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Case report

Rituximab for the therapy of systemic sclerosis: a series of 10 cases in a single center



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ABSTRACT

Systemic sclerosis (SSc) is a chronic autoimmune disease with a high morbidity and mortality. Although cyclophosphamide is effective for severe and refractory cases, there is demand for new treatments. The biological treatment with B-cell depletion with rituximab (RTX) has demonstrated efficacy for this demand in open-label studies.

Objective: This study was conducted with the aim to retrospectively evaluate all patients who used RTX for the treatment of SSc in our center.

Patients and methods: We retrospectively evaluated medical records of all patients with SSc who used RTX to treat this disease from January 2009 to January 2015. Systemic, cutaneous, and pulmonary involvement data and laboratory results before and six months after the first infusion of RTX were collected.

Results: Ten patients received treatment during the study period and were included in this series. All patients had a diffuse form of the disease. Five patients suffered from an early (duration of disease shorter or equal to four years), rapidly progressive disease, and another five received RTX at late stages of the disease. In both groups of patients, stabilization of the pulmonary picture was observed, with a fall in the skin score in those patients with early forms of the disease.

Discussion: Similar to findings in previous studies, RTX was effective in treating early and rapidly progressive forms of SSc. We also found that patients with long-term illness may benefit from the treatment.

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Tratamento da esclerose sistêmica com rituximabe: uma série de 10 casos em centro único

R E S U M O

Palavras-chave:

Esclerose sistêmica
Rituximabe
Fibrose pulmonar
Escore cutâneo modificado de Rodnan

A esclerose sistêmica (ES) é uma doença autoimune crônica de alta morbimortalidade. Ainda que a ciclofosfamida seja eficaz, para casos graves e refratários há demanda para novos tratamentos. A terapia biológica com depleção de células B com rituximabe (RTX) demonstrou eficácia para tal demanda em estudos abertos.

Objetivo: Avaliar retrospectivamente todos os pacientes que fizeram uso do RTX para tratamento de ES em nosso centro.

Pacientes e métodos: Foram avaliados retrospectivamente todos os prontuários de pacientes com ES que fizeram uso de RTX para tratamento da ES de janeiro de 2009 a janeiro de 2015. Dados de acometimento sistêmico, cutâneo, pulmonar e laboratoriais antes e seis meses após a primeira infusão de RTX foram coletados.

Resultados: Dez pacientes receberam o tratamento no período de estudo e foram incluídos na presente série de casos. Todos os pacientes tinham a forma difusa da doença. Cinco pacientes tinham formas iniciais (tempo de doença menor ou igual a quatro anos) e rapidamente progressiva da doença e cinco receberam o RTX em fases tardias da doença. Houve estabilização do quadro pulmonar em ambos os grupos de pacientes e redução no escore cutâneo nos pacientes com formas iniciais da doença.

Discussão: Similar ao encontrado em estudos prévios, o RTX foi eficaz no tratamento de formas iniciais e rapidamente progressivas da ES. Verificamos também benefício em pacientes com longa duração da doença.

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Introduction

Systemic sclerosis (SSc) is a chronic systemic autoimmune disease characterized by fibrosis, generalized vasculopathy and autoimmunity. The vasculopathy is characterized by Raynaud's phenomenon and pulmonary arterial hypertension. Fibrosis occurs mainly in the skin, causing sclerodactyly and skin thickening; in the lungs, SSc produces a progressive and irreversible interstitial lung disease.^{1,2}

Pulmonary fibrosis remains the leading cause of death in SSc. Notwithstanding that the conventional treatment with cyclophosphamide has been shown to be effective, there were no decreases in 5- and 10-year mortality and more severe forms of the disease may not respond to this treatment.³⁻⁵ It was also reported an improvement in skin involvement, assessed by the modified Rodnan skin score (mRSS); however, there is a tendency for recurrence of the condition when the therapy is discontinued.⁵ Cyclophosphamide is a highly-toxic drug and shall not be used above a cumulative dose of 18 g. Thus, new therapies are in order for serious forms of SSc, especially in patients with extensive cutaneous and pulmonary involvement.

