

Should Rituximab be Considered as the First-Choice Treatment for Severe Autoimmune Rheumatic Diseases?

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Abstract The present study aimed to assess the tolerance and efficacy of rituximab (RTX), a chimeric IgG1 monoclonal antibody directed against the CD20 receptor present in B lymphocytes, in patients with autoimmune rheumatic diseases (AIRD). For this purpose, patients treated with RTX and their respective clinical charts were comprehensively examined. Indications for treatment were a refractory character of the disease, inefficacy or intolerance of other immunosuppressors. Activity indexes (SLEDAI, DAS28, and specific clinical manifestations) were used to evaluate efficacy. Serious side effects were also recorded. Seventy-four patients were included. Forty-three patients had systemic lupus erythematosus (SLE), 21 had rheumatoid arthritis (RA),

8 had Sjögren's syndrome (SS), and 2 had Takayasu's arteritis (TA). RTX was well-tolerated in 66 (89%) patients. In 8 patients (SLE=3, SS=3, RA=2), serious side effects lead to discontinuation. The mean follow-up period was 12 ± 7.8 (2–35) months. The efficacy of RTX was registered in 58/66 (87%) patients, of whom 36 (83%) had SLE, 18/21 (85%) had RA, 3/8 (37%) had SS, and 1 had TA. The mean time of efficacy was 6.3 ± 5.1 weeks. A significant steroid-sparing effect was noticed in half of the patients. These results add further evidence for the use of RTX in AIRD. Based on its risk–benefit ratio, RTX might be used as the first-choice treatment for patients with severe AIRD.

Keywords Rituximab · CD20 · Rheumatoid arthritis · Systemic lupus erythematosus · Sjögren's syndrome · Pharmacogenomics

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Introduction

Advances in the understanding of the regulation of the immune system have enabled the identification of cellular and molecular targets that could potentially affect the pathogenesis of many autoimmune diseases (ADs). Although T cells have been considered the cornerstone of autoimmunity, interest has grown in the pivotal role of B cells in ADs. The latter participates in autoantibody secretion, autoantigen presentation, proinflammatory cytokine production, and regulation of dendritic cell function [1]. Thus, this cellular group has become an important therapeutic target in ADs.

Rituximab (RTX) is a chimeric monoclonal IgG1 antibody, directed against the CD20 receptor that is

presented in B lymphocytes; therefore, it is able to decrease the number of these cells. The antibody is an IgG1 kappa immunoglobulin containing murine light- and heavy-chain variable region and human constant region sequences [2]. The Fab domain (murine) of RTX binds to the CD20 antigen in B cells, and the Fc domain (human) recruits immune effector functions to mediate B cell lysis [2]. Mechanisms explaining B cell lysis include complement activation (complement-dependent cytotoxicity), antibody-dependent cellular cytotoxicity [2], and induction of apoptosis when cross-linked by Fc gamma receptor (FcγR)-bearing cells [3].

CD20 antigen (human B lymphocyte-restricted differentiation antigen, Bp35), is a hydrophobic transmembrane protein with a molecular weight of approximately 35 kDa located on pre-B and mature B lymphocytes [4, 5] as well as on >90% of B cell non-Hodgkin's lymphomas (NHL) [6]. CD20 is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues [7]. CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation [7], and possibly function as a calcium ion channel [8]. CD20 is not shed from the cell surface and does not internalize upon antibody binding [9]. Free CD20 antigen is not found in the circulation [4]. Its gene, at chromosome 11q12, have seven exons and it is highly polymorphic (http://www.ensembl.org/Homo_sapiens/geneview?gene=ENSG00000156738&db).

RTX is currently used in different autoimmune rheumatic diseases (AIRD), including rheumatoid arthritis (RA) [10–16], systemic lupus erythematosus (SLE) [13, 17–22], Sjögren's syndrome (pSS) [13, 23–25], and other ADs [26]. These observations prompted us to evaluate its tolerability and efficacy in Latin-American patients with these AIRD.

