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Original article

Intravenous cyclophosphamide *vs* rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial

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Abstract

Objectives. SSc is characterized by fibrotic changes in the skin and lung, and the mainstay of treatment has been CYC. B cell involvement suggests that rituximab (RTX) may also be of therapeutic benefit. The aim of the study was to compare the efficacy and safety of RTX compared with CYC in retarding the progression of interstitial lung disease and skin manifestations of primary SSc.

Methods. We randomly assigned 60 patients of dcSSc, age 18–60 years with skin and lung involvement, to monthly pulses of CYC 500 mg/m^2 or RTX 1000 mg $\times$ 2 doses at 0, 15 days. Primary outcomes were forced vital capacity (FVC) percent predicted at 6 months. Secondary outcomes were: absolute change in litres (FVC-l) at 6 months; modified Rodnan skin scores at 6 months, 6-min walk test, Medsgers score and new onset or worsening of existing pulmonary hypertension by echocardiographic criteria.

Results. The FVC [%mean (S.D.)] in the RTX group improved from 61.30 (11.28) to 67.52 (13.59), while in the CYC group it declined from 59.25 (12.96) to 58.06 (11.23) at 6 months (P = 0.003). The change of FVC was 1.51 (0.45) l to 1.65 (0.47) l in the RTX group, compared with 1.42 (0.49) to 1.42 (0.46) l in the CYC group. The mRSS changed from 21.77 (9.86) to 12.10 (10.14) in the RTX group and 23.83 (9.28) to 18.33 (7.69) in the CYC group after 6 months. Serious adverse events were more common in the CYC group.

Conclusion. RTX is a safe and effective alternative to CYC in the primary therapy of skin and lung manifestations of scleroderma.

Trial registration. Clinical Trials Registry – India, www.ctri.nic.in, CTRI/2017/07/009152.

Key words: diffuse systemic sclerosis, rituximab, cyclophosphamide, interstitial lung disease, forced vital capacity, modified Rodnan skin score

CLINICAL SCIENCE

Rheumatology key messages

- Interstitial lung disease is an important cause of morbidity and mortality in SSc.
- Rituximab is an effective treatment of interstitial lung disease in early SSc, with improvement in skin and lung function.
- The adverse event profile of rituximab is superior to cyclophosphamide.

Introduction

SSc is a CTD characterized by progressive cutaneous fibrosis and collagen deposition in other organs, notably in lung, heart and accompanied by a microvascular obliterative vasculopathy. Pulmonary fibrosis, leading to interstitial lung disease (ILD), is the leading cause of death, followed by pulmonary hypertension and cardiac involvement [1]. CYC has been shown to be efficacious in retarding progression of pulmonary disease in SSc [2–5]. However, it is associated with many adverse effects including infections, gonadal failure and malignancies [6]. Other agents used include MMF, sirolimus and alefacept [7]. B cells have been demonstrated in the skin and lungs of patients of scleroderma with ILD, and skin expression of B cell related genes has also been found [8–10]. Scleroderma patients have an expanded population of naïve B cells but a diminished population of

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memory B cells. However, these memory B cells are highly active and overexpress CD19$^+$ [11]. Thus, the B cell is a potential therapeutic target in SSc. Rituximab (RTX) has been used in patients with SSc with pulmonary and renal involvement and has shown efficacy in patients refractory to CYC [10, 12–18]. One proof-of-concept open label trial compared RTX to standard therapy; RTX improved forced vital capacity (FVC) by a median of 10.25% compared with a 5.04% deterioration in the control group [18].

There has been, to our knowledge, no direct head-to-head comparison between CYC and RTX in SSc. This open label, randomized, parallel group clinical trial has been designed to evaluate the safety and efficacy of RTX compared with CYC in the treatment of early SSc, with reference to pulmonary and skin manifestations.

Methods

Design and ethics

The present study was a prospective, randomized, open-label, parallel group, trial done at the Department of Rheumatology, Institute of Post Graduate Medical Education and Research, Kolkata, India. The protocol was approved by Institutional Ethics Committee, Institute of Post Graduate Medical Education and Research. Patients were recruited in the period from February 2016 to 2017 and were followed up with monthly visits for at least 6 months.

