Rituximab therapy in connective tissue disease associated interstitial lung disease - a retrospective single centre observational study.

Dr Ubaid Feroze Seedat

For the Submission of a Master of Medicine (Internal Medicine)

University of the Witwatersrand

2023

Declaration

I, Ubaid Feroze Seedat, declare that this research report is my own work, which is being submitted for the degree Master of Medicine (in the submissible format with my protocol and an extended literature review) in the department of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

…….

…20th… day of …November…2023

Acknowledgement

I would like to express my gratitude towards my supervisors, Dr GK Schleicher for granting me the opportunity to partake in such a project under his guidance, support, and knowledge. Dr B Christian for guidance and access to critical resources. Gratitude must be extended to Dr P Gaylard with her invaluable assistance in statistical analysis. The Wits Donald Gordan Medical centre and its staff, in particular Dr S Tager, the research team, and the radiology department, in particular Dr E Boshoff.

This project is dedicated to the men who helped raise and guide me, my late father, uncle, and grandfather.

Rituximab therapy in connective tissue disease associated interstitial lung disease - a retrospective single centre observational study.

Seedat UF[1], Christian B[1], Schleicher GK[1]

1. Wits Donald Gordon Medical Centre (WDGMC), University of the Witwatersrand, Johannesburg, South Africa.

Abstract

Introduction

Connective tissue disease associated interstitial lung disease (CTD-ILD) is a challenging clinical entity. Rituximab (RTX) is a chimeric monoclonal antibody targeted to CD20+ B-cells, resulting in B-cell depletion and has been suggested as a potential therapeutic modality in progressive disease.

Objectives

To investigate the therapeutic effects and safety of rituximab in patients with progressive CTD-ILD.

Methods

A retrospective observational analysis was performed at WDGMC between January 2010 and December 2020. A total of 19 patients with CTD-ILD were treated with RTX and various combinations of immunomodulatory therapy. The effects of RTX were investigated with serial pulmonary function testing (PFT), high resolution computed tomography (HRCT) of the chest, and the WHO functional class assessment (FC).

Results

At an average of 24-month follow up from baseline, the mean change in forced vital capacity (FVC) was not significantly different from baseline (0.01L, 95% CI -0.13 to 0.14L) (p=0.91). At an average of 24-month follow up, 17 follow up HRCTs were available of which 13 showed disease stability, 3 indicated progression and 1 indicated improvement. At an average of 24-months follow up, FC remained stable compared to baseline (p=0.083). No serious adverse drug reactions or mortalities occurred.

Conclusion

Rituximab is a potential therapeutic option in patients with progressive CTD-ILD and appears to result in stability in FVC, HRCT findings and FC over a 24 month period.

Presenters email: *ubaidseedat@gmail.com*

Table of contents

Abbreviations

CTD: Connective Tissue disease

ILD: Interstitial lung disease

CTD-ILD: Connective Tissue disease associated Interstitial lung disease.

RTX: Rituximab

SLE: Systemic lupus erythematosus

RA: Rheumatoid Arthritis

SSC: Systemic sclerosis

ANA: Anti-nuclear antibody

RF: Rheumatoid factor

ACCP: Anti–cyclic citrullinated peptide

IPF: Idiopathic pulmonary fibrosis

PFT: Pulmonary function tests

FEV1: Forced expiratory volume within 1 second.

FVC: Forced vital capacity.

DLCO: diffusing capacity of the lungs for carbon monoxide

HRCT: High-resolution computed tomography

UIP: Usual interstitial pneumonia

NSIP: Nonspecific interstitial pneumonia

Wits DGMC: Wits Donald Gordon Medical Centre

Protocol for the Submission of a Master of Medicine (Internal Medicine)

Rituximab therapy in connective tissue disease associated interstitial lung disease - a retrospective single centre observational study.