Patients and Methods

Patients

This was a retrospective study. Patients fulfilling the American College Criteria (ACR) for RA [27], SLE [28], the American-European consensus for pSS [29], the ACR criteria for Takayasu's arteritis (TA) [30], and treated with RTX were included in this study. These patients were seen in two tertiary hospitals in Medellín, Colombia and Cuenca, Ecuador. Patients and their clinical charts were systematically reviewed using a questionnaire that sought information about demographics, clinical variables concerning RTX indication, activity of the disease, and previous treatments.

Inclusion Criteria

In all the cases, RTX was given because of the refractory character of the AIRD, inefficacy, and intolerance of other immunosuppressors or by the patient's choice in one case. For RA, the refractory character of the disease was defined by the presence of at least eight swollen and eight tender joints and two of the following: a serum C-reactive protein level of at least 1.5 mg/dl, an erythrocyte sedimentation rate >30 mm/h or morning stiffness lasting longer than 1 h; despite treatment with at least one disease modifying antirheumatic drug (DMARD) in an adequate dosage. In patients with SLE, an active disease was defined by high activity index (SLE disease activity index [SLEDAI] >8) despite treatment with steroids and/or immunosuppressors. Patients with pSS presenting severe glandular involvement (i.e., persistent bilateral parotid swelling) and systemic manifestations such as cutaneous vasculitis or musculoskeletal involvement despite the treatment with steroids, antimalarial drugs, cyclophosphamide, and pilocarpine were chosen.

Treatment

The number of RTX infusions, as well as the dosage and protocols, were recorded in each patient. Concomitant medications, including immunosuppressant agents and steroids, were noted. Two protocols were used. First, RTX at a dose of 375 mg/m² was administered intravenously once a week for a total of four infusions (on days 1, 8, 15, and 22). The drug was reconstituted in normal saline to a concentration of 1 mg/ml. The second protocol was RTX administration of 1,000 mg every second week by two perfusions. All patients received concomitant methylprednisolone (40 mg) boluses and nonsteroidal antiinflammatory agents or analgesics as needed.

Assessment

Tolerance and adverse events were recorded for each patient. Modified Health Assessment Questionnaire (mHAQ) [31] and SLEDAI [32] values were recorded in patients with RA and SLE, respectively. In addition, Disease Activity Score 28 (DAS 28) [31] was recorded in RA patients. In patients with RA or SLE, efficacy was defined as a decrease of 40% or more of the initial mHAQ, DAS28, and SLEDAI values, respectively. In patients in whom DAS28, mHAQ or SLEDAI could not be obtained, effectiveness was evaluated about improvement in clinical complaints, signs, and symptoms (visual analogue scale [VAS] for pain, patient, and medical evaluation). In patients with pSS, efficacy was defined as a decrease of 50% or more of the initial disease activity according to the clinician in charge of the patient. Data were obtained for each clinical visit, and clinical

manifestations of the disease and side effects to therapy were recorded.

Statistical Analysis

Data were managed and stored using the SPSS program (V15 for Windows, Chicago, IL, USA). For comparison of absolute values before and after treatment, the two-tailed Wilcoxon signed rank test for paired data was used. A p value <0.05 was considered statistically significant.

Results

Patient Characteristics

The study included 43 patients with SLE, 22 patients with RA, 8 with pSS, and 2 with TA. One patient with RA also fulfilled the criteria for secondary SS (i.e., sicca symptoms, parotid swelling, anti-Ro, and anti-La antibodies). All RA patients were treated previously with methotrexate (MTX) (mean dose 15 ± 5 mg/week). Twelve and 10 RA patients had previously been treated with antitumor necrosis factor (anti-TNF) therapy and leflunomide, respectively. Nineteen SLE patients were previously treated with cyclophosphamide, 15 with mycophenolate mofetil (MMF) and 4 with intravenous immunoglobulins (IVIg).

