Case Report

Rituximab treatment in patients with systemic sclerosis and interstitial lung disease

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Abstract:

There is increasing interest in rituximab (RTX) as an alternative to cyclophosphamide for the treatment of interstitial lung diseases (ILDs) associated with systemic sclerosis (SSc). However, no report has addressed its efficacy in Saudi patients with SSc-ILD. To assess the efficacy of RTX treatment in Saudi patients with SSc-ILD, hospital records were reviewed between 2013 and 2016. Four female patients received at least 4 cycles of RTX (I cycle, consisting of two infusions of 1000 mg 2 weeks apart). Pulmonary function tests (PFTs) and chest high-resolution computed tomography (HRCT) were performed before and after treatment to assess the response. HRCT revealed improvement in one patient, stable disease in two patients, and worsening in one patient. Moreover, RTX prevented the further decline of forced vital capacity significantly in PFT. These results provide further evidence that RTX is an effective treatment for SSc-ILD.

Keywords:

Rituximab, systemic sclerosis, interstitial lung disease, high-resolution computed tomography

Systemic sclerosis (SSc) is a multisystem autoimmune disease. Pulmonary manifestations are common, occurring in more than 80% of patients with SSc, resulting in a significant morbidity and mortality.[1] Interstitial lung disease (ILD) represents the most frequent pulmonary manifestation in SSc and more than 40% of patients showed restrictive changes in pulmonary function test (PFT).

PFT is frequently used to assess lung involvement in SSc, and an abnormal forced vital capacity (FVC) has been reported as a predictor for progression to end-stage lung disease.[2] Moreover, a lower FVC at the time of diagnosis is associated with higher mortality.[3]

Treatments for SSc-associated ILD (SSc-ILD) have mainly relied on nonspecific immunosuppression in the form of cyclophosphamide or mycophenolate.[4,5]

Recently, few reports have suggested that rituximab (RTX), a chimeric monoclonal anti-CD20 antibody, may be an effective treatment option for SSc-related ILD.[6,7]

The aim of our study was to evaluate the effect of RTX on Saudi patients with SSc-ILD.

Methods

The current study included four patients with SSc-ILD, who attended Rheumatology Outpatient Clinic between 2013 and 2016 at King Fahad Medical City. All patients satisfied the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) 2013 criteria for SSc classification.[8]

Patients' records were reviewed. The following serological markers were detected by means of standard techniques, including anti-nuclear antibody (ANA), anti-Scl-70, PFT, high-resolution computed tomography (HRCT) as well as upper

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gastrointestinal endoscopy done for all patients [Table 1]. PFT measurements were done in the same respiratory laboratory. FVC was considered improved if there is <10% increment from the baseline.

HRCTs were reported by an expert radiologist, who had no knowledge about the patient's status. Local research ethics committee approval was obtained for retrospective review of patients' records.

Results

All patients were females, with positive ANA and anti-Scl-70, with mean disease duration of 7.25 years [Table 1]. ILD was detected in all patients. All patients received at least 4 cycles of RTX (1 g at day 0 and day 14 every 6 months). PFT and HRCT were done at baseline and after RTX, except one patient who lost follow-up. Patients were assessed following RTX by HRCT and PFT 6 months after the fourth cycle of RTX.

Statistical analysis

All patients had PFT before RTX treatment, with a mean ± SD of FVC of 63.4 ± 12.7. Following RTX, we observed improvement in FVC with a mean ± SD of 74.5 ± 6.8. HRCTs also improved in three out of four patients. In one patient (patient 1), PFT did not appear to change following treatment, but HRCT was worsening [Table 2].

Discussion

SSc is frequently complicated by ILD that often has a poor prognosis.[9] Cyclophosphamide has been used for the treatment of SSc-ILD but its efficacy seems to be not sustained,[10] and it is not suitable for every patient, because of its side effects. Therefore, more effective treatment with fewer adverse effects is needed such as RTX.[6,7,11] Data from experimental studies suggest that B-cells have a significant role in the process of fibrosis supporting the idea of using B-cell-depleting agents such as RTX as a potential therapeutic approach in SSc.[12,13]

As far as we know, we herein report the first retrospective study investigating four Saudi patients with SSc-ILD, showing that RTX treatment prevented the further decline of FVC significantly in PFTs of patients with SSc-ILD. Our findings are consistent with the results

