

Rituximab in refractory autoimmune diseases: Brazilian experience with 29 patients (2002-2004)

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Abstract

Objective

Rituximab, a monoclonal antibody against B-lymphocytes that express CD 20, is already available for the treatment of non-Hodgkin's lymphoma. Due to the increased relevance of B-cell regulation in the pathogenesis of autoimmune diseases, rituximab is being used in the treatment of patients whose condition is refractory to conventional therapy.

Methods

We retrospectively evaluated the short-term efficacy and tolerance of rituximab in patients with various autoimmune diseases who were treated at the Hospital Israelita Albert Einstein in the city of Sao Paulo.

Results

During the period 2002-2004, 29 patients with various autoimmune diseases were treated with rituximab 375 mg/m² for 4 consecutive weeks, or two doses of 1 g 2 weeks apart. We observed remarkable short-term results in all cases, except for one patient with thrombocytopenic purpura. Of note, we describe the results in two patients with diseases not previously treated with rituximab (hypergammaglobulinemic purpura of Waldenstrom and eosinophilic fasciitis with hypergammaglobulinemia). Treatment was well tolerated, with no unexpected adverse events. We also observed a marked reduction in steroid dosage.

Conclusion

Rituximab seems to be safe and effective in the treatment of patients with a variety of autoimmune diseases that are refractory to other modalities of treatment.

Key words

Arthritis, autoimmune diseases, B-lymphocytes, lupus erythematosus, thrombocytopenic purpura, rituximab.

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Introduction

Within the past several years, a significant body of evidence has been accumulated showing that, in addition to T-lymphocytes, B-lymphocytes also play a significant role in the emergence of autoimmune diseases (1, 2). B-lymphocytes are important in the production of autoantibodies, and also for autoantigen presentation (3, 4). Rituximab is a chimeric monoclonal antibody that specifically recognizes the CD-20 antigen that is present on the cell-surface membrane of mature B-lymphocytes. Rituximab thus represents a potential therapeutic agent in the treatment of patients with autoimmune diseases (5, 6). At the Hospital Israelita Albert Einstein, we have administered rituximab to patients with a variety of autoimmune diseases, and present herein the short-term results of such treatment.

Materials and methods

Patients in this series had refractory autoimmune diseases, and were treated at the Hospital Israelita Albert Einstein by five rheumatology or hematology specialists between 2002 and 2004. We retrospectively evaluated patients' charts, and tabulated demographic and clinical data on individuals who were treated with rituximab. We collected data on rituximab dose and schedule, treatment tolerance, and short-term results. Patients were informed of the refractory nature of their disease, of the availability and general safety of rituximab for another B-cell disease, namely non-Hodgkin's lymphoma, and of the potential benefit of rituximab in autoimmune diseases. Whenever possible, disease activity was assessed by specific scales, such as DAS28, in cases of rheumatoid arthritis (7), and the Systemic Lupus Erythematosus (SLE) Disease Activity Index (SLEDAI) (8).

Results

Patient characteristics

Twenty-nine patients with refractory autoimmune diseases were identified and included in the series. The most frequent indication for rituximab therapy was rheumatoid arthritis (n = 10), followed by idiopathic thrombocytopenic purpura (n = 8), SLE (n = 5), and

immune hemolytic anemia (n = 4). The demographic and clinical characteristics of these 27 patients are shown in Tables I to IV, according to the indication for treatment with rituximab. In addition to those patients, we treated one patient with hypergammaglobulinemic purpura of Waldenstrom, and one with eosinophilic fasciitis with hypergammaglobulinemia, thus totaling 29 cases. The patient with Waldenstrom purpura was a 32-year-old female with disease for 4 years with no clinical response to oral steroids and various immunosuppressive regimens. The patient with fasciitis was a 20-year-old female with disease diagnosis for six months before treatment. Patients were treated intravenously with one of two schedules of rituximab: (1) 375 mg/m² of body surface area, weekly for 4 consecutive weeks; or (2) two infusions of 1 g, administered 2 weeks apart.