Characteristics of RTX Administration and Concomitant Medications

Forty patients were assigned to weekly infusions of 375 mg/m^2 of RTX for 4 weeks, 30 patients were given 2 infusions of 1,000 mg, and a different dosage regimen was followed in 4 patients. Differences in efficacy and tolerability were not observed between the different protocols. Leflunomide was continued in six patients with RA. MTX was continued in six RA patients. MMF was continued in two RA patient and six SLE patients. Cyclophosphamide was stopped in all SLE and SS patients.

Tolerance and Safety

Twenty-one adverse events were observed in 12 patients (RA=4, SLE=4, pSS=3, TA=1), of which the most frequent were type β (cutaneous vasculitis in 5) [33]. Headache ($n=4$), dizziness ($n=3$), sleepiness ($n=3$), hypotension ($n=2$), dyspnea ($n=2$), fever ($n=1$), and hypertension ($n=1$) were also observed. Eight patients discontinued RTX treatment (RA=1, SLE=4, pSS=3) due to type β side effects ($n=4$), type ϵ ($n=3$), and infection in one.

Efficacy

The efficacy of RTX was registered in 58/66 (87%) patients, of whom 36 (83%) had SLE, 18/21 (85%) had RA, 3/8 (37%) had SS, and 1 had TA. The mean follow-up period was 12 ± 7.8 months (2–35 months), and the mean time of efficacy was 6.3 ± 5.1 weeks. A significant steroid-sparing effect was noticed in half of the patients. Twenty-nine patients could reduce corticosteroids dose. The mean dosage of steroids decreased from 14.67 ± 12 to 7.33 ± 5 mg/day ($p=0.001$). Death was not observed.

Patients with RA

There were 20 women and 2 men with a mean age of 49.2 ± 14 years and a mean duration of disease of 118.3 ± 89.7 months (1–396). Efficacy was registered in 18 (85.7%) patients, of whom 6 achieved complete remission. DAS 28 and mHAQ could not be obtained in five RA patients. The mean mHAQ decreased from 2.56 ± 0.79 (0.25–3.63) to 0.54 ± 0.44 (0–1.25) ($p=0.001$). The mean DAS 28 decreased from 6.96 ± 1.39 (4.56–7.84) to 3.58 ± 1.29 (2.38–5.69) ($p=0.001$). Improvement in both articular index and VAS for pain was observed in all RA patients. These results represent a reduction higher than 50% in all variables.

Patients with SLE

There were 40 women and 3 men with a mean age 30.5 ± 13.3 years and a mean duration of disease of 71.1 ± 58.6 months (0–240). Thirty-six (83.7%) patients had autoimmune cytopenias, 24 (55.8%) patients had nephritis, and 11 (25.6%) patients had central nervous system involvement. The mean SLEDAI value decreased from 12.5 ± 4.4 to 4.5 ± 4.8 ($p<0.001$), representing a reduction higher than 50% in SLEDAI score. Prednisone dosage could be reduced from 23 ± 15.65 to 13 ± 4.47 mg/day ($p<0.001$).

Patients with pSS

All the patients were women with a mean age of 37.3 ± 10 years and a mean duration of disease of 100.5 ± 86 months. The efficacy of RTX was observed in 4/7 (57%) patients with regression of parotid swelling, complete recovery of articular involvement, fatigue, and subjective dryness. There were three patients experiencing side effects. In one, RTX was stopped during the first infusion and cyclophosphamide was started. In the other patient, she had hypotension during the second perfusion and RTX was stopped. In spite of this, improvement was important and lasted to up to 23 months. The patient with RA fulfilling the criteria for secondary SS

had completed recovered from parotid swelling and articular involvement lasting for 24 months.

