SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2015; 32; 215-221

Efficacy and safety of rituximab in connective tissue disease related interstitial lung disease

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Abstract. *Background:* Pulmonary complications of connective tissue disease are being identified more frequently with the advent of more sophisticated radiological investigations. Limited previous studies have suggested Rituximab (RTX), a chimeric monoclonal antibody with activity against CD-20, may benefit connective tissue disease patients with pulmonary complications. We performed a retrospective analysis of the efficacy and safety of RTX in patients attending a tertiary referral centre. *Methods*: Ten patients treated with RTX for pulmonary complications of CTD in our institution were identified. Baseline demographics, pre- and post-treatment investigations and adverse events were documented. *Results:* Eight of ten patients had interstitial changes, two had rheumatoid nodules, one of whom had serositis also. Median follow up time-frame was 12.3 months (range: 3 - 27). For the patients with interstitial changes, a statistically significant improvement in pulmonary function was seen, with a median percentage increase of 22.69% (12.5 to 29.9%) in DlCO (% predicted), p=0.028, and a median percentage increase in FVC (% predicted) of 11.05% (4.22 to 25.94%), p=0.018. For the same group, there was a trend towards improvement in CT severity score. For the two patients without ILD, radiological improvement in nodule size and serositis was seen. No patient had a severe adverse reaction to RTX. *Conclusions:* Treatment with RTX resulted in an objective, measurable improvement in pulmonary function and/or radiological severity for the majority of patients included in the series. This was statistically significant despite the small numbers included. These results indicate a positive response to RTX with few complications of treatment. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 215-221)*

Key words: connective tissue disease, interstitial lung disease, Rituximab

Abbreviations List:

Anti-CCP - Anti-cyclic citrullinated peptide
CPI - Composite Physiological Index
CTD-ILD - Connective Tissue Disease Interstitial Lung Disease
CYC - Cyclophosphamide
DcSSc - Diffuse cutaneous systemic sclerosis
DLCO - Diffusing Capacity of the Lung for Carbon Monoxide
FVC - Forced Vital Capacity
HRCT - High Resolution Computed Tomography
LcSSc - Limited cutaneous systemic sclerosis
RA - Rheumatoid Arthritis
RTX - Rituximab
SSc - Systemic Sclerosis

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Introduction

Interstitial lung disease (ILD) commonly occurs in patients with connective tissue disease (CTD). Longitudinal studies have shown a thirty year cumulative incidence of 6.8% and a lifetime risk of 7.7% of ILD in patients with rheumatoid arthritis (RA) (1, 2). As the use of high resolution computed tomography (HRCT) has increased, radiological interstitial changes have been reported in 19 - 33% (3, 4). These patients have an excess mortality with a three-fold increased risk of death than RA patients without ILD and a median survival of 2.6 years from diagnosis (2). The European League Against Rheumatism Scleroderma Trial and Research (EUSTAR) analysed the cross-sectional prevalence of organ involvement in scleroderma. Interstitial lung disease was present in 53% of patients with diffuse cutaneous systemic sclerosis (SSc) and 35% of those with limited cutaneous SSc (5). Lung involvement is considered to be the leading cause of morbidity and mortality in SSc with ILD accounting for 33% of deaths (6).

The pathogenesis of interstitial lung disease in patients with connective disease is complex and is thought to be associated with pulmonary inflammation secondary to immune system dysfunction. More specifically, evidence from multiple *ex vivo* studies suggests that B-cells are essential to the development of CTD-ILD (7-9). Furthermore, B-cell depletion has been shown to be beneficial in the treatment of RA and SSC (10, 11). Rituximab (RTX) is a chimeric monoclonal antibody with activity against the CD20 antigen on B-cells and is effective in B-cell mediated diseases by causing rapid selective depletion of B-cells from the peripheral circulation. The hypothesis that RTX would therefore be efficacious in the treatment of CTD-ILD has been illustrated in several case reports and small studies (12-15, 19).

We performed a retrospective study to assess the efficacy and safety of RTX used in this context in a tertiary referral centre specialising in pulmonary complications of CTD.

