Rituximab therapy in severe connective tissue disease-associated interstitial lung disease: A retrospective single-centre observational study

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Background. Connective tissue disease-associated interstitial lung disease (CTD-ILD) that progresses despite first-line immunosuppressive therapy is a clinical challenge. Rituximab (RTX) is a chimeric monoclonal antibody targeted to CD20+ B cells, resulting in B-cell depletion, and has been used as a salvage therapeutic modality in severe disease.
Objectives. To investigate the therapeutic effects and safety of RTX in patients with severe CTD-ILD.
Methods. A retrospective observational analysis of patients with severe CTD-ILD treated with salvage RTX therapy and various combinations of immunomodulatory therapy at Wits Donald Gordon Medical Centre, Johannesburg, South Africa, between January 2010 and December 2020 was performed. A total of 19 patients with progressive CTD-ILD, sufficient data, and 24-month follow-up were analysed. The effects of adding salvage RTX to standard drug therapy were investigated with serial pulmonary function testing, high-resolution computed tomography (HRCT) of the chest, and World Health Organization functional class (FC) assessment.
Results. At 24-month follow-up from baseline, there was no significant deterioration in forced vital capacity (0.01 L; 95% CI –0.13 - 0.14) (p=0.91) after commencing RTX salvage therapy. Serial HRCT of the chest showed radiological disease stability or improvement in 13 of the 19 patients (68%). FC assessment showed no significant deterioration compared with baseline (p=0.083). No serious adverse drug reactions or deaths were recorded.
Conclusion. Salvage RTX therapy, in combination with various immunomodulatory treatments, resulted in disease stability in the majority of patients with severe CTD-ILD over a 24-month period.
Keywords. Connective tissue disease, interstitial lung disease, drug therapeutics.

Afr J Thoracic Crit Care Med 2024;30(3):e1431. https://doi.org/10.7196/AJTCCM.2024.v30i3.1431

Study synopsis
What the study adds. Connective tissue disease-associated interstitial lung disease (CTD-ILD) is a challenging clinical entity. Rituximab (RTX), a chimeric monoclonal antibody targeted to CD20+ B cells, resulting in B-cell depletion, has been suggested as a potential therapeutic modality in refractory or severe disease. A single-centre experience of RTX salvage therapy in progressive CTD-ILD is presented.
Implications of the findings. This small study suggests a possible role for RTX therapy in severe or refractory CTD-ILD.

Connective tissue disease-associated interstitial lung disease (CTD-ILD) is a complex and heterogeneous clinical entity, associated with significant morbidity and mortality.[1] Anti-inflammatory and immunomodulatory therapy has remained the cornerstone of treatment and highlights the immunological dysfunction critical to the underlying pathophysiology of the disease. Rituximab (RTX) is a chimeric monoclonal antibody targeted to CD20+ B cells, resulting in B-cell depletion.[2] On-label use of RTX in connective tissue disease (CTD) not responding to first-line disease-modifying antirheumatic drugs is currently limited to rheumatoid arthritis (RA), granulomatosis with polyangiitis, and microscopic polyangiitis.[3,4] However, RTX has been utilised as salvage therapy in refractory or severe CTD-ILD and has been shown to improve outcomes in observational studies.[5]

Severe CTD-ILD may manifest with progressive disease despite maximal conventional first-line therapy, such as corticosteroids and other immunosuppressives, and is associated with increased morbidity and mortality. Pulmonary antifibrotic drugs, the use and efficacy of which were originally studied in idiopathic pulmonary

fibrosis,[6] are reserved for patients with established and progressive pulmonary fibrosis.[7,8] Lung transplantation remains an option in a minority of patients. However, advanced multisystem disease, lack of organ availability, and a paucity of local transplant centres severely limit this therapeutic option. Data on specific predictors of prognosis and mortality in progressive CTD-ILD are limited.[9]

The use of RTX in CTD-ILD has evolved over the past decade.[5,10-12] Its use, albeit limited by small studies and off-label use, has shown potential as a feasible treatment option in slowing disease progression. Although conventional immunosuppressive drugs have remained the cornerstone of care in CTD-ILD, certain subgroups may require novel drugs as salvage therapy.