Participants

Inclusion criteria were: patients with dcSSc, fulfilling the ACR classification criteria 2013 [19]; positivity towards anti-Scl-70 antibody; age 18–60 years; presence of ILD by high resolution CT thorax (HRCT) criteria [4] and pulmonary function testing. Criteria for pulmonary function testing included predicted FVC of $<$80% but at least 45% and reproducible within 10% at the baseline visit (but $\leqslant$85%). The onset of the patient's first symptom of SSc (including RP) should be within 3 years of inclusion in the trial. Baseline dyspnea level should be New York Heart Association Class II and III. Exclusion criteria were: subjects who received any immunosuppression including CYC or RTX of any length before inclusion; patients with pregnancy or breast-feeding or patients with active systemic infections; presence of hepatitis B and C, HIV infections or active tuberculosis; patients with autoimmune overlap syndromes; the New York Heart Association functional class IV symptoms of shortness of breath; presence of moderate to severe pulmonary hypertension (mean pulmonary artery pressure by echocardiogram $>$40 mmHg), FVC of $<$45% predicted, ratio of FEV1 (forced expiratory volume during first second) to FVC of $<$65%, clinical evidence of substantial airflow obstruction, clinically significant abnormalities on HRCT not attributable to SSc; smoking within the past 6 months; persistent unexplained haematuria ($>$5 red blood cells per high power field); persistent leucopenia (white blood cell count $<4.0 \times 10^9$/l) or thrombocytopenia (platelet count $<150 \times 10^9$/l); clinically significant anaemia (haemoglobin $<$80 g/l); baseline liver enzymes (alanine aminotransferase and aspartate aminotransferase) 1.5 times the upper limits of normal; serum creatinine $>$1.3 mg/dl or presence of scleroderma renal crisis and uncontrolled congestive heart failure.

Randomization

A computer-generated random number table was used for simple randomization. Opaque, sequentially numbered envelopes were used to determine allocation sequence.

Procedures and interventions

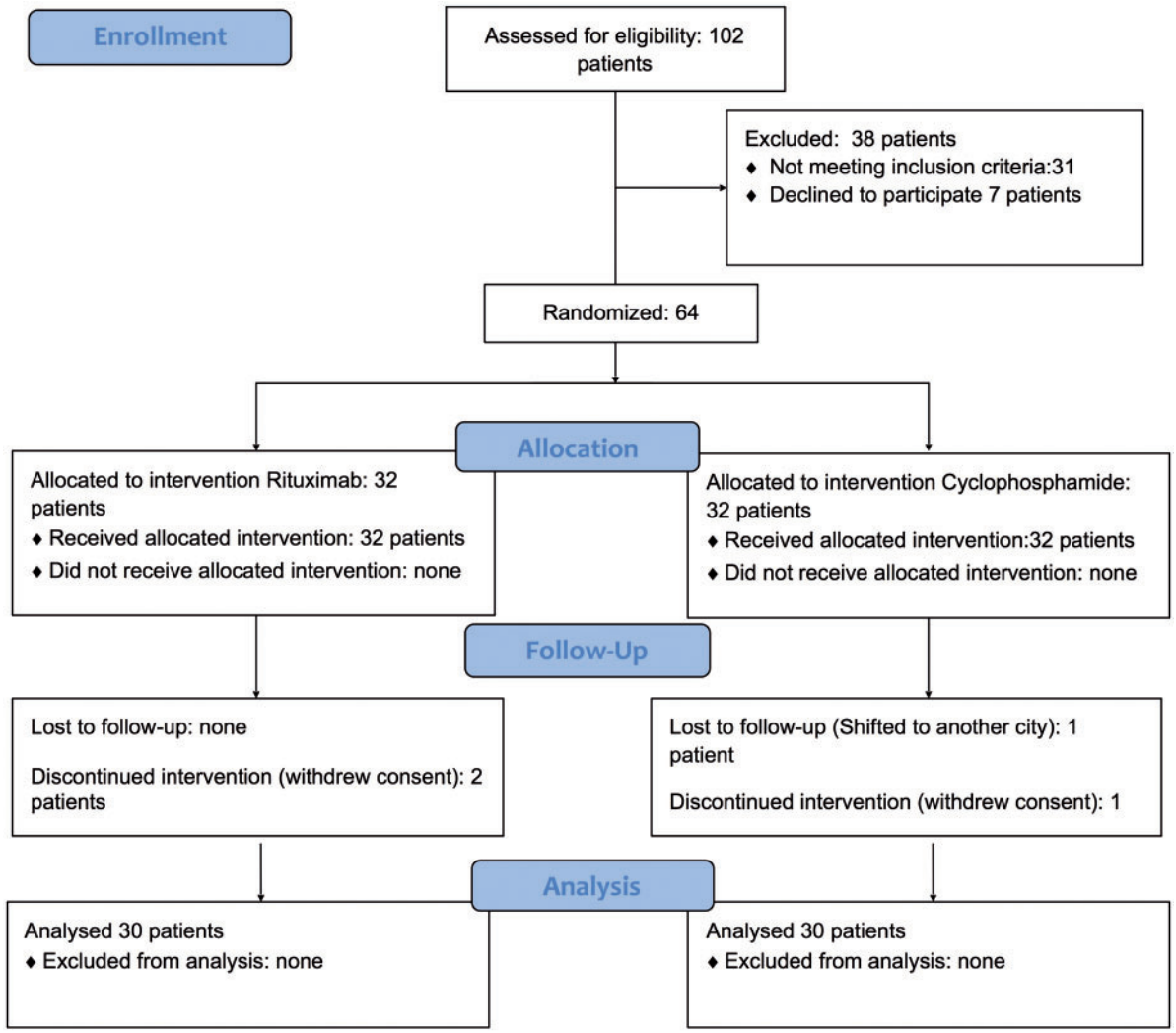
Baseline assessments included: detailed history and physical examination, complete hemogram, electrolytes, urea, creatinine, liver function tests, viral serology, ANA profile (Euroimmun, Germany), serum baseline immunoglobulin level, B cell count (CD19$^+$, CD20$^+$), ECG, urinalysis, chest C-ray, Mantoux test, echo-Doppler study, HRCT chest, pulmonary function testing and a 6-min walk test. The modified Rodnan skin score (mRSS) was done in all. All these parameters (except the Mantoux test and HRCT scan) were repeated at 24 weeks. A single assessor (G.S.) did the mRSS on both the occasions. Intra-rater reliability was previously calculated to be high (intraclass correlation coefficient was 0.96, 95% CI: 0.86, 0.99; $P < 0.001$).