Dr UF Seedat

Registrar in the Department of Internal Medicine

The University of the Witwatersrand

Student no. 543 789

Registrar training (W-number) no. W-05-01-47

Correspondence: Email: ubaidseedat@gmail.com; Cell number: 079 524 8897

Supervisors

Dr GK Schleicher

Specialist Physician and Pulmonologist

Wits University Donald Gordon Medical Centre

The University of the Witwatersrand

Dr B Christian

Specialist Physician and Rheumatologist

Wits University Donald Gordon Medical Centre

The University of the Witwatersrand

Declarations: None

Introduction and Literature review

Connective tissue disease associated interstitial lung disease (CTD-ILD) is a complex and heterogenetic entity comprising 15% of all ILD[1] and is associated with significant morbidity and mortality.[2] Anti-inflammatory, immuno-modulatory and more recently anti-fibrotic therapy has remained the cornerstone of treatment and highlights the immunological dysfunction critical to its underlying pathophysiology. Rituximab (RTX) is a chimeric monoclonal antibody targeted to CD20+ B-cells, resulting in B-cell depletion.[3] This drug has been utilised as salvage therapy in refractory CTD-ILD and has demonstrated improved outcomes in observational studies.[4] This retrospective case series analysis aims to identify patients with CTD-ILD treated with RTX, analyse the efficacy of RTX therapy, and identify patient subgroups who may benefit from this therapy in a single centre over a ten-year period.

CTD-ILD may manifest with severe and progressive disease despite maximal first line therapy. Initial treatment in CTD-ILD is based on connective tissue disease profile and radiological findings. To date, corticosteroids have remained the conventional backbone of care with immunosuppressant therapy such as mycophenolate mofetil, azathioprine and cyclophosphamide remaining key additions to therapy.[5] Some patients may manifest with severe and progressive disease despite initial therapy and this poses as a challenging clinical scenario associated with significant morbidity and mortality. A paucity of treatment options is available in this clinical situation, with palliative measures and lung transplantation previously the only options. In recent times anti-fibrotic agents have emerged, originally utilised in the therapy of idiopathic pulmonary fibrosis (IPF). The drugs nintedanib and pirfenidone have been shown to be safe and effective in the treatment of IPF, with both drugs being recommended for use in patients with IPF.[6] Data has also since emerged regarding the use of these agents in non-IPF pulmonary fibrosis.[7, 8.]

Emerging data has indicated that RTX is a potential salvage therapy, slowing disease progression in CTD-ILD. The basis of pulmonary disease in CTD-ILD is associated with immunological dysfunction, and its modulation may be key in disease control.[9, 10.] Notable early evidence highlighting the role of RTX in CTD-ILD emerged in 2012. A retrospective analysis by Kier et al.[4] concluded that 7 out their 8-patient cohort showed a favourable response to RTX. Parameters utilised to assess the response to RTX included pulmonary function tests (PFTs), high resolution computed tomography (HRCT) of the chest and clinical symptoms. Eight patients were selected and observed for 9-12 months post RTX therapy, patients all had severe baseline disease with a diffusion capacity for carbon monoxide (DLCO) of less than 25% (range 16–32%) and FVC of 45% (range 37–59%). The 8-patient cohort was varied in both disease profile and HRCT pattern, 5 patients were included with polymyositis (PM) /dermatomyositis (DM) related ILD, 4 of which were subtyped radiologically as NSIP and 1 as organising pneumonia (OP). Two patients with undifferentiated CTD related ILD were included (one with fibrotic NSIP and one with OP). The final patient had systemic sclerosis (SSC) related ILD radiologically typed as fibrotic NSIP. Statistically significant ($p<0.05$) responses were observed in this cohort of patients, both clinically, and assessed by serial PFT`s. A median improvement in DLCO of 22% (range 0–119%; $p=0.04$) and FVC of 18% (range 0–100%; $p=0.03$) was observed in 6 patients within the designated period following RTX therapy. This followed a period of clinical and functional decline prior to RTX therapy. The 7th patient (undifferentiated CTD-ILD with OP) had no baseline PFT's due to being mechanically ventilated but had radiological and symptomatic benefit. The 8th patient (SSC related-ILD) had no statistically significant benefit noted on serial PFTs, but symptomatic improvement was noted. The authors concluded that despite the shortcomings of an observational analysis in a small group of patients, RTX use was associated with statistically significant clinical and functional improvement. The study further went on to highlight the need for further investigation with larger, more varied patient groups.[4]