Biological therapy has revolutionized the treatment of other autoimmune diseases such as rheumatoid arthritis and, more recently, this therapeutic strategy has been proven effective in patients with systemic lupus erythematosus. In rheumatoid arthritis, the biological therapy, including anti-TNF agents, depletion of B-cells and anti-IL-6 agents, was effective in controlling disease activity and in decreasing the radiographic progression.⁶ In patients with Granulomatosis

with Polyangiitis, the therapy with B-cell depletion with the use of rituximab (RTX) was effective in inducing disease remission, with fewer side effects versus conventional therapy with cyclophosphamide.⁷ Among immunobiological agents, RTX has been the most widely used drug in other autoimmune diseases, in addition to rheumatoid arthritis.

The possibility of the use of RTX in the treatment of severe forms of SSc was considered after evidence that B lymphocytes perform a pathogenic role in this disease. Active B lymphocytes were isolated from lung and skin biopsies from patients with SSc.^{8,9} Lafyatis et al. demonstrated a reduction in cutaneous B cell infiltrates in SSc patients treated with RTX.¹⁰

In the face of biological evidence of effectiveness and considering the need for a systemic therapy superior to cyclophosphamide, the use of RTX was tested in open-label series of patients with severe and early forms of SSc. Smith et al. prospectively studied eight patients with less than two years duration of the diffuse form of SSc treated with two infusions of 1 g of RTX.^{11,12} There was a reduction in the modified Rodnan skin score and in disease activity scores, and no progression of diffuse interstitial pneumonitis was observed. Bosello et al. studied two open-label series of patients with a diffuse disease with less than three years duration and achieved similar results.^{13,14} In Giuggioli et al. series of 10 cases, these authors achieved a significant reduction of mRSS in most patients.¹⁵ In a proof-of-concept study, RTX was superior to conventional treatment in eight patients.¹⁶ In the Scleroderma Trials and Research (EUSTAR) database, rituximab was superior to conventional treatment.¹⁷ Currently, an ongoing prospective study is being conducted by EUSTAR. It is the *Rituximab in systemic sclerosis trial (RECOVER)*.¹⁸

Based on this evidence, RTX seems to be an alternative for the treatment of severe forms of SSc. It is likely that data from the RECOVER study will be useful for future guidance on this therapy. This study was conducted in order to retrospectively evaluate a series of patients with diffuse forms and with severe cutaneous and/or organ involvement treated with RTX in our center since 2009 to-date. Patients who received RTX with indication due to the severity of the impairment, regardless of disease duration, were studied.

Patients and methods

All medical records of SSc patients who had been treated with RTX with its first infusion from January 2009 to January 2015 were retrospectively reviewed. In this study, patients were included irrespective of indication of RTX and of the form of the disease. Patients with other concomitant systemic autoimmune diseases were excluded. In our series, the outcomes evaluated were safety and efficacy of RTX in the treatment of SSc. The treatment protocol was as follows: RTX 1 g IV followed by a second infusion after 15 days. Data obtained before and six months after the infusion of RTX were reviewed.

Demographic, clinical, laboratory and immunological (including positivity, title and pattern of antinuclear antibodies [ANA]) data were collected, as well as the presence of specific antibodies against SSc.

The reason for an indication of RTX, prior use of immunosuppressants, and cumulative dose of cyclophosphamide were evaluated. Laboratory data (erythrocyte sedimentation rate – ESR), and skin activity and pulmonary function findings were recorded before and six months after the infusion of RTX. As a routine of the Infusion Center in the Rheumatology outpatient clinic, patients are observed for drug safety parameters. We checked the occurrence of any infusion reaction (allergic, or of any other type, during infusion) and/or infection of any origin.