Methods:

Patient groups

Patients treated with RTX for pulmonary complications of CTD were identified from a RTX database kept in our institution from 1st January 2009 to 1st January 2014. Baseline demographics, pre-treatment pulmonary function and blood results were obtained from medical records. Pulmonary function results pre- and most recent post-treatment were obtained. Consent was obtained from patients or their next-of-kin as applicable. Ethical approval was obtained from the Clinical Research Ethics Committee affiliated with our institution.

Outcome assessment

HRCT scans of the thorax were assessed by two independent radiologists with a special interest in ILD. Extent of interstitial changes was determined using an ILD severity score first outlined by Wells et al (16), and further defined by Lopes et al (17). A higher score indicates more extensive interstitial disease. Baseline pulmonary function and radiological severity were compared to post-treatment values. The composite physiological index (CPI) is an estimation of severity of radiological fibrosis accounting for the presence of emphysema using pulmonary function test results (18). Smoking status was recorded and the CPI was calculated. Chart review and contact with primary care physicians identified any complications that occurred as a result of treatment. Any infection, acute admission to hospital and mortality was recorded.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, SPSS version 21.0 (SPSS, Chicago, Illinois, USA). The Wilcoxon signed rank test was applied to compare pre- and post-treatment values of forced vital capacity (FVC) (% predicted), FVC (L), diffusion capacity (DlCO) (% predicted), DlCO (ml/min/mmHg) and CT score. A p-value of <0.05 was considered statistically significant. Data are presented as median (interquartile range) or percentages (range) unless otherwise stated.

Rituximab treatment

One patient received 1000mg monthly for four months. Subsequently based on emerging evidence, the treatment protocol was altered and two patients

received 375 mg/m2 monthly for four months. Further studies published in the area demonstrated benefit with a protocol of RTX 1000mg administered on day 0 and day 14, repeated at 6 monthly intervals, which was received by seven patients.

Results

Study population

Ten patients were treated for pulmonary complications of CTD with RTX in our institution during the period studied. Six patients were treated for SSc-ILD and four patients for RA-related complications. Baseline demographics are shown in Table 1. The median (IQR) age was 55 (range: 40 - 77). 70% of patients were male and all were ex-smokers. Three of the six patients with SSc-ILD had previously received cyclophosphamide (CYC) and progressed on treatment, the others had contraindications to treatment with CYC at the time of diagnosis (two had a history of malignancy and one wished to preserve fertility). Two patients with RA had progressive interstitial changes while being treated with alternative immunosuppressants. Patient 7 had been on adalimumab followed by cyclophosphamide until one year prior to starting RTX. Patient 8 was on methotrexate followed by azathioprine prior to starting RTX. Patient 9 was initially treated with etanercept followed by leflunomide, and was transitioned to RTX due to progressively enlarging rheumatoid nodules on CT. Patient 10 had been treated with etanercept 4 years prior and presented acutely with severe serositis and enlarging rheumatoid nodules at which point treatment with RTX was initiated. All patients were discussed at a multi-disciplinary conference attended by a pulmonologist (MH), pulmonary radiologist and pulmonary histopathologist.

Three patients remained on CYC (dose 15 mg/kg) and four on prednisolone throughout treatment with RTX. All patients with RA were anti-cyclic citrullinated peptide (anti-CCP) antibody positive. Follow up investigations were available for nine patients. All nine patients exhibited a radiological and/or physiological improvement after treatment with RTX. One patient died of an aspiration pneumonia prior to reassessment.

HRCT

The ILD severity score improved or remained stable in six out of seven patients who had interstitial disease on pre-treatment scans. Comparison of pre-treatment and post-treatment HRCT of the seven showed a median reduction in severity score of 20% (-33 to 0%). The median score pre-treatment was 20 (8 to 30) *vs.* a post-treatment median of 12 (4 to 29), though this did not reach significance, p=0.168 (Figure 1). Both patients with nodules had a radiological improvement on follow-up HRCT and, for patient 10, the pleural and pericardial effusions completely resolved.

Table 1.