This retrospective case series analyses 19 patients with refractory CTD-ILD over a 24-month period after the first dose of RTX. All patients were treated at Wits Donald Gordon Medical Centre (WDGMC), Johannesburg, South Africa, between January 2010 and December 2020. The response to RTX was measured by serial pulmonary function testing (PFT), high-resolution computed tomography (HRCT) of the chest, and World Health Organization (WHO) functional class (FC) assessment.[13]

Methods

We performed a retrospective review of a patient database managed at a multidisciplinary clinic at WDGMC comprising pulmonologists, rheumatologists and radiologists. Among 50 patients treated with RTX between January 2010 and December 2020, 19 patients with progressive CTD-ILD, 24-month follow-up and complete data were identified. All the patients were aged ≥18 years, had a diagnosis of CTD-ILD made by a multidisciplinary team (MDT) consensus based on standardised criteria (European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) [14]), and had received at least one dose of RTX.

PFTs included the forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DL_{CO}). Data were collected at baseline prior to RTX therapy, and at regular intervals up to 24 months from initiation of RTX therapy.

The chest HRCT findings were standardised based on radiological criteria of CTD-ILD and MDT consensus. The radiological interstitial lung disease (ILD) subtypes were described prior to RTX therapy and at 6 - 12-monthly intervals up to 24 months. A qualitative visual descriptive assessment was performed based on an MDT discussion, and the terms 'stabilisation', 'improvement' or 'progression' of ILD based on HRCT findings were used. Baseline HRCT images were compared with follow-up images side by side, noting identical anatomical slices. Stabilisation of disease was defined as no change in the severity of fibrosis and/or ground-glass opacities compared with baseline HRCT. Progression of disease was defined as increasing fibrosis and/or worsening ground-glass opacities compared with baseline HRCT. Semi-quantitative and quantitative scoring systems were not utilised.[15]

A subjective patient functional assessment was performed based on the World Health Organization FC assessment (I - IV).[13] Values were recorded at baseline and then at 12 and 24 months, FC I indicating no limitation of ordinary physical activity, FC II slight limitation or breathlessness on ordinary physical activity, FC III marked limitation on ordinary physical activity, and FC IV discomfort or breathlessness at rest.

Statistical analysis included the extent of the change in PFT outcome from baseline to 24-month follow-up by repeated measures one-way analysis of variance (ANOVA). The change in FC from baseline to 24-month follow-up was determined by the Stuart-Maxwell test for paired categorical data. HRCT findings of the chest could not be analysed statistically owing to limited data points. Data analysis was carried out using SAS version 9.4 for Windows (SAS Institute, USA). A 5% significance level was used.

Ethical considerations

Ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee (ref. no. M220104).

Results

Nineteen patients, with a median age of 54 years (range 22 - 77), were included during the period January 2010 - December 2020. The

Table 1. Baseline demographics (*N*=19)

Characteristic	*n* (%)*
Age (baseline) (years)	
Median (IQR)	54 (40 - 60)
Range	22 - 77
Gender	
Female	14 (74)
Male	5 (26)
CTD profile	
RA	9 (47)
SSc	4 (21)
SLE	3 (16)
ASS	1 (5)
DM	1 (5)
Mixed CTD	1 (5)
Antibody profile, *n*	
ANA titre 1:80	1 (centromere 1)
ANA titre 1:160	4 (centromere 1, homogeneous 1, speckled 2)
ANA titre 1:320	2 (centromere 1, speckled 1)
ANA titre 1:640	3 (homogeneous 1, nucleolar 2)
ANA titre 1:1 280	1 (speckled 1)
ANA titre 1:2 560	3 (nucleolar 1, speckled 2)
RF	11
Anti-CCP	4
Anti-centromere	2
Anti-Ro-SSA	2
Anti-SCL-70	2
Anti-JO-1	1

