


## SHORT REPORT

## RHEUMATOLOGY

# Effect of short-interval rituximab and high-dose corticosteroids on kidney function in systemic sclerosis: Long-term experience of a single centre

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**Abstract**

**Introduction:** Scleroderma renal crisis (SRC) is a rare but one of the most recognised complications of systemic sclerosis (SSc). Corticosteroid (CS) use has been considered as a major risk factor for SRC. Several studies reported the efficacy of rituximab (RTX) with an acceptable safety profile in SSc. However, data on the long-term effect of high-dose CS concomitant to RTX on kidney function are lacking.

**Methods:** We retrospectively analysed SSc patients (n = 35) treated with a lower dosage and short-interval RTX and concomitant high-dose CS at the Department of Internal Medicine at the Medical University of Graz between 2010 and 2019. The kidney function was assessed using the estimated glomerular filtration rate (eGFR) at every RTX admission. The annual decline of kidney function was evaluated by linear mixed model analysis.

**Results:** At the RTX initiation, one patient had a decreased kidney function indicated by eGFR < 60 mL/min/1.73 m<sup>2</sup> (median: 96 mL/min/1.73 m<sup>2</sup>; interquartile range (IQR): 43-136). Patients received RTX and complementary high-dose CS for a median follow-up time of 3.4 years (range 0.6-9.5). A linear mixed model analysis with the patient as random effect and time from first RTX as fixed effect estimated an annual decline of 1.98 mL/min/1.73 m<sup>2</sup> of the eGFR (95% confidence interval: [-2.24, -1.72]; P < .001). During the follow-up period, no patient experienced SRC or a significant drop in kidney function.

**Conclusions:** A regular, high-dose CS given contemporary to RTX seems to be a safe option for kidney function in patients with SSc. Our findings provide additional knowledge in risk evaluation and planning of individualised therapies or designing clinical studies using RTX.

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## 1 | INTRODUCTION

Systemic sclerosis (SSc) is an immune-mediated multiorgan disease characterised by autoimmunity, inflammation, vasculopathy and progressive fibrosis.<sup>1</sup> Renal involvement associated with vasculopathy is commonly seen in SSc, which usually shows a benign course. In contrast, scleroderma renal crisis (SRC) is rare but one of the most recognised complications of SSc.<sup>2</sup> Despite distinct improvements in therapy, a significant proportion of patients with SRC develop end-stage renal disease (ESRD), and the survival remains poor.<sup>3</sup> Several risk factors are associated with SRC, including the recent use of corticosteroids (CS).<sup>2</sup>

In the last years, several studies, including randomised, controlled trials (RCTs) and open-label prospective studies, reported the efficacy of rituximab (RTX), and RTX biosimilar with an acceptable safety profile in SSc.<sup>4-8</sup> However, since some patients may experience infusion-related adverse reactions such as antibody-mediated hypersensitivity and non-antibody-mediated reactions, a premedication protocol with substantial CS use is not avoidable. According to the European League Against Rheumatism (EULAR) recommendations, SSc patients treated with CS should be carefully monitored for the development of SRC.<sup>6</sup> We previously reported a case series of SSc patients successfully treated with a lower dosage and short-interval RTX regime.<sup>9</sup> These data might favour a short interval application as a treatment of choice in SSc, but data on the safety of this protocol on kidney function regarding the frequent use of high-dose CS are lacking. Therefore, we aimed to describe the long-term effect and safety of high-dose CS on kidney function obtained longitudinally in SSc patients who received a short-interval RTX regime.