Pt	Age	Sex	Dx	Anti-bodies	Baseline FVC % pred	Baseline DLCO % pred	Prior Rx	RTX dose	No. RTX
1	40	F	LcSSc	ANA/ Cent	65.1	28.5	Nil	1 gm q1/12 x 4	1
2	58	M	LcSSc	ANA	65	27.1	CYC	375 mg/m2 weekly x4	1
3	67	M	Sine SCL	ANA/ Topo	87.6	75.7	Nil	1 gm day0/15	2
4	42	M	DcSSc	ANA	79.6	47.6	MTX/ MMF/CYC	1 gm day0/15	2
5	77	M	LcSSc	ANA/ Cent/Topo	75.4	38.9	Nil	375 mg/m2 weekly x4	1
6	40	M	LcSSc	ANA/ Cent	77.1	67.5	CYC/MTX	1 gm day0/15	5
7	61	M	RA	ANA/ RF/CCP	37.4	26.9	Pred/ADA/CYC	1 gm day0/15	2
8	64	M	RA	ANA/ RF/ CCP	98.6	90.9	MTX, AZA, Pred	1 gm day0/15	2
9	49	F	RA	ANA/ RF/ CCP	101.7	53.2	LEF/ ETA	1 gm day0/15	2
10	52	F	RA	ANA/ RF/ CCP	69.3	54.2	MTX/ETA	1 gm day0/15	2

LcSSC – Limited cutaneous systemic sclerosis; DcSSc – Diffuse cutaneous systemic sclerosis; Sine SCL – Scleroderma sine scleroderma ANA – Anti-nuclear antibody; Cent – Anti-centromere antibody; Topo – Anti-topoisomerase; RF – Rheumatoid Factor; CCP – Anti Cyclic-citrullinated antibody; CYC – Cyclophosphamide; Pred – Prednisolone; MTX – Methotrexate; LEF – Leflunamide; ADA- Adalimumab; ETA – Etanercept; MMF – Mycophenylate mofitil; AZA – Azathioprine

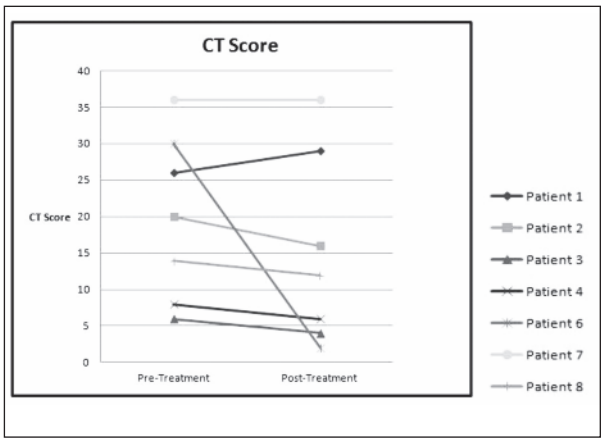

Fig. 1. CT Score pre- and post treatment

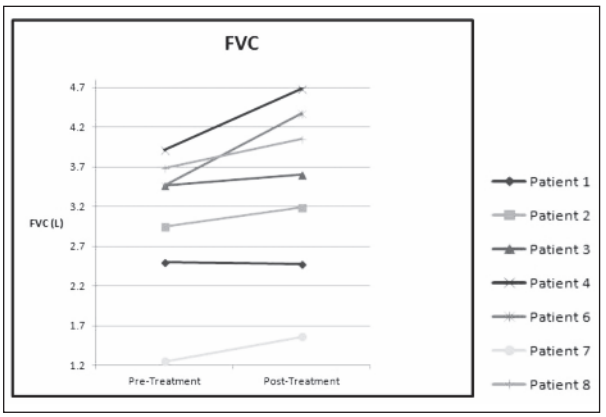

Fig. 2. FVC (L) pre- and post treatment

Pulmonary function

Pulmonary function tests were performed at least 3 months post first dose, with a median follow up time-frame of 12.3 months (range: 3 - 27) (Table 2). Of the seven patients with ILD who had pre- and post-treatment pulmonary function testing, there was a statistically significant improvement in pulmonary function.