Patients were randomized to the CYC or RTX groups. Patients in the CYC group received 500 mg/m^2 of CYC i.v. pulses every 4 weeks for 24 weeks. CYC powder was dissolved in 400 ml of normal saline and administered in i.v. route over 4 h. Patients in the RTX group received two RTX pulses of 1000 mg at 0 and 15 days i.v., dissolved in 400 ml of normal saline given over 4 h with the following premedications: paracetamol 500 mg along with 10 mg of prednisolone. Both groups received prednisolone 10 mg/day and calcium and vitamin D throughout the course. After 24 weeks, patients in the CYC group received AZA or MMF for maintenance according to the physician's preference. Patients in the RTX group received 1000 mg of RTX after 6 months as maintenance therapy, after checking CD19$^+$ and CD20$^+$ B cell counts and serum immunoglobulin levels. All patients gave written informed consent.

Outcome variables

Primary outcome was FVC percent predicted (FVC%) at 24 weeks. Secondary variables considered were: absolute change in litres (FVC-l) at 6 months; mRSS at 6 months, 6-min walk test, Medsgers score (sum of individual component score) and new onset or worsening of existing pulmonary hypertension (mean pulmonary arterial pressure) estimated by echocardiographic criteria. Change of mRSS was further categorized as improvement (reduced by $\geqslant$4 points), worsening (increased by $\geqslant$4 points) or stable (change in either direction $\leqslant$3 points). Change of FVC (%) was also categorized as improvement (improved by $>$10%), worsening (worsened by $>$10 points) or stable (change in either direction $\leqslant$10 points).

Fig. 1 Participant flow diagram



Statistical analysis

To calculate the sample size needed for a non-inferiority margin, the mean of FVC (%) after completion of CYC therapy in the Scleroderma lung study [2] was considered. Considering that the final mean FVC% was 66.6 (1.7%) and considering a 2% improvement over this value to be within a non-inferiority margin, we calculated that a sample size of 52 patients (26 in each group) would be needed to achieve a power of 80% with an alpha error probability of <0.05. The final number of patients to be recruited was planned to be around 60, with 30 in each group assuming 10% attrition.

Continuous variables were expressed as mean (S.D.) and categorical variables as percentage (fraction). T tests, Wilcoxon signed rank test and Mann–Whitney *U* test were used, as appropriate, for continuous variables and Fisher's Exact test/Chi-square tests for categorical variables were used. The results were analysed on a per protocol basis. $P < 0.05$ were considered significant.