Table 1: Patients' characteristics

	Age	Sex	Disease duration (years)	Gastroscopy	ANA	Anti-SCL70	Number of RTX cycles
Patient 1	39	Female	6	Linear ulcer with spastic esophageal ring-GERD2	>1/160	Positive	4
Patient 2	56	Female	8	Spastic esophageal ring	>1/160	Positive	4
Patient 3	54	Female	5	Mild chronic gastritis	>1/160	Positive	4
Patient 4	37	Female	10	Mild chronic gastritis	>1/160	Positive	4

GERD = Gastroesophageal reflux disease, ANA = Anti-nuclear antibody, Anti-SCL70 = Anti-scleroderma 70 (anti-topoisomerase I), RTX = Rituximab

Table 2: High-resolution computed tomography and pulmonary function test before and after rituximab

	HRCT before RTX	HRCT after RTX	PFT before RTX	PFT after RTX
Patient 1	Minimal bronchiolectasis and minimal honeycombing	Worsening of interlobular septal thickenings as well as subpleural reticulations, mild bronchiolectasis, and subpleural honeycombing	TLC 74.1% FEV 71.8 FVC 69.7 Ratio 106.9 DLCO 62.8	TLC 74 FEV 75.9 FVC 75.8 Ratio 100 DLCO 69.3
Patient 2	Evidence of bilateral subpleural reticular opacity	Stable	TLC 47.4 FEV 52.1 FVC 55 Ratio 109 DLCO 81	TLC 54.9 FEV 70.1 FVC 67.1 Ratio 113 DLCO 82
Patient 3	Interstitial lung disease related to scleroderma	There is improvement in the status of the lung changes	TLC 75% FEV 90.84 FVC 50.7 Ratio 115.5 DLCO 82	Not done
Patient 4	Patchy areas of mosaic perfusion predominantly in both lower lung lobes in bases and patchy areas of air trapping on expiration in bases of both lungs with mild dilatation of bronchioles	Stable	TLC 95.1% FEV 68.1 FVC 78.1 Ratio 87.1 DLCO 71	TLC 85.1% FEV 86.6 FVC 80.6 Ratio 107.5 DLCO 80

HRCT = High-resolution computed tomography, RTX=Rituximab, PFT = Pulmonary function tests, TLC = Total lung capacity, FEV = Forced expiratory volume, FVC = Forced vital capacity, Ratio = FEV1/FVC ratio, DLCO = Diffusing capacity of the lungs for carbon monoxide

of previous studies[14-16] showing a possible role of RTX inpatients with SSc-ILD.

As ethnicity has been reported to affect the responsiveness to therapy,[17] further research in different populations is necessary to identify the effectiveness of RTX in SSc-ILD patients. This study highlights the effectiveness of RTX treatment in Saudi SSc-ILD patients. However, it is important to collect more cases and confirm the efficacy and safety of RTX therapy in Saudi patients.

In our study, HRCT revealed improvement in one patient [Figure 1], stable disease changes in two patients, and worsening in one patient, which is likely to be due to advance fibrosis (honeycombing appearance) at baseline and the presence of bronchiectasis; however, this worsening was not associated with deterioration in PFT.

In this study, a favorable response was demonstrated following RTX in the treatment of SSc-ILD. Nevertheless, administration of RTX to patients with autoimmune diseases might induce or lead to worsening of ILD.[18,19]

Our study has its limitations. It is a retrospective study, with the possibility of data loss and the lack of a control group. It also has a small number of patients and different patient characteristics in terms of disease duration and severity. Therefore, a large randomized controlled trial is needed for further exploration of RTX efficacy in the treatment of SSc-ILD.

To our knowledge, this is the first study reporting the effectiveness of RTX in Saudi patients with SSc-ILD.

Conclusion

RTX may improve SSc-ILD. Taking into consideration the limitations of our study, definite conclusions may not be reached. Nevertheless, our data could be an approach for multicenter studies to determine the effect of RTX in the treatment of SSc-ILD.

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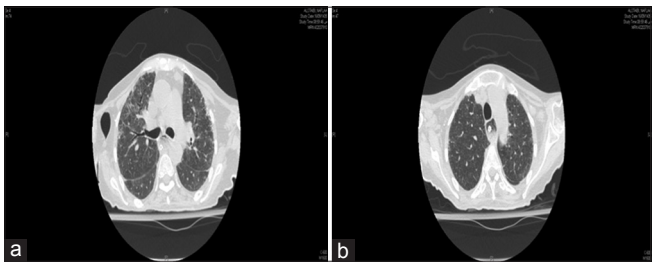

Figure 1: (a) High-resolution computed tomography for a patient before rituximab. (b) High-resolution computed tomography for the same patient after rituximab

Conflicts of interest

There are no conflicts of interest.

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