IQR = interquartile range; CTD = connective tissue disease; RA = rheumatoid arthritis; SSc = systemic sclerosis; SLE = systemic lupus erythematosus; ASS = anti-synthetase syndrome; DM = dermatomyositis; ANA = antinuclear antibody; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide; anti-ro-SSA = anti-Sjögren's-syndrome-related antigen A; anti-SCL-70 = anti-topoisomerase I antibody; anti-JO-1 = anti-histidyl tRNA synthetase.
*Except where otherwise indicated.

patients' CTD diagnosis and ILD pattern were determined by an MDT consensus based on standardised international criteria (EULAR/ACR). Baseline demographics and disease profile were recorded (Table 1).

Pre-rituximab therapy

Immunosuppressive therapy administered prior to and concurrent with RTX was recorded and compared (Fig. 1). All patients received corticosteroids, as well as initial induction therapy with cyclophosphamide, mycophenolate mofetil, or both. Various immunosuppressive drug combinations were used according to the patients' underlying CTD.

Decision to treat with rituximab

The addition of RTX was based on clinical, radiological and biochemical factors indicating disease progression despite first-line induction immunosuppressive therapy. These factors included clinical disease progression as well as objective measures such as PFT indices and HRCT findings. Despite a paucity of pre-RTX data owing to patients being referred from other centres, the baseline indices of the cohort were comparable to those observed in other studies.[10,11] The MDT decision to initiate RTX therapy also took into account limited published evidence at the time regarding the use of RTX, its availability and safety profile, the need for additional therapeutic modalities, and the risks of long-term corticosteroid and cyclophosphamide exposure.

Drug administration

RTX administration was in accordance with the registered product information for RA. A dose of 1 000 mg is given intravenously and then repeated after 2 weeks.[4,16] This dosing protocol was repeated at 6-monthly intervals. The degree of B-cell depletion was monitored using a high-sensitivity flow cytometry technique. Over the 24-month period, 16 of the 19 patients (84%) received all scheduled doses (eight doses totalling 8 g), 1 patient received six doses (total of 6 g), and 2 patients received four doses (total of 4 g).