## 2 | METHODS

### 2.1 | Study design and patients

We retrospectively analysed SSc patients treated with RTX at the Department of Internal Medicine at the Medical University of Graz between 2010 and 2019. Thirty-nine patients received a lower dosage and short-interval RTX 500 mg on day 0 and day 14, and then twice every three months. Intravenous systemic prednisone at a fixed 100 mg dose was administered 30 minutes before every RTX application. We ultimately analysed 35 out of 39 patients because, in the remaining patients, we were unable to obtain the initial kidney function parameters ( $n = 2$ ), or the patient had SRC and/or was on haemodialysis ( $n = 2$ ) before RTX treatment. The kidney function using the estimated glomerular filtration rate (eGFR assessed by CKD-EPI formula) was assessed at every RTX admission.<sup>10</sup> The last observation occurred when the SRC occurred, the patient died, the patient left the practice, or the study ended in June 2020. The study protocol was reviewed and approved by an independent ethics committee of the local institution (Ethics Committee of the Medical University of Graz – EK-Numbers: 31-171 ex 18/19 and 24-184 ex 11/12).

### What's known

- Corticosteroid (CS) use has been considered as a major risk factor for scleroderma renal crisis.
- A short interval application of rituximab (RTX) as a treatment of choice in SSc might be favoured, but data on the safety of this protocol on kidney function regarding the frequent use of high-dose CS are lacking.

### What's new

- Our findings provide additional knowledge in risk evaluation and planning individualised therapies or designing clinical studies using RTX.

## 2.2 | Statistical analysis

Patient characteristics at the time of first RTX were descriptively summarised using median and interquartile range (IQR) for continuous parameters and absolute and relative frequencies for categorical parameters. A linear mixed model analysis was performed to estimate the eGFR trend over time. In the model, the patient was used as a random effect due to the repeated measurements, and time from first RTX at the respective time of eGFR measurement was used as a fixed effect. The analyses were performed using R version 4.0.3.

## 3 | RESULTS

Table 1 gives the characteristics of the SSc patients at the start of RTX, SRC risk factors, RTX indications, and the number of therapy cycles. Most of the 35 patients had at least one SRC risk factor at the time of RTX initiation: 8 (23%) were male, 28 (80%) had diffuse cutaneous SSc, 11 (31%) a modified Rodnan skin score (mRSS) >20, 2 (6%) cardiac involvement, and 8 (23%) used angiotensin-converting enzyme inhibitors (ACEi). Anti-RNA-Polymerase III measurement was available only in 10 patients, and none was positive.

The median number of RTX cycles was 21, and thus the median cumulative dose was 2100 mg. The lowest cumulative dose given was 500 mg (5 cycles), while the highest cumulative dose was 5100 mg (51 cycles) among the study patients. Five patients received antihypertensive agents newly prescribed during the follow-up period. However, in only two cases was development of arterial hypertension was observed, and an ACE-inhibitor with beta-blocker or a CCB was prescribed. CCBs have been prescribed to prevent peripheral small vessel changes in the other three cases.

At the time of RTX initiation, one patient had a decreased kidney function indicated by eGFR < 60 mL/min/1.73 m<sup>2</sup>. The median eGFR was 96 mL/min/1.73 m<sup>2</sup> (interquartile range (IQR): 43-136). Patients received RTX and complementary high-dose CS for a median follow-up time of 3.4 years (range 0.6-9.5). A linear mixed model analysis with the patient as random effect and time from

**TABLE 1** Clinical characteristics of the study population at the time of rituximab initiation

Total number of patients, n	35
Age, y	52 (29-71)
Female, n (%)	27 (77)
BMI (kg/m <sup>2</sup> )	23.5 (17.4-45.9)
SSc-related data	
lcSSc, n (%)	7 (20)
dcSSc, n (%)	28 (80)
MCTD, n (%)	5 (14)
mRSS	16 (3-39)
Antibody profile	
ANA, n (%)	34 (97)
ENA, n (%)	23 (66)
CENP-B, n (%)	3 (9)
Anti-Scl-70, n (%)	19 (54)
Anti-U1-RNP, n (%)	3 (9)
Ro, n (%)	7 (20)
Kidney function	
Creatinine (mg/dL)	0.70 (0.48-1.91)
eGFR (mL/min/1.73 m <sup>2</sup> )	96 (43-136)
eGFR < 60 mL/min/1.73 m <sup>2</sup> , n (%)	1 (3)
Proteinuria ≥ 2+ by dipstick	0 (0)
RTX cycles, steroid dose, and indication	
RTX cycles	21 (5-51)
Cumulative steroid dose (mg) <sup>a</sup>	2100 (500-5100)
Skin involvement, n (%)	14 (40)
Lung involvement, n (%)	26 (74)
Esophageal involvement, n (%)	5 (14)
Heart involvement, n (%)	2 (6)
Muscle involvement, n (%)	1 (3)
Joint involvement, n (%)	2 (6)
Antihypertensive therapy	
ACEi, n (%)	8 (23)
ARB, n (%)	0 (0)
CCB, n (%)	7 (20)
Beta-blocker, n (%)	3 (9)