The trial is registered in the Clinical Trials Registry of India, at www.ctri.nic.in, and the registration number is CTRI/2017/07/009152.

Results

There were 102 patients of scleroderma assessed for eligibility, of which 64 patients were randomly assigned to either of the groups (32 patients in both CYC and RTX groups, Fig. 1). Two patients withdrew consent in the RTX group (1 and 3 months after enrolment) and one patient was lost to follow up in the CYC group after she moved to another city (before the third month). Another patient withdrew consent in the CYC group at 2 months. Thirty patients in each group completed the study and were analysed. Baseline characteristics are given in Table 1.

Median age of the entire cohort was 36 years [interquartile range (IQR): 28–42 years], disease duration 24 months

Table 1 Baseline characteristics of patients

Parameter	Rituximab group (30 patients)	Cyclophosphamide group (30 patients)	*P*-value
Age, years	34.67 (8.13)	36.50 (9.73)	0.43
Sex, females, *n* (%)	25 (83)	25 (83)	0.99
Duration of disease, months	21.57 (8.49)	23.0 (10.14)	0.56
Modified Rodnan skin score	21.77 (9.68)	23.83 (9.28)	0.41
6-min walking test, metres	359.63 (65.95)	335.9 (89.3)	0.25
Forced vital capacity, %	61.30 (11.28)	59.24 (12.96)	0.51
Forced vital capacity, l	1.51 (0.45)	1.42 (0.49)	0.45
Ejection fraction, %	62.65 (6.94)	60.30 (14.67)	0.78
Haemoglobin, g/dl	11.87 (1.01)	11.41 (1.98)	0.86
Medsger's score	8.33 (3.04)	9.60 (2.44)	0.08
Creatinine, mg/dl	0.75 (0.19)	0.75 (0.14)	0.99
>20% Lung involvement on CT, *n* (%)	25 (83)	25 (83)	1.00
Pulmonary arterial hypertension present, *n* (%)	4 (13)	5 (16)	0.74

Values in mean (S.D.) unless otherwise indicated.

(IQR: 15.5–29.5) and FVC was 1.37 l (IQR: 1.11–1.85). Median body weight of the patients with RTX group was 44 kg (IQR: 42–51) and that of CYC group was 43 kg (IQR: 40–49). Average cumulative dose of CYC received per patient was 3.9 (0.2) g There were no significant differences in baseline values with respect to any of the primary or secondary outcomes between the two groups. Ground glass opacities in the HRCT scan were present in 58 out of 60 patients. HRCT findings were classified as nonspecific interstitial pneumonitis in 48 out of 60 patients and predominantly fibrosis and honeycombing (consistent with the usual interstitial pneumonia-like pattern) in two patients and a mixed picture in the remaining 10 patients. In each group there were 25 out of 30 patients who had >20% lung involvement in the CT scan. There were no differences in the HRCT findings in the two groups. $CD19^+$ cell counts in the patients receiving RTX fell from an average of 52.02% at baseline to 23.88% at 6 months.

The primary outcome measure was percent-predicted FVC at 6 months. There was a significant improvement in the percent-predicted FVC in the RTX group [from 61.30 (11.28) at baseline to 67.52 (13.59) at the end of the study; $P = 0.002$] (Table 2). On the other hand, in the CYC group FVC had a slight but statistically insignificant fall [from 59.25 (12.96) at baseline to 58.06 (11.23) at the end of 6 months; $P = 0.496$]. Mean difference in FVC (percent predicted) was in favour of RTX group and was 9.46 (95% CI: 3.01, 15.90; $P = 0.003$). The lower limit of 95% CI of the mean difference of FVC (percent predicted) was 3.01, which was greater than the non-inferiority margin (−2%).

The following secondary outcome measures were also analyzed at 6 months (Table 2): FVC (l), mRSS, 6-min walk distance, Medsger severity scale and presence of pulmonary hypertension. All the secondary outcome measures (like FVC-l, mRSS, Medsger severity score) improved significantly in the RTX group (all $P < 0.001$). Improvement in the skin score was more in the RTX group (−9.67) compared with the CYC group (−5.5). However, in the CYC group only mRSS and Medsger severity score improved significantly over 6 months, but FVC-l and 6-min walk test did not. All of these secondary outcome parameters favoured RTX, and a trend towards higher FVC-l was observed in the RTX group compared with the CYC group.