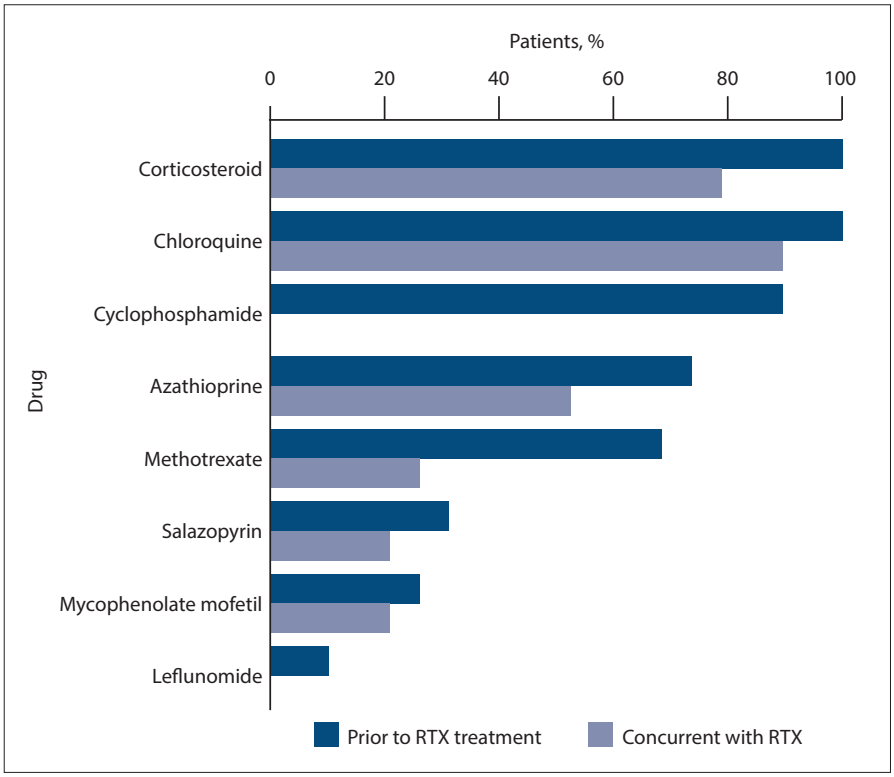

Fig. 1. Drug therapy prior to and concurrent with RTX. (RTX = rituximab.)

Post-rituximab treatment course

Pulmonary function testing

Serial spirometry findings were analysed for all 19 patients. At the 6-month follow-up from baseline (Table 2), the mean change in FVC was not significantly different from baseline values (p=0.41). At the 24-month follow-up from baseline (Table 2), the mean change in FVC was again not significantly different from baseline values (p=0.91). Owing to incomplete data, DL_{CO} values could not be analysed statistically. The available PFT data were plotted throughout the RTX therapy study period (Figs 2 and 3).

High-resolution computed tomography of the chest

Interstitial lung disease patterns of the 19-patient cohort were described by radiological criteria as per the official European Respiratory Society/American Thoracic Society research statement.[17] Open lung biopsy was not performed owing to the high surgical risk in patients with progressive ILD. Baseline HRCT patterns were reported in all patients: 15 patients (79%) had a radiological pattern consistent with nonspecific interstitial pneumonia (NSIP), and 4 (21%) a pattern consistent with usual interstitial pneumonia (UIP). During RTX therapy, serial HRCT scans of the chest were performed in all 19 patients and radiological changes were documented. Owing to missing data and the small sample size, statistical analysis was not feasible. The radiological changes of ILD were described as improvement, stability or progression of disease by a single radiologist with experience in CTD-ILD (Fig. 4).[15]

Functional class assessment

Serial FC changes using the WHO classification were assessed in all 19 patients. FC did not differ significantly from baseline to 24 months (p=0.083) (Fig. 5).

Table 2. Disease parameters, baseline and at 6- and 12-month follow-up

PFT index	Baseline, median (IQR); range	6-month follow-up, mean change (95% CI)	24-month follow-up, mean change (95% CI)
FVC (L)	2.2 (1.4 - 2.8); 0.52 - 3.6	0.09 (–0.14 - 0.32)	0.01 (–0.13 - 0.14)

PFT = pulmonary function test; IQR = interquartile range; CI = confidence interval; FVC = forced vital capacity.