Note: Continuous variables are expressed as median (interquartile range, q1-q3), categorical variables as n (%).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ANA, antinuclear antibody; ARB, angiotensin receptor blocker; AZA, azathioprine; BMI, body mass index; CCB, calcium channel blocker; CENP-B, centromere protein B; CS, corticosteroid; dc, diffuse cutaneous; eGFR, estimated glomerular filtration rate; ENA, extractable nuclear antigen; lc, limited cutaneous; MCTD, mixed connective tissue disease; mRSS, modified Rodnan skin score; RTX, rituximab; SRC, scleroderma renal crisis; SSc, systemic sclerosis.

<sup>a</sup>Cumulative steroid dose concomitant to rituximab therapy during the observation period, 100 mg per cycle

first RTX as fixed effect estimated an annual decline of 1.98 mL/min/1.73 m<sup>2</sup> of the eGFR (95% confidence interval: [-2.24, -1.72];  $P < .001$ ; Figure 1). At the end of the observation period, the

median eGFR was 88.4 mL/min/1.73 m<sup>2</sup> (IQR: 76.7-99.4), while the serum creatinine was 0.8 mg/dL (IQR: 0.6-0.9). During the follow-up period, no patient experienced SRC or a significant drop in kidney function.

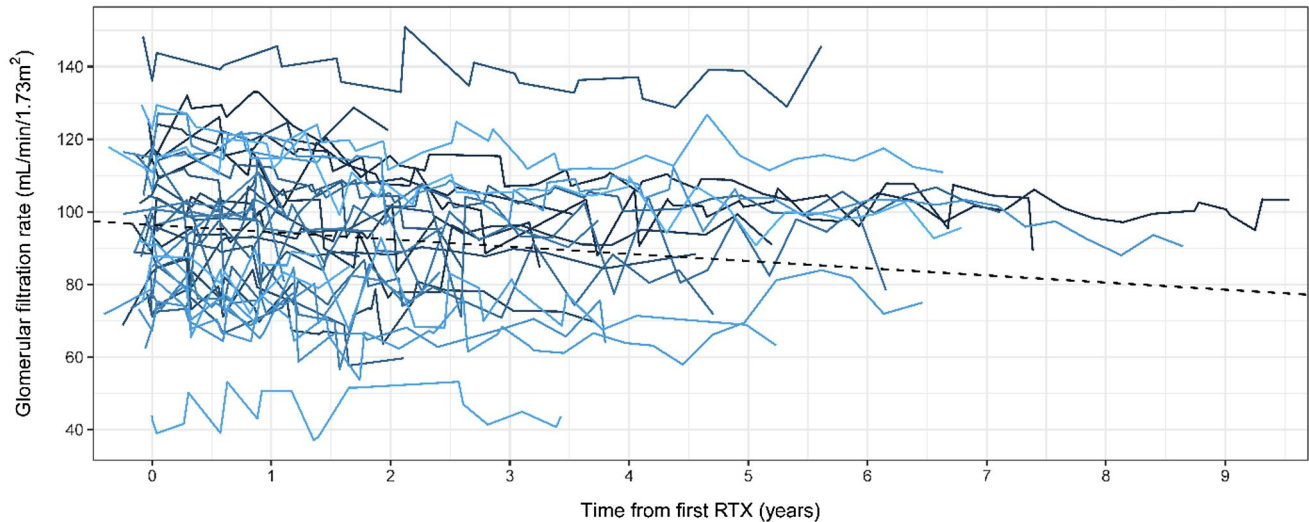
## 4 | DISCUSSION

In this study investigating SSc patients who received a high dose of systemic prednisone given to a short-interval RTX regime, we observed no SRC or significant drop in kidney function during the observation period.

