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Review

# Rituximab in the treatment of patients with systemic sclerosis. Our experience and review of the literature

Dilia Giuggioli [a], Federica Lumetti [a], Michele Colaci [a], Poupak Fallahi [b], Alessandro Antonelli [b], Clodoveo Ferri [a,*]

[a] Chair and Rheumatology Unit, University of Modena and Reggio Emilia, Medical School, Azienda Ospedaliero-Universitaria, Policlinico di Modena, Modena, Italy
[b] Department of Internal Medicine, School of Medicine, University of Pisa, Pisa, Italy

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ABSTRACT

*Background:* The treatment of systemic sclerosis (SSc) represents a great clinical challenge because of the complex disease pathogenesis including vascular, fibrotic, and immune T- and B-lymphocyte-mediated alterations. Therefore, SSc should be treated by combined or sequential therapies according to prevalent clinico-pathogenetic phenotypes. Some preliminary data suggest that rituximab (RTX) may downregulate the B-cell over expression and correlated immunological abnormalities.
*Methods:* Here, we describe a series of 10 SSc patients (4 M and 6 F, mean age 46 ± 13.5SD years, mean disease duration 6.3 ± 2.7SD years; 5 pts had limited and 5 diffuse SSc cutaneous subset) treated with one or more cycles of RTX (4 weekly infusions of 375 mg/m$^2$). The main indications to RTX were interstitial lung fibrosis, cutaneous, and/or articular manifestations unresponsive to previous therapies; ongoing treatments remained unchanged in all cases. The effects of RTX were evaluated after 6 months of the first cycle and at the end of long-term follow-up period (37 ± 21SD months, range 18–72 months). An updated review of the world literature was also done.
*Results:* RTX significantly improved the extent of skin sclerosis in patients with diffuse SSc at 6 months evaluation (modified Rodnan skin score from 25 ± 4.3 to 17.2 ± 4.6; p = .022). A clinical improvement of other cutaneous manifestations, namely hypermelanosis (7/7), pruritus (6/8), and calcinosis (3/6) was observed. Moreover, arthritis revealed particularly responsive to RTX showing a clear-cut reduction of swollen and tender joints in 7/8 patients; while lung fibrosis detected in 8/10 remained stable in 6/8 and worsened in 2/8 at the end of follow-up. Pro-inflammatory cytokines, namely IL6, IL15, IL17, and IL23, evaluated in 3 patients with diffuse cutaneous SSc, showed a more or less pronounced reduction after the first RTX cycle.
These observations are in keeping with the majority of previous studies including 6 single case reports and 10 SSc series (from 5 to 43 pts), which frequently reported the beneficial effects of RTX on some SSc manifestations, particularly cutaneous sclerosis, along with the improvement/stabilization of lung fibrosis. Possible discrepancies among different clinical studies can be related to the etiopathogenetic complexity of SSc and not secondarily to the patients' selection and disease duration at the time of the study.
*Conclusion:* The present study and previous clinical trials suggest a possible therapeutical role of RTX in SSc, along with its good safety profile. The specific activity of RTX on B-cell-driven autoimmunity might explain its beneficial effects on some particular SSc clinical symptoms, namely the improvement of skin and articular involvement, and possibly the attenuation of lung fibrosis.

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**Contents**



* Corresponding author at: Chair and Rheumatology Unit Dpt of Internal Medicine, University of Modena and Reggio E. Policlinico di Modena Via del Pozzo, 71 41100 Modena, Italy, Tel +39 059 4224053; fax +39 059 4224178.
*E-mail address:* clferri@unimore.it (C. Ferri).

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## 1. Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by specific autoimmune abnormalities, diffuse microangiopathy, and accumulation of collagen and other matrix constituents in the skin and target internal organs [1,2]. Clinically, SSc appears as multifaceted disorder consequent to the variable contribution of the above pathogenetic mechanisms, through a multistep process responsible for different clinical phenotypes. These latter represent a variable combination and degree of typical SSc symptoms: from vascular manifestations, i.e. skin ulcers, pulmonary arterial hypertension, and/or renal scleroderma crisis, to fibrotic cutaneous and visceral organ involvement [1–4]. Abnormal humoral and cellular immune activation may decisively contribute to both vascular and fibrotic SSc manifestations [1–4]; however, the complex and pleiotropic nature of the immune response in SSc constitutes a great therapeutic challenge [1–6]. The effects of nonselective immunosuppressive treatments, usually employed during the early phases of SSc to control skin and lung inflammation, are often unpredictable. In addition, they tend to lose their efficacy once the disease enters a chronic phase, and consequently their long-term treatment is not recommendable considering their potential severe side-effects [4].

Given the close interrelationship between altered immune response and initiation/propagation of the other SSc pathogenetic events, the usefulness of novel immunomodulating therapies targeting specific cellular and/or molecular immune effectors requires to be carefully investigated [6]. In particular, the rationale for the use of rituximab (RTX), able to downregulate the B-cell over expression, is largely demonstrated in different autoimmune diseases [7–14]; moreover, some important experimental data suggested a key role for B cells in regulating both inflammatory and fibrotic alterations that characterize several SSc manifestations [4,6,15,16]. On the basis of laboratory investigations, during the last years preliminary clinical trials have suggested the therapeutical usefulness of RTX also in SSc [17,18].

Here we report our experience with RTX treatment in a series of SSc patients along with the updated review of the world literature on this topic.

### 1.1. Patients and methods

The present study included 10 SSc patients (4 M and 6 F, mean age 46 ± 13.5SD years, mean disease duration 6.3 ± 2.7 SD years) treated with one or more cycles of RTX and evaluated during a mean follow-up period of 37 ± 21SD months, range 18–72 months (Table 1). All patients, followed at our University-based Rheumatology Unit, satisfied EULAR/ACR 2013 criteria for SSc classification [19].