Overall mRSS was stable in 18.3% (11/60), improved in 75% (45/60) and worsened in 6.7% (4/60). The mRSS was improved in 86.7% (26/30) in the RTX group *vs* 63.3% (19/30) in the CYC group and the mRSS worsened in 10% (3/30) in the RTX group and 26.7% (8/30) in the CYC group ($P = 0.147$).

FVC (%) improved in 16.7% (10/60) and worsened in 6.7% (4/60) of the subjects. The rest (76.7%, 46/60) had stable FVC (%). A significantly higher percentage of patients experienced an improvement of FVC (%) in the RTX group *vs* the CYC group (26.7%, 8/30 *vs* 6.7%, 2/30, respectively, $P = 0.038$). However, the rate of worsening of FVC (%) was similar in the RTX and CYC treated patients (3.3%, 1/30 *vs* 3%, 10/30; $P = 0.612$). At baseline, mild pulmonary hypertension was present in four patients in the RTX group and five patients in the CYC group. At the end of 6 months, one additional patient in the RTX group also developed mild echocardiographic evidence of pulmonary arterial hypertension.

Adverse effects are tabulated in Table 3. One patient developed severe pulmonary arterial hypertension 5 months after the completion of the trial (in the RTX group) and died. Another patient, in the CYC group, developed scleroderma renal crisis and died 3 months after the sixth dose of CYC. One patient in the CYC group developed adenocarcinoma of the breast 9 months after the sixth dose of CYC. Three patients developed mild infusion reactions in the RTX group, and did not require any additional hospital stay. One patient developed gangrene in the CYC group (in winter) in spite of continuing vasodilators (APS and other causes of gangrene were excluded). The total number of patients having an adverse event was lower in the RTX group (30%, 9/30) and in the CYC group (70%, 21/30) ($P = 0.02$). However, only one patient required hospitalization for pneumonia (in the CYC

Table 2 Outcome measures at baseline and 6 months in each treatment group

Parameter	Rituximab ($n=30$)			CYC ($n=30$)			Difference at 6 months	
	Baseline, mean (S.D.)	6 months, mean (S.D.)	*P*-value	Baseline, mean (S.D.)	6 months, mean (S.D.)	*P*-value	Mean (95% CI)	*P*-value
Forced vital capacity, %	61.30 (11.28)	67.52 (13.59)	0.002[a]	59.25 (12.96)	58.06 (11.23)	0.496[a]	9.46 (3.01 to 15.90)[*]	0.003[b]
Forced vital capacity, l	1.51 (0.45)	1.65 (0.47)	<0.001	1.42 (0.49)	1.42 (0.46)	0.356	0.23 (−0.013 to 0.47)[**]	0.091[b]
Modified Rodnan skin score at baseline	21.77 (9.86)	12.10 (10.14)	<0.001	23.83 (9.28)	18.33 (7.69)	<0.001	−6.23 (−10.88, −1.58)[***]	0.001[b]
Medsgers severity scale	8.33 (3.04)	4.67 (2.35)	<0.001	9.60 (2.44)	5.96 (2.81)	<0.001	−1.30 (−2.64, 0.04)[#]	0.036[b]
6-min walking test, m	359.63 (65.95)	409.60 (69.29)	<0.001	335.90 (89.30)	349.14 (99.75)	0.428	60.46 (16.07, 104.84)[****] [##]	0.001[b]
Pulmonary hypertension present (%)	4 (13)	5 (16)		5 (16)	5 (16)			

[a]Statistical comparison for FVC (%) before and after therapy for each group was done with paired *t*-test. For all other outcome variables, the same analysis was run with Wilcoxon signed rank test and reported *P*-values are two-tailed only. [b]Denoted comparison of outcome variables at 6 months between the two treatment groups, that is, rituximab *vs* CYC. *P*-values were calculated by Mann–Whitney *U* test and reported *P*-values are two-tailed only. [*]$P=0.005$; [**]$P=0.063$; [***]$P=0.01$; [****]$P=0.008$; [#]$P=0.057$; [##]$P=1$.