Treatment results according to indication

The characteristics of the ten patients with rheumatoid arthritis are shown in Table I. All these patients were being treated with high doses of prednisone, and all had previously failed to treatment with tumor necrosis factor (TNF) antagonists. In 8 patients who received 1.0g, the oral dose of prednisone was increased to 60 mg on days 2 through 7 tapering to 30mg daily on days 8 through 14. Patients continued taking methotrexate if they were already receiving it, usually at a dose of 10 to 25 mg per week. In 6 of the patients for whom pre- and post-treatment DAS28 values were available, there was a reduction after treatment with rituximab. Furthermore, the dose of prednisone could be reduced in most patients, often by more than 20 mg per day. In 3 patients, prednisone could be discontinued.

As shown in Table II, 8 patients received rituximab for refractory idiopathic thrombocytopenic purpura. Except for one patient, all the others had their platelet counts within normal limits 3 months after treatment with rituximab (Fig. 1).

Table III shows the results in 5 patients with SLE who were treated with ritux-

Table I. Demographic and clinical data on patients with rheumatoid arthritis treated with rituximab.

Patient	Sex	Age (years)	Disease duration (years)	Rituximab schedule	DAS28		Prednisone dose (mg)		Efficacy*	TNF (n) failures
					Before	After	Before	After		
1	F	71	5	1.0 g x 2			20	5.0	Positive	7
2	F	62	8	1.0 g x 2			20	2.5	Positive	13
3	F	38	10	1.0 g x 2			40	5.0	Positive	4
4	F	56	10	1.0 g x 2	6.2	1.8	20	-	Positive	6
5	F	42	6	1.0 g x 2	5.2	1.6	10	-	Positive	4
6	F	50	8	1.0 g x 2	7.3	2.1	20	5	Positive	6
7	F	48	10	375 mg/m ² x 4	5.3	1.5	10	-	Positive	5
8	F	38	15	375 mg/m ² x 4	6.0	2.1	10	5	Positive	7
9	F	35	6	1.0 g x 2	5.1	1.6	20	2.5	Positive	8
10	F	58	11	1g x 2	-	-	15	5	Positive	5

DAS: disease activity score; F: female; M: male.

*Evaluation after 3 months.

Efficacy was defined as a significant reduction in the disease activity score when available, or by a reduction in signs, symptoms and the daily prednisone dose.

TNF failures described by the individual physician after prolonged use (n refers to the number of infliximab infusions administered before Rituximab was introduced).

Table II. Demographic and clinical data on patients with thrombocytopenic purpura treated with rituximab.

Patient	Sex	Age (years)	Rituximab schedule (x 4 infusions)	Disease duration (years)	Efficacy*
1	F	8	375 mg/m ²	2	Positive
2	M	51	375 mg/m ²	15	Positive
3	F	30	375 mg/m ²	2	Positive
4	F	45	375 mg/m ²	8	Negative
5	F	16	375 mg/m ²	6	Positive
6	F	38	375 mg/m ²	6	Positive
7	F	42	375 mg/m ²	10	Positive
8	F	40	375 mg/m ²	10	Positive

F: female; M: male.

*Evaluation after 3 months.

Efficacy was defined as a 3-fold elevation compared to the value before therapy.

imab. These patients were refractory to treatment with high doses of prednisone (60 mg daily) and were previously treated with monthly cyclophosphamide for 3 consecutive periods and 2 cycles of pulsed corticosteroid therapy. In all 5 patients, there was improvement in clinical and laboratory parameters, including renal function, after treatment with rituximab. In all patients with rising creatinine (4/5 cases) evaluation after 3 months showed normal renal function. In 2 patients with severe anemia hemoglobin levels improved from 7.1 and 8.2 g/dl to 11.0 and 10.8 g/dl respectively.

The characteristics of 4 patients with immune hemolytic anemia are shown

in Table IV. All these patients had hemoglobin levels within normal limits 3 months after treatment with rituximab. These results are shown in Figure 2, along with the pre- and post-treatment hemoglobin levels in one patient with autoimmune hemolytic anemia secondary to SLE. Infusion reactions were seen in 2 of the 4 patients with immune hemolytic anemia: one patient had transient hypotension, and one had fever. We saw 2 patients with diseases who, to our knowledge, had not been treated with rituximab previously. One of these patients was a 32-year-old woman with hypergammaglobulinemic purpura of Waldenström receiving initially 60 mg and then 40 mg of pred-

nisone daily with minimal or no clinical response. This patient had a complete clinical remission after rituximab treatment. Her immunoglobulin (Ig) G level, which was 3.6 g/dL before treatment, decreased to 1.9 g/dL after treatment, and stayed below 2.0 g/dL. With a 3-month follow-up, she had no further skin lesions, which were very frequent before treatment. Follow up for this patient was done for one year with no recurrence of disease.