Scleroderma cutaneous and visceral organ involvement, including pulmonary, cardiac, renal, and gastrointestinal alterations, as well as routine blood chemistry, urinalysis, and immunological alterations were evaluated according to previously described methodologies [3,5]. The following serological markers were detected by means of standard techniques: anti-nuclear (ANA), anti-centromere (ACA), anti-nucleolar (ANoA), and anti-extractable nuclear antigen (ENA) antibodies; these latter included anti-Scl70, -Sm, -RNP, -SSB, -SSA, -PCNA, -SL, and Jo1 [3].

**Table 1**
Epidemiological and clinico-serological features of SSc patients before/after rituximab treatment.

| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Age/sex | 70/M | 74/F | 68/F | 80/F | 74/F | 24/F | 29/M | 45/M | 41/F | 39/M |
| SSc dur. (yrs) | 22 | 13 | 25 | 20 | 9 | 3 | 12 | 2 | 4 | 5 |
| SSc cutaneous subset | Limited | Limited | Limited | Limited | Limited | Diffuse | Diffuse | Diffuse | Diffuse | Diffuse |
| Autoantibodies | ACA | ACA | ACA | ACA | ACA | ANoA | Anti-Scl70 | Anti-Scl70 | Anti-Scl70 | Anti-Scl70 |
| Indication to RTX | L, A | L, A, DU | L, C | L, A, C, DU | L, A, DU, C | A, DU, C, S | L, DU, C, S | L, A, S | L, A, S, DU | A, S |
| RTX cycles | 5 | 2 | 2 | 2 | 3 | 1 | 5 | 2 | 4 | 2 |
| Other therapies | B, Ccb, Cs | B, Ilo, Ccb, Cs | Ilo, Ccb, Cs | Ilo, Ccb, Cs | Ilo, Lef, Ccb, Cs | B, Ilo, Mmf, Ccb, Cs | B, Ilo, Mmf, Ccb, Cs | Ilo, Lef, Ccb, Cs | B, Ilo, Mmf, Ccb, Cs | B, Ilo, Ccb, Cs |
| Follow-up (months) | 72 | 72 | 30 | 18 | 30 | 18 | 48 | 18 | 36 | 24 |
| *Clinical features (baseline/6mth/end of follow-up)Skin* | | | | | | | | | | |
| mRSS | 6/6/6 | 4/4/4 | 6/6/6 | 4/4/4 | 4/4/4 | 33/22/30 | 24/18/20 | 22/20/20 | 24/16/18 | 26/10/10 |
| Digital ulcers[a] | −/−/− | +/+/+ | −/−/− | +/+/+ | +/+/+ | +/+/+ | +/+/+ | −/−/− | +/+/+ | −/−/− |
| Calcinosis (I/U/W) | −/−/− | −/−/− | +/u/u | +/u/u | +/u/u | +/i/i | +/i/i | −/−/− | +/i/i | −/−/− |
| Melanodermia | +/i/u | −/−/− | −/−/− | −/−/− | +/i/u | +/i/i | +/i/i | +/i/i | +/i/i | +/i/u |
| Pruritus | −/−/− | −/−/− | +/i/u | +/u/u | +/u/u | +/i/i | +/i/i | +/i/i | +/i/i | +/i/i |
| Lung[b] | +/u/u | +/u/u | +/u/u | +/u/u | +/u/u | −/u/u | +/u/w | −/−/− | +/u/w | +/u/u |
| *Cardiovascular inv.* | | | | | | | | | | |
| LV involvement (ECHO) | +/u/u | +/u/u | −/−/− | +/u/w | −/−/− | −/−/− | −/−/− | −/−/− | −/−/− | −/−/− |
| PAH | +/u/w | +/u/w | +/u/u | +/u/w | −/−/− | −/−/− | −/−/− | −/−/− | −/−/− | −/−/− |
| Esophagus dysphagia | +/u/u | −/u/u | +/u/u | −/u/u | −/−/− | +/u/u | +/u/u | −/−/− | +/u/u | −/−/− |
| Kidney | −/−/− | −/−/− | −/−/− | −/−/− | −/−/− | −/−/− | −/−/− | −/−/− | −/−/− | −/−/− |
| Arthritis | +/i/u | +/i/i | −/−/− | +/u/u | +/i/i | +/i/i | −/−/− | +/i/i | +/i/i | +/i/i |
| *Cumulative results* | | | | | | | | | | |
| 6 months | i (A) | i (A) | u | u | i (A) | i (A, C, S) | i (C, S) | i (A, S) | i (A, C, S) | i (A, S) |
| End of follow-up | u[c] | i (A)[c] | u | u[c] | i (A) | i (A, C, S) | i (C, S) | i (A, S) | i (A, C, S) | i (A, S) |

L: lung; A: arthritis; DU: digital ulcers; C: calcinosis; S: skin involvement evaluated by modified Rodnan skin score (mRSS); i/u/w: improved/unchanged/worsened; ECHO: ecocolorDoppler cardiography; B: bosentan; Lef: leflunomide; Ilo: iloprost; Mmf: mycophenolate mofetil; Cs: corticosteroids; Ccb: calcium channel blockers; ACA: anticentromere; ANoA: antinucleolar; anti-Scl70: antitopoisomerase 1 antibodies.

[a] Digital ulcers detected at baseline in 6/6 pts were unresponsive to RTX needing in all cases of other systemic and local treatments.

[b] Interstitial lung involvement evaluated by means of HRCT, FVC, Dlco, and 6-minute walking test.

[c] Deceased due to the progression of pulmonary arterial hypertension (PAH).

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