Patients with TA

There were two women, 25 and 29 years old, respectively, with a disease duration of 84 and 96 months, respectively. Both patients had received MTX and anti-TNF therapy with no response. Successful recovery was achieved in one patient. The other patient did not respond to RTX and was switched to the combination of cyclophosphamide and azathioprine.

Discussion

This study adds further evidence for the usefulness of RTX in the treatment of AIRD. Tolerance was good, and efficacy was observed in almost all of the patients. In addition, RTX therapy allowed for a reduction of oral corticosteroids.

The first main experience of RTX in RA comes from a controlled trial [12]. In that study, 43% (RTX and MTX) and 41% (RTX and cyclophosphamide) of patients with RA achieved 50% improvement according to the ACR criteria compared with 13% of patients given MTX alone. RA patients negative for rheumatoid factor (RF) could fail therapy with RTX [26]. In our study, all RA patients who participated tested positive for RF. Our results compare well with that of the controlled trial, showing similar efficacy and tolerance of RTX in patients not under controlled trial conditions, including 11 RA patients in failure of anti-TNF therapy. Collectively, data suggest that RTX could be considered before anti-TNF therapy [10, 14].

The first published open study of SLE treated with RTX included six patients with severe SLE receiving high-dose steroids and cyclophosphamide, which led to clinical improvement in five patients [18]. The same group reported the results of six patients with nephritis; four of them experienced a marked improvement of lupus activity and of serologic and renal features [34]. Another group reported the efficacy of RTX added to current therapy in 18 SLE patients [19]. Clinical activity of lupus markedly decreased in 10 patients in whom B cells were depleted, and no overall change in serum levels of anti-dsDNA antibodies was observed [19]. In the present study, 20 of the 24 patients with active nephritis and 16 without nephritis (but with high SLEDAI index) responded well to RTX. These results suggest the potential use of RTX in severe SLE [13, 17–22]. In addition, RTX had a marked corticosteroid-sparing effect.

In pSS, the first published observation described self-reported subjective improvement of oral and ocular dryness in pSS after therapy with RTX for parotid marginal zone

lymphoma [24]. The clinical evolution of four patients treated with RTX for pSS-associated lymphoma was reported [25]. Type II mixed cryoglobulinemia, observed in three patients, disappeared. No information was given concerning the evolution of sicca syndrome. In the present study, extraglandular symptoms, notably swelling of the parotid gland and arthralgias were sensitive to RTX. Improvement was important, in spite of having interrupted RTX treatment in the second perfusion in a pSS patient.

Some patients with adverse events experienced intolerance with other previous treatments (IVIg and cyclophosphamide, respectively). These patients did not have renal function impairment. These adverse events were transient and reversible. It is worth noting that these patients improved in spite of the incomplete regimen they received. This observation, together with the similar response regardless of the regimen administered, raised the question concerning the appropriate dose and protocol for the administration of RTX in AIRD. In patients who experience relapse, clinical manifestation of the disease is often preceded by the reappearance of B cells and/or autoantibodies [35]. In our study, we did not evaluate the levels of B cells CD20+. Further studies in our population about this topic need to be considered. In addition, it could be important to consider that *CD20* gene polymorphism may influence the therapeutic response to RTX. Besides, CD20 RTX interacts with other molecules such as IgG Fc receptor (FCGR3A), which could also affect the clinical outcome of therapy [36, 37]. Genotyping of the *FCGR3A* gene could also be considered important in evaluating the risk of efficacy of RTX in AIRD [36–38]. Further studies on pharmacogenomics in AIRD are warranted, since some patients may fail treatment and *CD20* as well as *FCGR3A* genes polymorphism may vary among populations.

In summary, our results add further evidence for the use of RTX in AIRD, such as SLE, RA, pSS, and possibly other ADs. B lymphocyte depletion therapy in AIRD can provide major clinical benefits. Based upon its risk–benefit ratio, RTX might be used as the first-choice treatment for patients with severe AIRD.

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