A larger retrospective review conducted at the Bristol CTD-ILD service in 2016 by Sharp et al.[11] analysed RTX therapy in refractory CTD- ILD who failed to respond to conventional immunomodulatory therapy. Twenty-four patients were identified, specifically those who

failed to respond to prior immunosuppressive therapy with 6 cycles of cyclophosphamide at 15mg/kg at 3-week intervals, high dose intravenous methylprednisolone, and mycophenolate mofetil. Patient demographics were varied; of the 24 patients, 16 were female and 8 were male with a mean age of 51.4 years (SD of 14.9). Thirteen patients had myositis related disease (10 with anti-synthetase syndrome (ASS) and 3 with DM), 3 with SSC, 2 with Sjogren's syndrome (SS), 2 with systemic lupus erythematosus (SLE) and 4 with unclassifiable CTD. Radiological subtyping was identified in 11 patients, with 9 having NSIP, 1 with lymphocytic interstitial pneumonia (LIP) and 1 with hypersensitivity pneumonitis (HP). Prior to RTX therapy, there was a progression of disease with a decline in FVC of -3.3% (95% CI - 5.6, -1.1) and DLCO of - 4.3% (95% CI - 7.7, -0.9). Following RTX administration, PFT`s were assessed at 6 and 12 months. Results showed that FVC improved after therapy, with a mean change of 4.1% (95% CI 0.9, 7.2; P = 0.01) and DLCO remained stable, with a mean change of 2.1% (95% CI 1.0, 5.2; P = 0.18). Of note, subgroup analysis based on disease profile, with subtyping into a myositis and non-myositis group, showed that patients in the myositis group yielded a greater response in FVC (P = 0.002) as well as DLCO (P = 0.009). Radiological parameters were also analysed by HRCT; 22 patients had available imaging studies and radiological criteria indicated that imaging had deteriorated for 9/22 patients while 13/22 showed disease stability or improvement. Despite this analysis suggesting a trend in improved radiological appearances before and after treatment with RTX, no statistically significant differences were demonstrated (P = 0.223).[11]

Larger studies have also emerged in recent publications. A 2020 publication by Atienza-Mateo B et al.[12] identified 34 patients from May 2016 until March 2020 in a single Spanish centre. Of the 34 patients, 8 were excluded due lung transplantation, insufficient data, or loss of follow up. The 26 remaining patients represented a diverse cohort which included 13 males and 13 females with a mean age of 58.9 years (±10.2) at the onset of RTX therapy. Seven patients had SSC, 6 with idiopathic inflammatory myositis, 6 with rheumatoid arthritis (RA), 5 with interstitial pneumonia with autoimmune features (IPAF), 3 had primary SS and 2 had myeloperoxidase-ANCA positive vasculitis. Radiological subtyping was also identified, with 13 patients falling into the usual interstitial pneumonia (UIP) subtype (2 with probable UIP or indeterminate UIP pattern), 12 with NSIP pattern and 1 with a non- NSIP pattern. Immunomodulatory therapy both prior to, and concomitant to RTX, was identified. The efficacy of RTX was evaluated in these patients at time dependant intervals and PFTs

and radiological data was analysed. RTX therapy resulted in an improvement in multiple PFT parameters. An increase in mean FVC values (5.8% at 6 months, 0.5% at 1 year and 4.2% at 2 years), forced expiratory volume within the first second (FEV1) (2.5% at 6 months and 3.4% at 2 years), and DLCO (0.4% at 1 year and 10.6% at 2 years) was observed. Serial HRCT of the chest showed stabilization of interstitial lung abnormalities in 15/23 patients (65.2%), a worsening from baseline in 5/23 patients (21.7%), and a marked improvement in 3/23 patients (13.1%). Limitations of the study were highlighted, noticeably RTX therapy being initiated at differing points throughout the patient's immunosuppressive regimen. Furthermore, some PFT values were incomplete. Despite this, the paper concluded that RTX constitutes a promising therapeutic option to preserve lung function in patients in this clinical scenario, regardless of their underlying pattern of CTD or radiological profile.[12]

