2.
- 37 Balsa A, Carmona L, Gonzalez-Alvaro I, Belmonte MA, Tena X, Sanmarti R. Value of disease activity score 28 (DAS28) and DAS28-3 compared to American College of Rheumatology-defined remission in rheumatoid arthritis. *J Rheumatol* 2004;31:40–6.
- 38 van der Heijde DM, Jacobs JW. The original 'DAS' and the 'DAS28' are not interchangeable: comment on the articles by Prevoo *et al.* *Arthritis Rheum* 1998;41:942–5.
- 39 Lim SH, Zhang Y, Wang Z *et al.* Maintenance rituximab after autologous stem cell transplant for high-risk B-cell lymphoma induces prolonged and severe hypogammaglobulinemia. *Bone Marrow Transplant* 2005;35:207–8.
- 40 Dervite I, Hober D, Morel P. Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. *N Engl J Med* 2001;344:68–9.
- 41 Hamaki T, Kami M, Kusumi E *et al.* Prophylaxis of hepatitis B reactivation using lamivudine in a patient receiving rituximab. *Am J Hematol* 2001;68:292–4.
- 42 Hernandez JA, Diloy R, Salat D, del Rio N, Martinez X, Castellvi JM. Fulminant hepatitis subsequent to reactivation of precore mutant hepatitis B virus in a patient with lymphoma treated with chemotherapy and rituximab. *Haematologica* 2003;88:ECR22.
- 43 Bestard O, Cruzado JM, Ercilla G *et al.* Rituximab induces regression of hepatitis C virus-related membranoproliferative glomerulonephritis in a renal allograft. *Nephrol Dial Transplant* 2006;21:2320–4.
- 44 Bruchfeld A, Saadoun D, Cacoub P. Treatment for glomerulonephritis in HCV-associated mixed cryoglobulinaemia—anti-viral therapy vs rituximab. *Rheumatology* 2006;45:783–4; author reply 4–5.
- 45 Bryce AH, Dispenzieri A, Kyle RA *et al.* Response to rituximab in patients with type II cryoglobulinemia. *Clin Lymphoma Myeloma* 2006;7:140–4.
- 46 Cervetti G, Mechelli S, Riccioni R, Galimberti S, Caracciolo F, Petrini M. High efficacy of rituximab in indolent HCV-related lymphoproliferative disorders associated with systemic autoimmune diseases. *Clin Exp Rheumatol* 2005;23:877–80.
- 47 Ramos-Casals M, Lopez-Guillermo A, Brito-Zeron P, Cervera R, Font J. Treatment of B-cell lymphoma with rituximab in two patients with Sjogren's syndrome associated with hepatitis C virus infection. *Lupus* 2004;13:969–71.
- 48 van der Kolk LE, Baars JW, Prins MH, van Oers MH. Rituximab treatment results in impaired secondary humoral immune responsiveness. *Blood* 2002;100:2257–9.
- 49 Stewart M, Malkovska V, Krishnan J, Lessin L, Barth W. Lymphoma in a patient with rheumatoid arthritis receiving methotrexate treatment: successful treatment with rituximab. *Ann Rheum Dis* 2001;60:892–3.
- 50 Bennett AN, Peterson P, Zain A, Grumley J, Panayi G, Kirkham B. Adalimumab in clinical practice. Outcome in 70 rheumatoid arthritis patients, including comparison of patients with and without previous anti-TNF exposure. *Rheumatology* 2005;44:1026–31.
- 51 Bombardieri S, Ruiz AA, Fardellone P *et al.* Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. *Rheumatology* 2007;46:1191–9.
- 52 Di Poi E, Perin A, Morassi MP, Del Frate M, Ferraccioli GF, De Vita S. Switching to etanercept in patients with rheumatoid arthritis with no response to infliximab. *Clin Exp Rheumatol* 2007;25:85–7.
- 53 Gomez-Reino JJ, Carmona L. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. *Arthritis Res Ther* 2006;8:R29.
- 54 Kramm H, Hansen KE, Gowing E, Bridges A. Successful therapy of rheumatoid arthritis with rituximab: renewed interest in the role of B cells in the pathogenesis of rheumatoid arthritis. *J Clin Rheumatol* 2004;10:28–32.
- 55 Finckh A, Ciurea A, Brulhart L *et al.* B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. *Arthritis Rheum* 2007;56:1417–23.
- 56 Caballero C, Galarza C, Laurindo I, Massardo L, Cardiel M, Pons-Estell Bb. Retos para el diagnóstico y tratamiento de la AR en América Latina. *Barranquilla: Ediciones Uninorte*, 2006.
- 57 Londono JL, Szekely M. 'Distributional surprises after a decade of reforms: Latin America in the nineties.' *Latin America after a decade of reforms: what comes next?* Washington, DC: Inter-American Development Bank, 1997.
- 58 Barile-Fabris L, Sánchez M, Abud C *et al.* Efficacy and safety of rituximab (RTX) in rheumatoid arthritis (RA) patient. *Ann Rheum Dis* 2005;64(Suppl 3):1465.
- 59 Pereira E, Jarpa E, Martínez M, Gutiérrez M, Massardo L. Clinical experience with the use of rituximab in six patients with difficult rheumatologic diseases. *J Clin Rheumatol* 2006;12:211.
- 60 Ramos-Sánchez M, Aranda-Baca L, Sauza-Del Pozo M, Becerra-Márquez A, Mejía-Holguín Y, García-Cervantes M. Experience with rituximab in the treatment of systemic lupus erythematosus (SLE). *J Clin Rheumatol* 2006;12:207.
- 61 Santiago M, Reis E, Lima I, Reis M. Use of rituximab for the treatment of systemic lupus erythematosus' thrombocytopenia: clinical efficacy and co stimulatory molecules effect. *Rev. bras. reumatol* 2006;46:153–6.
- 62 Scheinberg M, Hamerschlag N, Kutner JM *et al.* Rituximab in refractory autoimmune diseases: Brazilian experience with 29 patients (2002–2004). *Clin Exp Rheumatol* 2006;24:65–9.
- 63 Zúñiga K, Chigne O, Huamanchumo R, Calvo A. Therapy with rituximab in severe SLE. *J Clin Rheumatol* 2006;12:210.

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