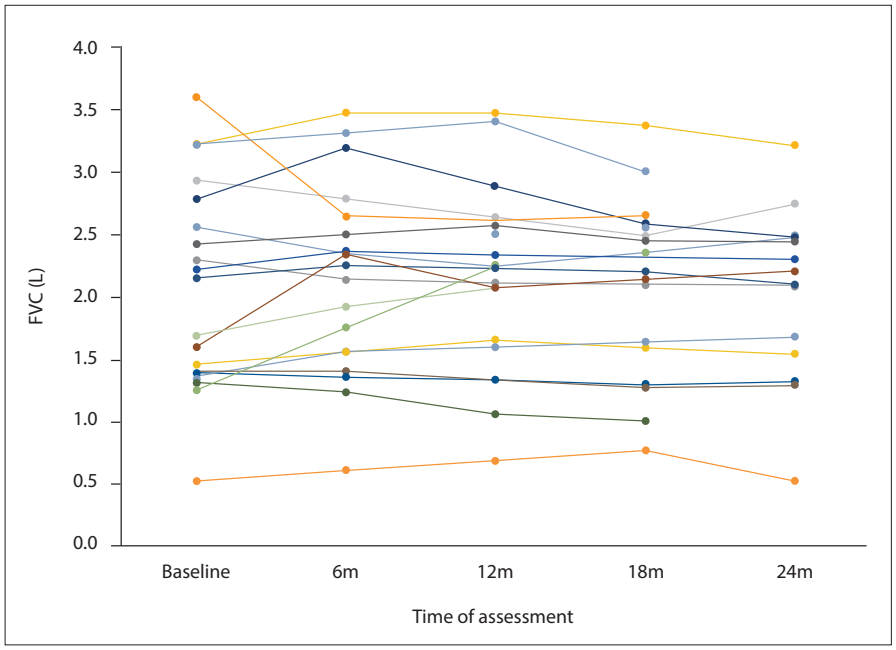

Fig. 2. FVC changes over time (24 months). (FVC = forced vital capacity.)

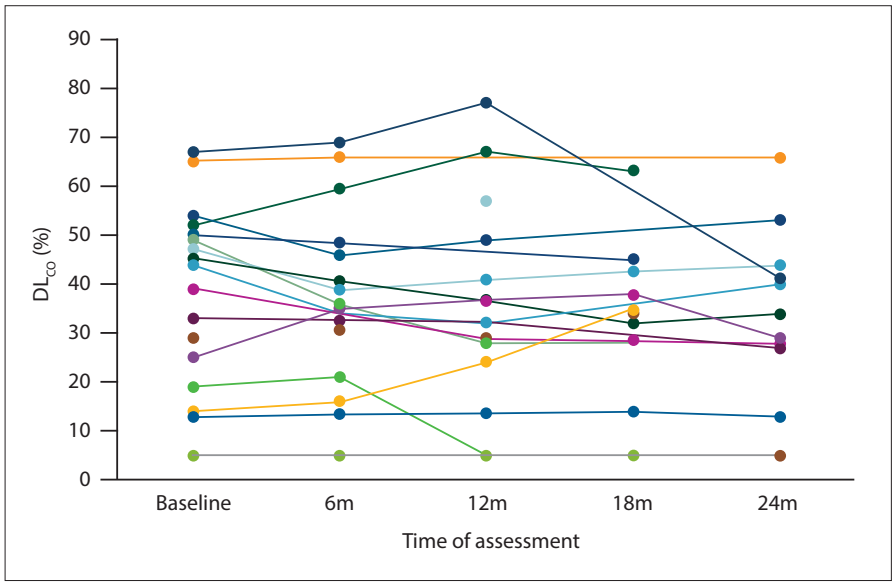

Fig. 3. DL_{CO} changes over time (24 months). (DL_{CO} = diffusion capacity for carbon monoxide.)

Adverse events

No significant or life-threatening adverse events related to drug therapy were recorded. There were no patient deaths during the study period.

Discussion

ILD remains a common and important manifestation of CTDs and is associated with significant morbidity and mortality.[2] Early identification of CTD-ILD has pertinent clinical implications regarding therapeutic modalities. The presence of ILD in CTD is an independent factor associated with decreased survival, with 5-year mortality rates exceeding 10% (10 - 39%).[18-20] Parameters utilised to assess the response to therapy include PFT, HRCT of the chest, FC and clinical symptoms. The primary goal of treatment in this clinical scenario is to halt disease progression, preserve pulmonary function, and prevent associated complications and mortality. Current first-line therapies consist of corticosteroids and immunomodulatory drugs such as azathioprine, mycophenolate mofetil and cyclophosphamide.[19] The underlying dysregulated immune response to host tissue highlights how modulation of autoimmunity remains key to disease control.[20] RTX, a chimeric monoclonal antibody targeted to CD20+ B cells, results in B-cell depletion,[3] causing a decrease in humoral-mediated autoimmunity and associated tissue damage.[21]