The median FVC (% predicted) pre-treatment compared to post-treatment was 77.1% (65 to 87.6%) *vs.* 91.3% (65.9 to 98.9%), p=0.018. The median percentage increase in FVC (L) was 10.05% (3.75 to 24.8%) (Figure 2).

Pre-treatment median DlCO (% predicted) was 44.9% (27.1 to 75.7%) compared to a post-treatment median of 58.4% (26.9 to 85.6%), p=0.028. The median percentage increase in DlCO (ml/min/mmHg) was 22.09% (11.62 to 28.84%) (Figure 3).

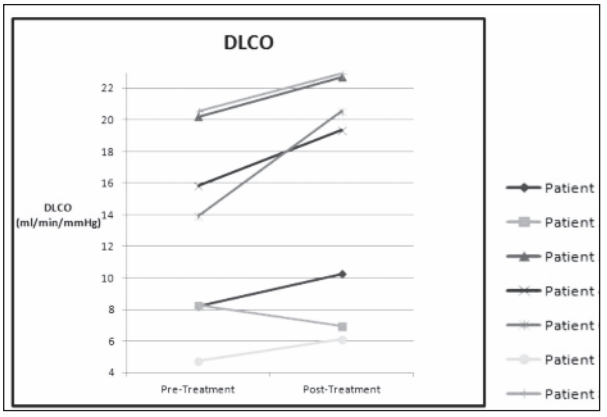

Fig. 3. DLCO (ml/min/mmHg) pre- and post-treatment

The CPI also improved following treatment with RTX, but did not reach statistical significance, median 78.334 (59.32 to 83.63) *vs.* 84.705 (52.85 to 82.19), p=0.128.

Table 2. Pulmonary Function Tests pre- and post-treatment with percentage change for each patient

Pt	DlCO % pred pre	DlCO % pred post	% change	FVC % pred pre	FVC % pred post	% change	Months post RTX
1	28.5	36.1	+26.67	65.1	65.9	+1.23	27
2	27.1	23	-15.13	65	70.8	+8.92	17
3	75.7	85.6	+13.08	87.6	91.3	+4.22	3
4	47.6	58.4	+22.69	79.6	95.8	+20.35	13
5	38.9	N/A	N/A	75.4	N/A	N/A	N/A
6	44.9	67.5	+50.33	77.1	98.9	+28.27	26
7	20.7	26.9	+29.95	37.4	47.1	+25.94	4
8	80.8	90.9	+12.50	98.6	109.5	+11.05	5
9	63.3	53.2	-15.96	101.7	98.3	-3.34	14
10	53.4	54.2	+1.50	69.3	61.7	-10.97	13

Adverse events

One patient died before follow-up investigations were performed due to aspiration pneumonia secondary to dysphagia on a background of previous stroke. Immunoglobulin levels post-RTX in this case were 17.22 g/L (normal range: 6.0 - 16.0 g/L). Two patients were treated for cellulitis by primary care physicians and did not require admission to hospital. No patient in our cohort developed a pulmonary complication of RTX and there was no incident of progressive multifocal leucencephalopathy.

Discussion

The use of RTX in patients with CTD-ILD has a growing evidence base. Treatment with RTX has resulted in an objective, measurable improvement in pulmonary function and/or radiological severity for the majority of patients included in our series.

Regarding patients with interstitial changes on HRCT, severity improved in five out of seven patients on follow-up scans, and was unchanged in one patient. Only one patient had an increase in severity score on follow up scan, which was performed 6 months post treatment (Patient 1), and who declined further imaging. Pulmonary function in the same patient improved significantly over the following years, with the first sign of decline in DlCO occurring three years post last dose of RTX.