Regarding the efficacy of the drug, the parameters evaluated were mRSS and pulmonary function assessed by pulmonary function tests (PFTs) before and after the infusion of RTX. Cutaneous activity was assessed using mRSS in 17 body areas; the test was performed before and six months after RTX, always by the same female examiner. Although mRSS has been performed in a non-blind way, the evaluation was carried out with an interval of 6 months and the examiner did not have access to the previous result. A good intra-examiner reproducibility of mRSS, when applied by an experienced examiner, was demonstrated; however, the inter-examiner reproducibility has not been proven.¹⁹ In this context, we consider mRSS as a possibly reliable test only when applied by an experienced examiner. Pulmonary activity was evaluated before and after the infusion of RTX through PFTs and high-resolution computed tomography (HRCT). In PFTs, forced vital capacity (FVC) and carbon monoxide diffusing capacity (DL_{CO}) were evaluated before and after the infusion of RTX. HRCT reports were reviewed before and six months after administration of RTX with the use of a qualitative score. The following rating scores were assigned: 1. Normal; 2. The presence of a ground glass pattern; 3. The presence of a ground glass pattern and bronchiectasis; 4. The

presence of a ground glass pattern, bronchiectasis and bronchiolectasis; 5. The presence of consolidation areas; 6. The presence of honeycombing areas, or of pulmonary fibrosis.²⁰ The stabilization of lung function, in accordance with other studies which evaluated the treatment of pulmonary fibrosis associated with SSc, was considered as a satisfactory response to treatment.^{5,17} The protocol was approved by the Research Ethics Committee of our hospital.

Statistical analysis

For the analysis of continuous variables (with normal distribution) of FVC and mRSS values, the Student t test was used. We considered as statistically significant *p* values < 0.05.

Results

Ten patients, all of them with diffuse disease (nine female and one male) received RTX for the treatment of severe manifestations of SSc during the study period. Table 1 summarizes the clinical and immunological profile, the indication of RTX and laboratory, skin and lung activity data before and six months after the treatment with RTX. The mean age was 38.3 ± 12 years; disease duration 6.6 ± 4.3 years, and mean cumulative dose of cyclophosphamide 12.9 ± 5.2 g. All patients were in concomitant use of an immunosuppressive agent; eight patients were being medicated with azathioprine 2 mg/kg/day and two used mycophenolate mofetil 2 g/day. No patient was being treated with corticosteroids. Regarding the safety endpoint, no patient had an adverse event within 6 months after the use of RTX.

We identified patients with two types of profiles; the first type was that of patients with disease duration ≤ 4 years and a fast pulmonary and/or skin involvement (patients 1–5). All patients in this group showed a rapidly progressive clinical picture and had been refractory to treatment with cyclophosphamide. Four of them had nucleolar ANA in high titers and three patients were also positive for anti-topoisomerase I (anti-Scl-70), typifying an immunological profile prognostic of a greater severity in most cases. Patients 1–3 suffered from a severe skin condition (all with mRSS > 14) and had been refractory to prior therapy with cyclophosphamide. As to the pulmonary picture, we found that, although these 3 patients did not exhibit a severe restrictive syndrome, all of them progressed to interstitial lung disease when under treatment with cyclophosphamide. According to clinical records, patient 1 had a history of FVC decrease, from 90 to 71; patients 2 and 3 had a history of worsening in their HRCT score, from 1 to 4; in all patients, this occurred during treatment with cyclophosphamide in the previous year. Patient 4 was suffering from a severe restrictive syndrome, with maximum HRCT score and mRSS = 51 even after cyclophosphamide therapy. Patient 5 showed a 10-point worsening in mRSS without the presence of a severe pulmonary involvement; however, she had a myopathy with muscle weakness and high levels of muscle enzymes. After therapy with RTX, patients 1–4 showed a significant reduction in mRSS. Patient 1 showed improvement in her cutaneous lesions from leucomelanoderma. Patient 5 showed a slight decrease in mRSS (from 18 to 16) and improved

Table 1 – Disease duration, indications, cumulative doses of cyclophosphamide, pulmonary function and laboratory data before and after treatment with rituximab.