We report our experience of RTX use in CTD-ILD in a patient cohort at WDGMC, adding to the limited data available on its use in our geographical setting. Data emerging during the preceding decade have highlighted RTX as a potential drug choice in severe or refractory CTD-ILD. A retrospective analysis by Keir *et al.*[5] in 2012 concluded that 7 out of their 8-patient cohort showed a favourable response to RTX. More recent evidence from Atienza-Mateo *et al.*[11] concluded that RTX constitutes a promising therapeutic option to preserve lung function in patients with CTD-ILD, regardless of their underlying pattern of CTD or radiological profile. The Recital trial published in 2023 compared RTX with cyclophosphamide as induction therapy in patients with CTD-ILD and demonstrated non-superiority of RTX, although RTX was associated with fewer adverse events.[12]

Our cohort of patients had varied CTD profiles, with RA being the most common diagnosis (n=9). As a whole, the patient cohort had significantly impaired baseline indices despite prior treatment with first-line therapies, with values comparable to other studies.[10,11] All patients had received at least four other immunosuppressive drugs prior to the decision to start RTX. The majority of our patients achieved disease stability of severe CTD-ILD, which is considered a positive response to treatment in this challenging clinical scenario. The progressive decline in pulmonary function stabilised, with a mean decrease in FVC from baseline of 0.01 L (95% CI –0.13 - 0.14) at the 24-month follow-up.

Radiological features of CTD-ILD can be assessed qualitatively. In the present study, we relied on visual descriptive changes of ILD on HRCT interpreted by a single experienced radiologist. HRCT findings were used in combination with other clinical parameters to assess the course of disease. At 24 months' follow-up, 17 patients had HRCTs available for review. Of these, 13 were interpreted as disease stability, 3 showed disease progression, and 1 showed improvement. Most of the benefit appeared to be in the radiological NSIP group, with progressive disease seen in 3 of the 4 patients with radiological UIP.

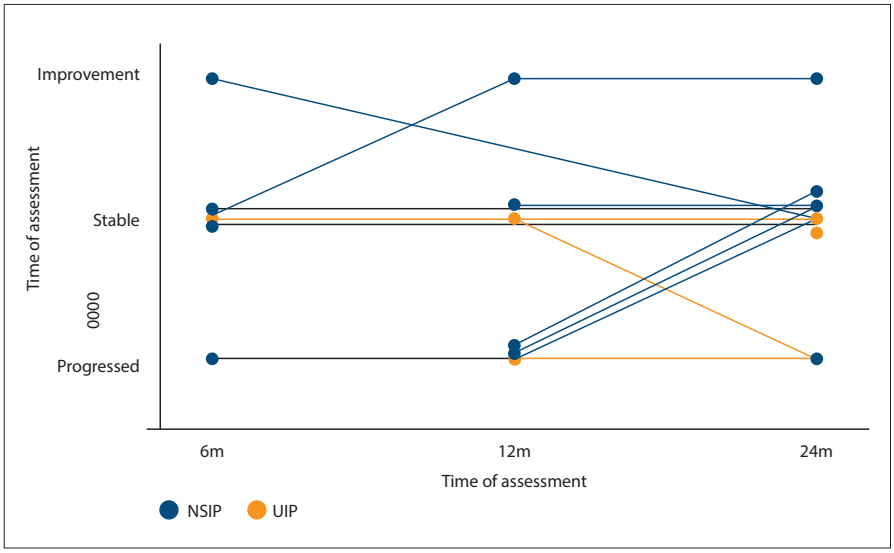

Fig. 4. Chest HRCT changes over time (24 months). (HRCT = high-resolution computed tomography; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.)