In another retrospective analysis [13], a multi-centre mixed cohort of patients in six Portuguese centres in 2019 included 49 patients with varied underlying CTD pathology. The majority (30 patients) having RA, 4 patients had SS, 4 with SLE, 3 with SSC, 2 with SSC/ PM overlap, 2 PM, 2 with ASS, 1 with DM and 1 with SLE/ SS overlap syndrome. All patients included were treated with RTX for lung involvement at some point during disease course, furthermore patients on RTX for non-pulmonary disease were also included. Assessment was performed at baseline (no more than 6 months before starting RTX) and a revaluation of PFTs were performed again at least 6 to 12 months following initial administration of RTX. Results showed improving or stable PFTs after one year of RTX administration, with stabilisation of DLCO (mean + 5.4%, $p = 0.12$) and an improvement of FVC (mean + 4.3%, $p = 0.03$). Further subgroup analysis indicated patients with UIP had less impressive results, with one-year post-RTX PFT`s remaining stable (DLCO + 2.5%, $p = 0.77$; FVC + 4.2%, $p = 0.16$). RTX therapy was however discontinued in two patients due to infection. Several limitations of this study were identified, disease duration prior to therapy was not indicated neither was previous or concomitant drug therapy. Patient receiving RTX therapy for non-pulmonary indications were also included, confounding treatment regimens and study outcomes.

The efficacy of RTX in CTD-ILD has also been studied in less heterogeneous populations, in both SSC- ILD and RA-ILD. A comprehensive systemic review and meta-analysis done by Goswami et al.[14] in 2021, identified 20 studies of patients with SSC-ILD treated with RTX. In this meta-analysis, 575 patients were included from 2 randomised controlled trials (RCTS), 6 prospective studies, 5 retrospective studies and 7 conference abstracts. Key indices utilised to assess a clinical response were limited to the FVC and DLCO. Despite key limitations highlighted by the authors, noticeably the inclusion of case reports/series and the absence of significant RCTS (the two trials included were not double blinded), the 6 and 12 month follow up indices yielded modestly positive results. There was a 4.49% (95%, CI 0.25, 8.73) improvement in FVC at 6 months of RTX therapy and 7.03% (95%, CI 4.37, 9.7) improvement if FVC at 12 months. A similarly modest improvement in DLCO was observed, with RTX treated patients showing improved DLCO at 6 months by 3.47% (95% CI 0.99, 5.96) and at 12 months by 4.08% (95% CI 1.51, 6.65). Adverse events related to RTX therapy were also included in this review, which identified that patients treated with RTX had a lower chance of developing infections compared with controls (odds ratio 0.256 (95% CI 0.104, 0.626), $I^2 = 0\%$, $P = 0.47$). The authors concluded that RTX in SSC-ILD was associated with an improvement of both FVC and DLCO during the first year of treatment. RTX use was also associated with fewer infectious adverse events. Further comments did indicate that longer follow up indices should be utilised, and descriptions of concomitant immunomodulatory therapy will further bolster evidence of this drug.

Further evidence in less heterogenous populations has also emerged, specifically RTX use in RA-ILD. A single centre, 10-year observational study by Yusof et al.[15] conducted in 2017, in the United Kingdom assessed the effect of RTX on RA-ILD. In this retrospective observational study, 700 patients with RA were treated with RTX, with 56 patients having RA-ILD (median age of 64 (59-72), with 36 patients being female and 28 males). Antibody profile was expanded upon with 98% of the cohort being seropositive (rheumatoid factor and/or anti-cyclic citrullinated peptide) while outcome analysis was performed for both pulmonary and musculoskeletal disease. For the purpose of this review only the pulmonary outcomes in RA-ILD were included. In the preceding 6-12 months prior to RTX therapy there was a decline in FVC with a median relative change of 2.4% (IQR 7.1+0.8). Following RTX therapy however there was an improvement in FVC of 1.2% (IQR 6+8.6; median difference +4.2%; P = 0.025). Similarly promising results were identified in DLCO, with a

median improvement observed post RTX therapy of 3.7%; P = 0.045. Overall, based on PFT parameters, disease progression was stabilised in 68% of the cohort and improved in 19%, whilst 13% showed deterioration. Radiological analysis was also performed in this analysis and was limited to 14 pairs of HRCTs (pairs consisted of pre and post RTX therapy). One patient showed radiological improvement, 6 had stabilisation of disease, and 7 indicated disease progression. Of note, however, those that who showed a poorer response or disease progression on RTX therapy all had poorer baseline PFT indices and were subtyped radiologically as UIP.