SRC is a potentially life-threatening complication of SSc.<sup>11</sup> So far, CS use is considered as a significant risk factor for SRC irrespective of whether medium-, high, or prolonged use of low doses are applied.<sup>12</sup> In some clinical situations, the usefulness of CS has been considered, particularly in patients with very early disease and in those with initial organ involvement.<sup>12-14</sup> Moreover, glucocorticoids remain a part of the therapeutic strategy in SSc patients with musculoskeletal involvement.<sup>12-14</sup> Nevertheless, the need for CS therapy in SSc patients should be carefully considered, and individualised risk stratification in every patient is required. Since RTX is often used in the management of SSc, particularly in patients with interstitial lung disease, inflammatory arthritis, skin involvement, and overlap syndrome, adverse events such as SRC due to contemporary CS use must be considered.<sup>4,5,7,13</sup> Previously, RTX regimes applied in the different studies used a subsequently lower total CS dose during a shorter median follow-up time than our protocol.<sup>4,5,7</sup> Because CS given in higher doses has been extensively described as associated with higher SRC incidence and outcome, a close follow-up of kidney function in our patients was essential.<sup>15</sup> Importantly, in our cohort, 80% of the patients had diffuse cutaneous disease subset, and most of them had at least one SRC risk factor. However, no SRC occurred, and only in two cases were a newly developed arterial hypertension observed that necessitated antihypertensive therapy initiation.

The control of blood pressure in SSc patients is challenging.<sup>16</sup> In our cohort, most of the patients received ACEi due to previously diagnosed arterial hypertension at baseline. Despite the clear benefit of ACEi in SRC and certain patient populations, including those with chronic kidney disease (CKD),<sup>17</sup> data on their effect on preventing SRC and the development of CKD in patients with SSc are controversial. In an early study that investigates patients with SSc with proteinuria, ACEi initiation led to decreased proteinuria.<sup>18</sup> In contrast, recent publications concluded that ACEi might represent an independent risk factor for the development of SRC, particularly in those with proteinuria.<sup>16,19</sup> Therefore, the use and safety of ACEi should be considered carefully in SSc patients receiving CS, and studies on different antihypertensive agents should focus in more detail on this population.

Despite the smaller number of patients involved in our study, our data with nearly fully administrated kidney function during RTX therapy could demonstrate a safe option for using a frequent, high-dose CS given to RTX. Notably, patients receiving RTX who have severe internal organ involvement or poor prognostic features and are



**FIGURE 1** Kidney function over time in patients with systemic sclerosis received rituximab and contemporary high-dose corticosteroid

most likely to receive additional CS or those treated with potentially nephrotoxic medications should be more carefully followed for SRC.

Controlled trials are needed to confirm the beneficial effects of a short interval and low-dosage RTX regime on various organ involvements in patients with SSc. Here, the possible negative impact of the frequent use of high-dose CS must be implemented by all physicians deciding for RTX. Nevertheless, in this analysis, we demonstrated that this regime using a regular, high-dose CS given contemporary to RTX seems to be a safe option for kidney function in patients with SSc. Our findings provide additional knowledge in risk evaluation and planning individualised therapies or designing clinical studies using RTX. Despite these results, we recommend continuing the tight control of kidney function and blood pressure during RTX application in SSc.

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#### DISCLOSURE

The authors declare no conflicts of interest.

#### DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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