The other case was a 20-year-old man with eosinophilic fasciitis with hypergammaglobulinemia. Before treatment with rituximab, this patient had an IgG level of 2.6 g/dL. After treatment, his skin lesions disappeared, his previous eosinophilia normalized, and his IgG level decreased to 1.1 g/dL.

Discussion

This retrospective study has shown that patients with a variety of autoimmune diseases that are refractory to standard therapies may be safely treated with rituximab. In spite of the fact that our results have the drawbacks of a retrospective study we feel it definitively shows a trend towards efficacy and at least for the short period of evaluation not associated with significant side effects during the infusional period or development of serious infection. In addition, our study suggests that such treatment is effective in a large propor-

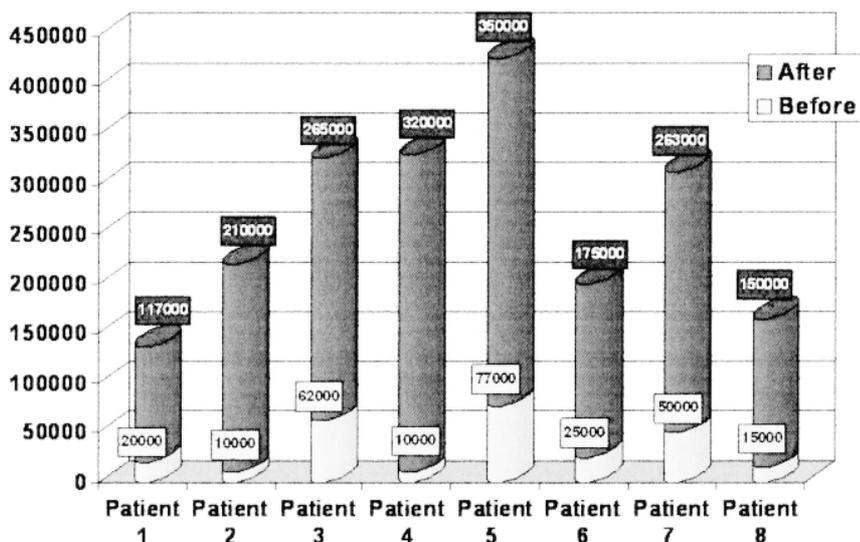


Fig. 1. Platelet counts in patients with thrombocytopenic purpura before and after treatment with rituximab (x 1000/uL).

Table III. Demographic and clinical data on patients with systemic lupus erythematosus treated with rituximab.

Patient	Sex	Age (years)	Clinical data	Rituximab schedule	Prednisone (mg)		SLEDAI	
					Before	After*	Before	After*
1	F	29	Arthritis/Renal insufficiency	375 mg/m ² x 4	60	10	8	2
2	F	19	Arthritis/Renal insufficiency and anaemia	375 mg/m ² x 4	60	2	8	2.5
3	F	38	Arthritis/Renal insufficiency Pleuropericarditis	1.0 g x 2	80	25	8	3.1
4	F	34	Arthritis/ Hematologic alteration	1.0 g x 2	60	40	8	2.8
5	F	9	Arthritis/ Severe anaemia / Renal insufficiency	375 mg/m ² x 4	40	5	-	-

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; F: female; M: male.
*Evaluation after 3 months.

Table IV. Demographic and clinical data on patients with immune hemolytic anemia treated with rituximab.

Patient	Sex	Age (years)	Rituximab schedule (x 4 infusions)	Disease duration (years)	Efficacy*
1	F	36	375 mg/m ²	10	Positive
2	M	75	375 mg/m ²	10	Positive
3	F	70	375 mg/m ²	5	Positive
4	F	30	375 mg/m ²	2	Positive

F: female; M: male. *Evaluation after 3 months.

tion of patients. The heterogeneity of the patients and their diseases, and the relatively short follow-up for many of the patients preclude more definitive conclusions about the efficacy of rituximab, but we believe three main findings emerge from our data: (i) approximately 80% of our patients had clinical and laboratory improvement; (ii) most patients had their daily corticosteroid dose reduced or even discontinued; and (iii) patients with hemolytic anemia secondary to autoimmune diseases seem to have benefited from rituximab.