Comparative analysis has largely been scarce in direct head-to-head comparison of RTX to other drug therapies. The RECITAL trial[16] a double-blind, double-dummy, phase 2b trial compared RTX to cyclophosphamide in adults with severe or progressive ILD related to scleroderma, idiopathic inflammatory myositis, or mixed CTD. The study's primary endpoint was identifying the change in FVC at 24 weeks, multiple secondary endpoints were also included such as other PFT indices, 6-minute walk distance, symptom questionnaires and treatment indices. Regarding the primary endpoint, the unadjusted mean change from baseline in FVC was a gain of 99 mL (SD 329; relative change 4·35% [SD 15·67]) in the cyclophosphamide group and 97 mL (234; 4·31% [11·80]) in the RTX group. Comparative analysis indicated that based on the FVC and quality of life in individuals with CTD-ILD, that RTX was not superior to cyclophosphamide, however treatment with RTX was associated with fewer adverse events as well as a reduction in corticosteroid exposure compared with cyclophosphamide and thus could be considered as a therapeutic option.[16]

The utilisation of other modalities in CTD-ILD has further expanded in recent times. Anti fibrotic agents nintedanib and pirfenidone have been utilised beyond its original indication of IPF. The RELIEF trial[7], a multi-centre, double-blind, randomised, placebo-controlled, parallel phase 2b trial performed in Germany identified 127 patients with fibrotic ILD due to CTD-ILD, fibrotic non-specific interstitial pneumonia (NSIP), chronic hypersensitivity pneumonitis or asbestos-induced lung fibrosis. The study was prematurely terminated based on an interim analysis highlighting futility due to slow recruitment. However emergent data has suggested that adding pirfenidone to existing treatment in patients with fibrotic ILDs, other than IPF, who deteriorate despite conventional therapy, might reduce disease progression as measured by a decline in forced vital capacity (FVC).[7] The INBUILD trial[8]

published in 2020 investigated the efficacy and safety of nintedanib versus placebo in patients with progressive fibrosing ILD other than IPF. This was a randomised, double-blind, placebo-controlled, parallel group trial done at 153 sites in 15 countries, identified 663 patients, of which 26% had CTD-ILD. Results suggested that nintedanib reduced the rate of ILD progression, as measured by FVC decline, in patients who have a chronic fibrosing ILD, irrespective of their underlying ILD diagnosis.[8] Despite the promising evidence, limitations of these agents are well established in our setting, with pricing and long-term efficacy restricting widespread use. [9] Lung transplantation remains an option, however advanced multi-system disease, selection criteria and organ availability result in an option feasible only in a very selective patient group. Furthermore, data regarding specific predictors of prognosis in this setting are limited.[17]

Despite advancing treatments, RTX has remained a possible therapeutic modality with improved access over anti-fibrotic agents and transplantation. RTX, being an anti-CD 20 monoclonal antibody, is associated with noticeable adverse effects, the most common being infusion reactions and an increased infection risk owing to its potent immunosuppressive effects. Despite these concerns, evidence has demonstrated safety in its use as therapy. Evidence presented at the 2019 ACR/ARP conference by Mesa et. al[18], concluded that RTX is safe in CTD-ILD, and combined with other immunosuppressants, the side effect profile remained similar.

<u>Objectives</u>

- To Investigate the effect of RTX on clinical, PFT, and radiological outcomes in CTD-ILD. Patient outcomes are analysed based on PFTs, functional class (FC) assessment, and HRCT of the chest.

    - Pulmonary function test indices utilised include the spirometry indices of forced vital capacity (FVC), forced expiratory volume within the first second (FEV1) and diffusion capacity for carbon monoxide (DLCO).

        - Indices are recorded prior to therapy and then at pre-defined periods during RTX therapy.
        - Periods of assessment are recorded prior to RTX therapy, at baseline and then at periods of 3-9, 9-15, 15-21 and 21-27 months from initiation of RTX therapy.