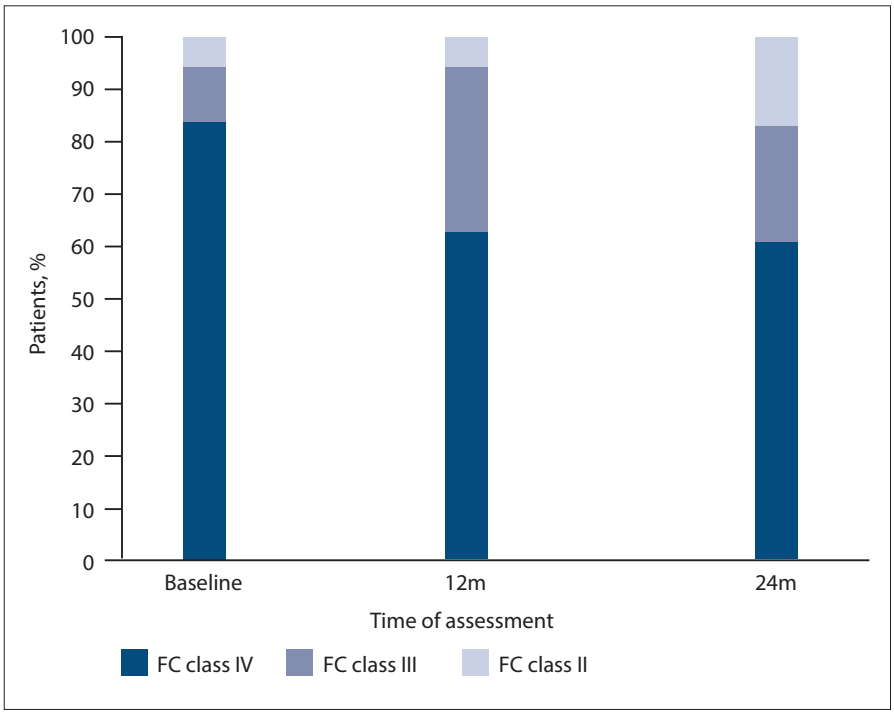

Fig. 5. FC assessment over time (24 months). (FC = functional class.)

The WHO FC assessment (I - IV) for effort tolerance was utilised as a subjective measure of functional impairment. Results were varied, with some patients reporting symptomatic improvement while others had progressive functional impairment. Overall, FC did not show significant worsening from baseline to 24 months' follow-up (p=0.083).

Another important aspect of our study was the analysis of immunosuppressive drug use prior to and concurrent with RTX treatment. RTX therapy was associated with use of fewer concurrent drugs, possibly mitigating other drug-related adverse events.

Limitations of our study include the small sample size, a single-centre cohort of patients, limited statistically significant findings and subgroup analysis, the absence of histological diagnosis, lack of a control group, non-standardised immunosuppressive drug therapies, and the retrospective design of the study. Insufficient pre-RTX data points also prevented plotting of the trend of clinical decline prior to RTX use. Despite these limitations, our study suggests that RTX is a promising therapeutic option in a challenging patient population, with stabilisation of FVC decline and functional impairment. Our data add to the growing pool of evidence that RTX can be considered in progressive CTD-ILD, with an acceptable safety profile.

Conclusion

We report our experience of RTX in severe and progressive CTD-ILD at our centre. The addition of RTX to first-line immunosuppressive therapy as a salvage therapeutic modality may result in disease stability as measured by radiological changes, PFT and subjective measures of disease severity. Further studies are required to investigate the role of RTX as a therapeutic option in the challenging clinical scenario of severe CTD-ILD.

Declaration. The research for this study was done in partial fulfilment of the requirements for UFS's MMed (Int Med) degree at the University of the Witwatersrand.

Acknowledgements. We thank the WDGMC Research Office and its staff, DGMC Radiology, Dr Sue Tager, and the patients under the care of the attending physicians.

Author contributions. UFS collected and collated data, drew up the protocol and manuscript. GKS served as the primary supervisor and manuscript editor. GKS and BC provided the data set. PEB reported the HRCT scans and assisted with the interpretation of radiological data. PG assisted with data interpretation, statistical analyses, and preparation of the figures.

Funding. None.

Conflicts of interest. None.

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Received 23 August 2023. Accepted 14 June 2024. Published 11 October 2024.