Patient number	Disease duration	RTX indication	Cumulative dose of CTX	ESR before and after RTX	FVC% before and after RTX	DL _{CO} % before and after RTX	HRCT before and after RTX	mRSS before and after RTX	ANA and antibodies
1. 1. F, 39 years	3 years	Pulmonary disease refractory to CTX	12 g	65/25	71/70	NA	4/4	21/14	Nucleolar 1:640 + aScl70
2. 2. F, 39 years	3 years	Pulmonary and skin disease and refractory to MMF	0 g Previous use of MMF	16/20	85/84	NA	4/4	14/4	Nucleolar 1:320 + aScl 70
3. 3. F, 23 years, brown	4 years	Pulmonary and cutaneous disease refractory to CTX	12 g	15/5	90/90	NA	4/4	18/14	Nucleolar 1:640 + aScl70
4. 4. F, 56 years, Caucasian	4 years	Pulmonary and cutaneous disease refractory to CTX	12 g	5/5	58/61	60/60	6/6	51/28	Nucleolar 1:160
5. 5. F, 50 years, Caucasian	3 years	Worsening of 10 points in mRSS after maximum dose of CTX	12 g	5/5	77/77	NA	3/3	18/16	1:160 finely stippled
6. 6. F, 38 years, AA	13 years	Pulmonary function worsening	12 g	45/10	40/40	6/NA	6/6	18/6	Nucleolar 1:320 + aScl-70
7. 7. F, 62 years, Caucasian	10 years	Pulmonary function worsening	12 g	30/5	37/39	28/30	6/6	14/6	Nucleolar 1:320 + aScl-70
8. 8. M, 51 years, Caucasian	13 years	Pulmonary function worsening	18 g	10/10	71/71	37/40	6/6	7/4	Nucleolar 1:160
9. 9. F, 34 years, brown	5 years	Pulmonary function worsening	12 g	15/10	66/65	NA	6/6	10/4	Nucleolar 1: 160 + aScl-70
10. 10. F, 37 years, Caucasian 11.	6 years	Significant cutaneous worsening	12 g	47/20	52/56	66/66	4/4	40/32	Nucleolar 1:640 + aScl-70

CTX, cyclophosphamide; RTX, rituximab; mRSS, modified Rodnan skin score; ANA, antinuclear factor; aScl-70, anti-topoisomerase I antibody; NA, not available.

Table 2 – FVC (forced vital capacity) and mRSS (modified Rodnan skin score) values before and six months after the rituximab infusion.

	Mean before RTX	Mean six months after RTX	p-value
FVC	66.4 (SD 17.9)	71.2 (SD 17.6)	0.38
mRSS	20.9 (SD 13.8)	12.8 (SD 9.8)	0.003 ^a

SD, standard deviation.
^a Statistically significant.

her myopathy, with a recovery of strength and normalization of muscle enzymes. All patients showed stabilization of their lung disease six months after RTX infusion, under the protocol described in the study (Table 1).

As to patients in the second group (patients 6–10), RTX was indicated due to a sharp worsening of their pulmonary or skin condition, after a lapse of more than four years of illness. These patients had an immunological profile of ANA with a nucleolar pattern, and also with the presence of anti-Scl-70 in four patients who, despite this, showed a protracted evolution of the disease, seemingly with a predominantly irreversible fibrosis (HRCT score = 6 in patients 6–9). The values of FVC% and DL_{CO}% were sharply reduced in patients 6, 7, 9 and 10. The patient 8 showed a history of quick decrease in FVC% (from 80 to 71%) in the last year, even when he was taking mycophenolate mofetil, and with a cumulative dose of cyclophosphamide of 18 g. mRSS was above 14 in only two patients, indicating also a lower activity of skin disease. But these patients responded well to treatment, with improvement in mRSS and reports of improved exercise ability. There was no increase in the values of FVC% and DL_{CO}%, but all patients reported improvement in dyspnea; and one female patient discontinued the use of supplemental oxygen.

Considering the whole group of patients, a statistically significant improvement in mRSS was noted. There was no significant improvement in FVC, but a stabilization of lung function did occur. Table 2 summarizes FVC and mRSS values before and after treatment in all 10 patients.