We showed an improvement in pulmonary function and radiological severity in this cohort. Data provided by Daoussis et al (14) and Keir et al (13, 15) are consistent with our results. Daoussis et al performed a prospective study in eight patients with scleroderma-related ILD and showed a sustained improvement in pulmonary function and skin thickness over a two year period with six monthly courses of RTX (4 weekly pulses of 375 mg/m2). Their data showed that the improvement was statistically significant at one year but not at six months, suggesting that multiple courses of RTX are required to achieve significant benefit. Keir et al performed an observational review of eight patients with severe CTD-ILD (median DlCO of 25%) treated with RTX (1,000mg on day 0 and day 14 in the majority). They reported a statistically significant improvement in DLCO and FVC for six out of eight patients within nine to twelve months of RTX treatment. They found that this improvement occurred rapidly in most patients, and was also statistically significant at 6 months post-treatment. A further study by Keir et al evaluated the efficay of RTX as rescue therapy for 50 patients with progressive ILD of varying aetiology (15). RTX use in these patients had a particularly favourable effect in those patients suffering from CTD-ILD in whom there was some improvement in FVC and stabilisation of DlCO. The baseline pulmonary function in this study was severely impaired (median DlCO 25% predicted). The authors point out that earlier use of RTX, before a severe impairment develops, may be beneficial.

In our cohort, the median baseline DlCO (% predicted) was 44.9% and median FVC (% predicted) was 77.1%. indicating a less severe impairment that has been seen in previous studies. Seven patients had pulmonary function tests within six months of the first dose of RTX and, of these, six already had an improvement documented by that time. The two patients who had follow up pulmonary function tests after two or more doses of RTX showed continued improvements (patient 4 and patient 6). The most significant improvement in pulmonary function as well as radiological severity occurred in the patient who had the longest follow-up and received maintenance RTX (Patient 6, CT pre-treatment and post-treatment, Fig.4), which has been previously reported (19). This supports the growing evidence base that maintenance treatment with RTX results in sustained benefit.

Limitations to this study include its small numbers and retrospective nature. Given the increasing use of RTX for this indication we can expect to have long term follow-up data in the years to come. Many of the patients in our cohort were receiving concomi-

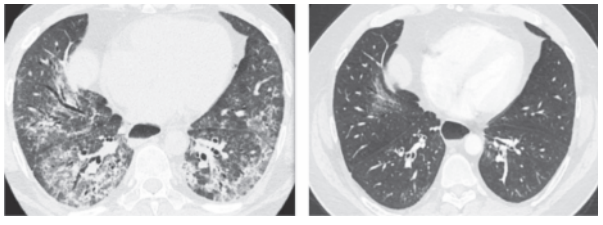

Fig. 4. CT Thorax Patient 6 pre- and post-treatment

tant treatment with other disease modifying agents and the possibility of a response to these medications cannot be out-ruled in this small group. However, these patients were treated with RTX due to deterioration on their preceding regimen. None of our patients were started on a second new treatment at the same time as RTX. Thus the addition of RTX was the most likely reason for the statistically significant improvement that was achieved. The recording of adverse events was based on documentation in medical notes and the records of general practitioners and therefore cannot be definitely complete, though every effort was made by the investigators to identify events.

Despite the small numbers included in this study, the use of RTX resulted in a statistically significant improvement in pulmonary function for patients who have been diagnosed with what is a fundamentally progressive and, up to now, irreversible condition. This is a difficult patient group to treat, and the use of RTX is in its infancy. This study supports the role for RTX in the treatment of CTD-ILD with a good therapeutic response and the urgent need for prospective studies on RTX to confirm this data.

Acknowledgements

The supervising author and guarantor of this article is Dr. Michael T Henry.

Fitzgerald DB coordinated the study, collected and analysed data and wrote the manuscript.

Moloney F and Twomey M reviewed the radiology, assessed the severity of disease and assisted with manuscript composition.

Cronin O and Harty L had full access to data and performed the statistical analysis and assisted with manuscript composition.

Harney S and O'Connell OJ contributed to the study design and manuscript composition.