Table 3 Adverse events in rituximab and CYC groups

Adverse event	Rituximab group (30 patients)	CYC group (30 patients)
Upper respiratory tract infections	2 (6.67)	2 (6.67)
Pneumonia	1 (3.34)	4 (13.4)
Urinary tract infections	1 (3.3)	2 (6.67)
Herpes zoster	1 (3.3)	3 (10)
Cholecystitis (requiring cholecystectomy)	1 (3.3)	0
Premature ovarian failure	0	2 (6.67)
Gangrene	0	1 (3.34)
Malignancy	0	1 (3.34)
Leukopenia	0	2 (6.67)
Vomiting	0	4 (13.4)
Transfusion reactions	3 (10)	0

Values are *n* (%) of the total patient population.

group). Major adverse events, including those requiring admission (ovarian failure, hospitalization for infection, gangrene and malignancy), occurred in the CYC group only.

Discussion

This is the first randomized controlled trial to examine the efficacy and safety of RTX compared with CYC as the primary treatment of SSc with ILD. We reported a greater increase of percent-predicted FVC as well as mRSS with RTX compared with CYC. RTX appeared to be safe in terms of malignancy, gangrene and ovarian failure, albeit with higher rates of minor infusion reactions.

Evidence suggests that B cells play an important role in the pathogenesis of scleroderma. The tight-skin mouse (TSK/+), a murine model for human SSc, demonstrates overexpression of $CD19^+$, with B cell expression, which is hyper-responsive and produce autoantibodies [20]. In humans, increased population of naïve B cells and reduced number of memory B cells and plasmablasts characterizes SSc. The memory b cells overexpress CD80 and CD86, which are critical co-stimulators and activation markers of B cells [11]. A novel subpopulation of $CD80^+$ memory B cells have also been described, which can produce class switched immunoglobulins and can effectively present antigens and activate T cells [21].

RTX effectively depletes B cells from the circulation as well as skin. Lafyatis *et al*. administered 1000 mg of RTX in 15 patients of dcSSc, and demonstrated disappearance of dermal B cells at 6 months. In a negative study by Lafyatis *et al*. [22], circulating B cells were depleted at 3 months but a partial recovery occurred between 6 and 12 months. Moazedi-Fuerst *et al*. [16] demonstrated a decrease in autoantibody titres in scleroderma patients during long-term treatment, and Bosello *et al.* [10] demonstrated that IL-6 levels decreased with RTX therapy in nine patients with SSc. Skin biopsy changes with RTX in patients with scleroderma, along with reduction of cytokines

Table 4 Studies of RTX in scleroderma lung disease

References	Type of study	No. of patients	Predicted FVC improvement (%)
Daoussis *et al.* [18]	Open label RCT, $n = 14$	$n = 8$, RTX 375 mg/m^2 weekly for 4 weeks at baseline and 6 months $n = 6$ (usual therapy)	At 12 months: +10.25% (68.13 *vs* 75.63%) *vs* −4.33% (86 *vs* 81.67%)
Daoussis *et al.* [27]	Follow-up study	$n = 8$, 4 cycles of RTX	At 2 years: +9% (68.13% vs 77.13%)
Daoussis *et al.* [15]	Open label non-RCT	$n = 33$, $\geqslant 2$ cycles of RTX $n = 18$, AZA, MTX, MMF	At 24 months: +6.3% (80.6 *vs* 86.9%) *vs* +0.13% (77.72 *vs* 77.59%)
Jordan *et al.* (EUSTAR) [25]	Retrospective nested case-control study	$n = 9$, RTX 1000 mg, two infusions, 2 weeks apart	At 6 months: +0.7% (60.6 *vs* 61.3%)
Bosello *et al.* [24]	Prospective open-label non-comparative observational studies	$n = 20$, RTX 1000 mg two infusions, 2 weeks apart, eight patients received variable number of repeat infusions	At 12 months: +3.3% (87.4 *vs* 90.7%) At 48 months: +8.2% (87.4 *vs* 95.6%)
Lafyatis *et al.* [22]	Prospective open-label non-comparative observational studies	$n = 15$ RTX 1000 mg two doses at 0 and 2 weeks apart	At 6 months: +3.5% (89.2 *vs* 92.7%)

RTX: Rituximab; RCT: Randomized controlled trial; EUSTAR: European Scleroderma Trial and Research Group

and cytokine receptors, have also been previously demonstrated [23].

Previous clinical studies have demonstrated the efficacy of RTX in SSc (Table 4). A preliminary study undertaken to demonstrate the safety of RTX failed to find improvement in mRSS scores [22]. Bosello *et al.* [24] demonstrated, in an observational study on 20 patients with SSc, improvements in FVC and diffusion capacity of carbon monoxide, as well as skin parameters in 20 patients of SSc treated with RTX. Giuggioli *et al*. [17], in a case series of 10 patients of SSc, showed improvement in mRSS, calcinosis and articular manifestations. Retrospective data from Brazil showed similar results in a series of 10 patients [12].