Discussion

Our results suggest that, in agreement with previous studies, RTX is a safe and effective therapy for the treatment of severe forms of SSc. We found no improvement in FVC, DL_{CO} or HRCT; however, the stabilization of the patients' lung disease did occur. A significant improvement was observed in skin condition, according to the assessment by mRSS. Considering that all patients had been medicated with high cumulative doses of cyclophosphamide, RTX was an alternative to the continuation of treatment. There were no infusion reactions or infections within 6 months after the first infusion. In this context, the safety of treatment with RTX in patients with SSc is one of the main results of our study.

The first group of patients in our study has a profile similar to patients in the studies of Smith et al., Bosello et al., Daoussis et al., and Giuggioli et al.^{11–15} These initial studies evaluated series consisting of 10–20 patients in an open-label strategy.

These were patients with short-term disease and with rapidly progressive forms, characterized by an extensive skin involvement (mRSS > 14), with an incipient pulmonary disease, and refractory to conventional treatment with cyclophosphamide. Smith et al. also reported a sustained safety and efficacy after two years of follow-up.¹² Also, according to the literature, our group of patients with this profile showed a good response to treatment with RTX, with a significant decrease of mRSS in most patients and with stabilization of lung function in all female patients. It is possible that in this population of patients with early forms of the disease, RTX is beneficial in the long term in a role of a disease modifying agent.

Giuggioli et al. reported improvement in other manifestations of SSc, such as leucomelanoderma and calcinosis.¹⁵ We also found that one of our female patients showed improvement in her leucomelanoderma and another patient improved her myopathy. This result, although described in isolated cases, is noteworthy since these manifestations are typically refractory to all therapeutic arsenal. While not constituting a life-threatening or serious organ damage risk, these manifestations generate a huge esthetic and functional impact, affecting the quality of life of patients.

In a review, McQueen and Solanki commented that although the package insert of RTX does not indicate its use in the treatment of SSc, the results of open-label studies are encouraging.²¹ The authors argue that, given this evidence, it may not be appropriate to wait for the results of controlled studies to indicate the treatment with RTX in patients exhibiting a more severe profile. In our study, we included patients with a more severe disease and in a high-mortality risk. According to the review, we speculated that the mortality in our patients would be reduced with the introduction of RTX, in anticipation of the publication of prospective controlled studies.

More recently the results of the EUSTAR database, which retrospectively assessed SSc patients treated with rituximab, have been published.¹⁷ A greater number of patients (63 in 42 centers) and a control group of patients with similar profiles and whose members received only a conventional immunosuppressant treatment were included. An absolute improvement of 25% in mRSS was observed in those patients treated with RTX. Similar to our results, there was also an improvement in patients living with long-term illness. These data suggest that the benefits are not exclusive to patients with early forms of the disease. An improvement was also noted in patients with more than three years' disease. In EUSTAR patients treated with RTX, the authors observed stabilization of lung function, based on an assessment by pulmonary function tests. In the control group, a significant worsening of FVC was observed. Our study lacks a control group; but the EUSTAR results confirm our impression that, in these patients, the stabilization of lung function corroborates its efficacy. These results suggest that RTX may also be used in patients with longer-duration forms and with more serious organ damage. It is argued that in the early years of this disease, it is possible that a spontaneous improvement comes up, being difficult to attribute the results to the drug. However, in previous studies its patients had already proved to be refractory to treatment during the first year of disease with

cyclophosphamide. This outcome, coupled with the evidence from the EUSTAR database and from the Daoussis' proof-of-concept study, suggests that the improvement should not be attributed to the natural history of the disease, but to the pharmacological treatment. This question shall be answered with the results of the RECOVER trial, that prospectively includes a group of treatment with rituximab and a control group.¹⁸

However, our study has its limitations. It has a retrospective design, with the possibility of data loss. There is also the lack of a control group, and we could not guarantee that the improvement would have occurred, even in untreated patients. It was not possible to perform a volumetric quantitative assessment of HRCT changes. The follow-up period was also relatively short; thus, it was not possible to assess whether there would be better results in a longer term.

Further studies with the inhibition of B cells as a therapy for SSc at earlier stages of the disease and with precise indications are necessary and can change the course of this disease, with its high morbidity and mortality.

Conflicts of interest

The authors declare no conflicts of interest.

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