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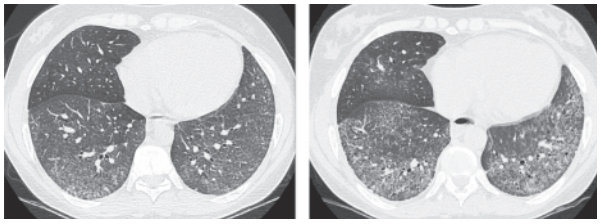
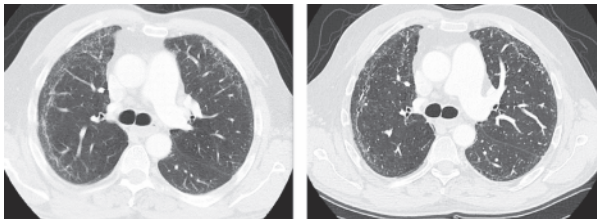
Appendix:
Representative CT scans pre- and post-treatment for all patients



Patient 1



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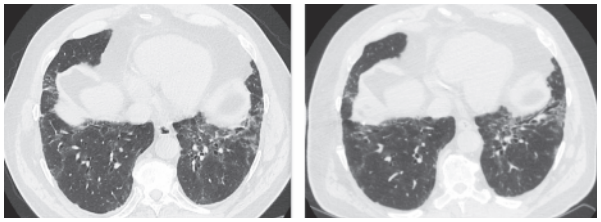

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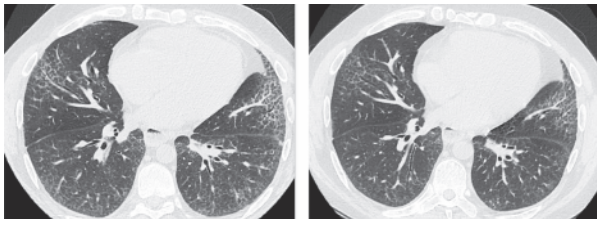

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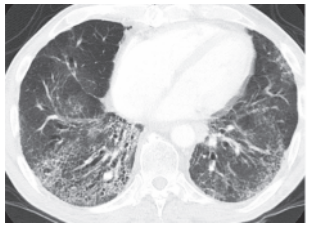

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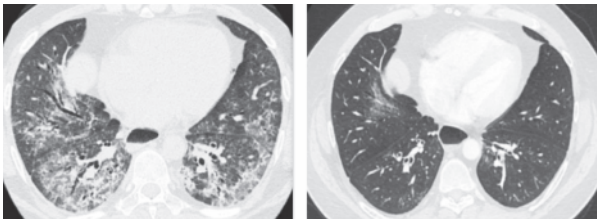
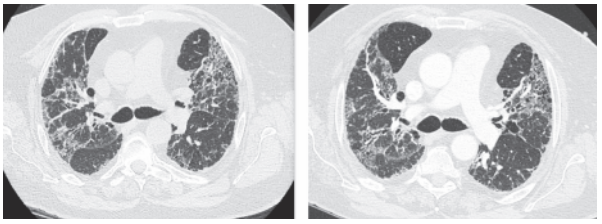


Patient 6



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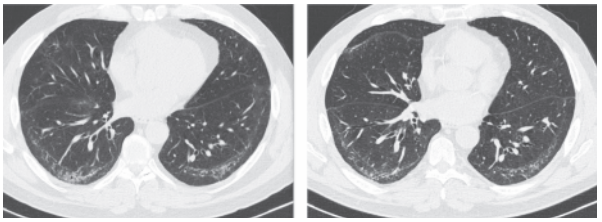
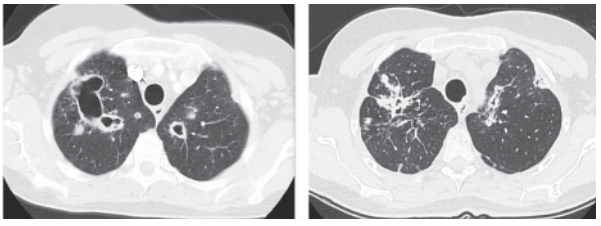
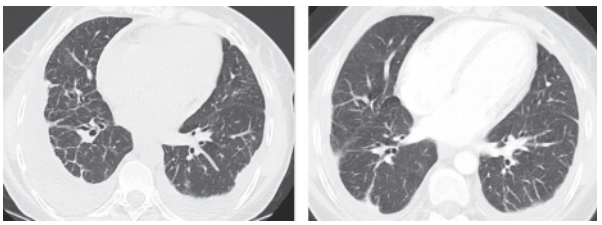


Patient 8



Patient 9



Patient 10