In our study, all patients with rheumatoid arthritis had favorable responses to rituximab, confirming the observations by Edwards and coworkers (9). Those authors conducted a randomized trial and found that the addition of rituximab significantly increased the proportion of patients with a 50% improvement in disease symptoms according to ACR criteria, when compared with patients treated with methotrexate alone. Our patients differ from those enrolled in the study by Edwards *et al.*, since they had been previously treated with TNF antagonists.

All five patients with SLE included in this series had improvement in disease activity, although SLEDAI was available only for 4 patients. However, it is worthwhile to note that 3 of them had SLEDAI below 3 after treatment with rituximab. One of these patients was refractory to treatment with immunosuppressant drugs and two cycles of pulsed therapy with corticosteroids, which were not able to increase the hemoglobin levels above 7.0 g/dL. After treatment with rituximab, there was an increase in hemoglobin (to 10 g/dL) and concurrent decrease in the creatinine level. Within the past few years, several authors have reported their favorable experience with rituximab for SLE. In one of these series, 5 out of 6 patients had an improvement, and in another, 10 out of 18 responded to rituximab (10-12).

At our hospital, the first patient with autoimmune disease who was treated with rituximab had idiopathic thrombocytopenic purpura, a condition in which the benefit of this monoclonal antibody was first reported (13, 14).

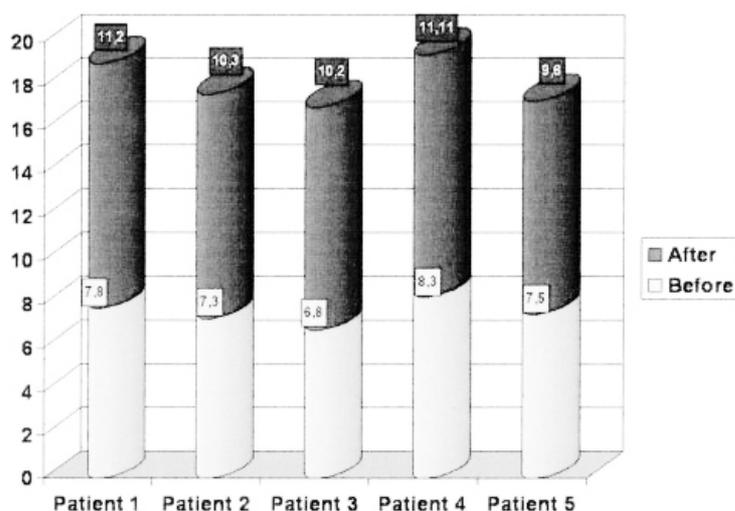


Fig. 2. Hemoglobin levels in patients with autoimmune hemolytic anemia, before and after treatment with rituximab. In one patient, autoimmune hemolytic anemia was associated with systemic lupus erythematosus (g/dl).

With the exception of one patient, all the cases in our series had excellent tolerance and a prolonged (>3 months) response to rituximab. Also, 4 patients with immune hemolytic anemia that was refractory to conventional therapy had rapid and satisfactory responses, confirming other reports on the benefit of rituximab for this clinical condition (16).

We also add two novel diagnoses to the list of autoimmune diseases that may benefit from rituximab therapy, namely hypergammaglobulinemic purpura of Waldenstrom and eosinophilic fasciitis with hypergammaglobulinemia. Both of these conditions are associated with variable degrees of B-lymphocyte hyperactivity (17, 18). Although patients with these diseases may present with variable clinical courses, with periods of remissions and exacerbations, the rapid response to rituximab leads us to speculate that an anti-CD-20 mechanism is involved. In the patient with hypergammaglobulinemic purpura of Waldenstrom, there was no other associated autoimmune disease, and high doses of corticosteroids were not able to control the lower-limb skin lesions. Treatment with rituximab produced a dramatic and almost immediate response.

Our study is limited by its retrospective nature and the lack of explicit criteria for patient enrollment. However, our

data suggest that rituximab is safe for patients with a variety of autoimmune diseases. In addition, our series confirm that treatment with rituximab may be of benefit to selected patients who are refractory to standard therapies. The rapidity of the response, and the reductions in corticosteroid doses in many patients are very encouraging. Recently, French investigators have also reported favorable results among 43 patients with systemic autoimmune diseases (18). These and other promising findings notwithstanding the definitive role of rituximab will have to be demonstrated in controlled studies evaluating individual autoimmune diseases (19-21).

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