The European Scleroderma Trial and Research Group (EUSTAR) cohort described patients with SSc treated with RTX *vs* matched controls, and demonstrated improvements in mRSS in the RTX group than matched controls [−24.0 (5.2%) *vs* −7.7 (4.3%)]. Lung function tests also stabilized [0.4 (4.4%) *vs* −7.7 (3.6%)] with RTX [25]. The RECITAL trial is planned to evaluate CYC and RTX in a head-to-head comparison in CTD [26].

Our study met its primary end point—demonstrating that RTX improved the FVC (% predicted) outcomes compared with CYC. This was supported by the improvements in the secondary end points—improving the 6-min walking distance, mRSS and Medsger severity score.

In the Scleroderma Lung Study (SLS) [2] CYC produced only a modest benefit over placebo. In the Scleroderma Lung Study II (SLS II), which did not meet its primary outcome, mycophenolate and CYC improved the FVC by 2.19 and 2.88 percentage points, respectively, at 24 months [5]. The authors concluded a similar benefit with both mycophenolate and CYC. We, however, observed a 6.22% improvement in the RTX group at 6 months. Similar results have been obtained with RTX compared with conventional regimens by Daoussis *et al.* [15] where a 6.3% increase in FVC was demonstrated. Three aspects need further elaboration. Firstly, there was inclusion of patients with early scleroderma (mean duration around 22 months), which is less compared with previous trials, in which mean duration was 30 months in SLS II and 38 months in SLS [2, 5]. Possibly, earlier recruitment of our patients overlapped with a therapeutic window of opportunity. However, the concept of window of opportunity in scleroderma is not widely prevalent. It is still possible that we observed a favourable response due to younger age and shorter duration of disease before intervention and perhaps ethnicity also contributed. However, it is notable that we observed actual increment in FVC rather than the stabilization of FVC seen with earlier studies. Again, our duration of follow-up was shorter and further follow-up of our results is awaited. Secondly, our cohort is homogeneous in terms of participants as we included only those with diffuse scleroderma with anti-Scl70 positivity. Previous cohorts were mostly composed of a heterogeneous selection of patients with both diffuse and limited scleroderma. We bring up this point as these two diseases, though within the umbrella of SSc, may behave differently in terms of pulmonary involvement and therapeutic outcome. Anti-SCL70 is an important predictor of pulmonary involvement and with a homogeneous population the results of our clinical trial are directly translatable in day-to-day clinical practice. Lastly, we did not include patients with previous exposure to the study drugs or other immunosuppressive agents. This allowed us to examine the therapeutic effect of these drugs without the interference of residual effects of other immunosuppresive agents.

Our study has a few limitations: short duration of follow up; single-centre, open-label design; inability to measure the diffusion capacity of carbon monoxide and right heart catheterization due to financial constraints. A blinded assessor did not do the mRSS, and this is a limitation imposed by the open-label design. The skin score showed a larger improvement than expected form previous studies. The effect of open label design and bias of non-blinding could not be excluded. We excluded smokers, and this might have some beneficial effect on the FVC outcome.

This is the first randomized trial that showed an appreciable increase in FVC in early patients with scleroderma after treatment with RTX, a result that was functionally supported by improvements in the 6-min walking distance and Medsger severity score. Our study also met its primary end point and effect of RTX on percent predicted FVC at 6 months was higher than the non-inferiority margin. In fact, percent predicted FVC at 6 months in the RTX group was statistically significantly higher than the CYC group. However, our study was not set up to detect superiority. In terms of adverse effects, RTX was safer.

In conclusion, we found that RTX as primary treatment for SSc was associated with at least similar efficacy and had significantly fewer major adverse events than CYC over the study period of 6 months. Our patients were younger compared with previous cohorts like the SLS and SLS II [2, 5]. Further, all of our patients were of diffuse cutaneous type and had positive anti-Scl 70 antibody. The fall of mRSS observed in cohort may be attributable, at least partially to these factors. However, generalizability of our results to other ethnicities may not be feasible at this point in time. A larger clinical trial of RTX with long-term follow-up should be planned in patients with scleroderma for better assessment of durability and generalizability of its clinical efficacy.

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