    - The World Health Organisation Functional Class assessment[19] will be utilised as a subjective measure of patient functional and symptomatic change throughout RTX therapy at set intervals of 12 months.
        - Class I: no limitations on physical activity.
        - Class II: slight limitation on physical activity.
        - Class III: marked limitation on physical activity, asymptomatic at rest.
        - Class IV: severe limitations, symptomatic at rest, overt right heart failure.

    - HRCT descriptions of the chest are recorded on a standardised protocol based on radiological criteria of CTD-ILD. Radiological ILD subtypes will be ascertained prior to RTX therapy as well as any changes following RTX therapy at set 6-12 monthly intervals. Qualitative assessments of severity of ILD are recorded as ‘stabilisation’ or ‘progression’ of disease based on HRCT findings. Monitoring of disease activity is based on radiological review of HRCT of the chest by a MDT of a radiologist, pulmonologist, and rheumatologist during RTX therapy.

- Sub-group analysis of patient populations showing potential benefit from RTX therapy was analysed based on demographics, underlying CTD pathology, serology profile, and timing of therapy.

Methodology and design

- A retrospective case series review with descriptive elements and data analysis.

- Assessment of clinical response based on serial PFTs, HRCT imaging, and effort tolerance (FC) assessed in a specified population of patients with CTD-ILD treated with RTX, with sub-group analysis of demographics, primary CTD diagnosis, radiological and antibody profile.

Study population and sample

- A retrospective case analysis was performed at the Wits Donald Gordan Medical Centre (WDGMC), from January 2010 till December 2020. Fifty patients with CTD-ILD treated with RTX were screened and 19 patients were included in the final analysis.

- Patients included are diagnosed with CTD-ILD based on standardised criteria (EULAR/ACR). [20]

- Demographics including age, gender, co-morbidities, CTD subtype, CTD-ILD subtype, and antibody profile will be included.

- Initiation of RTX therapy will be clearly described, as well as other immunosuppressive therapy utilised prior to, or concurrently with, RTX.

- Decision to treat was based on attending clinicians' judgement based on available clinical evidence and identified patient population. i.e., disease progression or poor response to conventional immunomodulatory therapy.

- Rituximab administration is in accordance with product information protocol. [21,22]
    - RTX related adverse events will be recorded.

Inclusion criteria

- Age more than 18 years.
- Patients diagnosed with CTD-ILD based on standardised diagnostic criteria.
- Patients that have received at least one dose of RTX.

Exclusion criteria

- Patients on specific pulmonary anti-fibrotic agents (0 patients).
- Insufficient clinical and radiological data or lost to follow up (31 patients).

Data collection and statistical analysis.

- Primary data collection will entail extrapolation of required parameters from patient files compromising clinical notes, PFTs and HRCT findings. Findings were applied into a Microsoft Excel spreadsheet (see template below).
- All patients included will have parameters assessed at set intervals of therapy, from baseline to periodic intervals, and finally the last available date prior to December 31, 2020. Periods of assessment will be done prior to RTX therapy, at baseline and then at periods of 6, 12, 18 and 24 months from initiation of RTX therapy.

- Changes in PFT indices will be assessed and expressed as the percentage change at the periodic intervals of assessment. To evaluate response to therapy, categorical variables of change (worse, stable or improvement) will be detailed.

- The extent of the change in each PFT outcome at follow-up (from baseline) was determined by repeated measures one-way Analysis of Variance (ANOVA). The change in functional class at follow-up (from baseline) was determined by the Stuart-Maxwell test for paired categorical data.

- Data analysis was carried out using SAS version 9.4 for Windows. The 5% significance level was used.

- HRCT descriptions of the chest will be recorded, and findings will be standardised based on radiological criteria of CTD-ILD. Radiological ILD subtype will be ascertained prior to RTX therapy as well as any changes that were recorded on RTX therapy at set 6-12 monthly intervals. Qualitative assessment will occur utilising terms: ‘stabilisation’ or ‘progression’ of disease based on HRCT findings. Monitoring of disease activity is based on surrogate findings of new ‘ground glass opacities’ on HRCT of the chest during RTX therapy.
    - Stabilisation of disease will be defined as: No change in severity or extent of the abnormal interstitial findings, inferring no new abnormalities related to the ILD.
    - Progression of disease will be defined as: An increase in severity or extent of the interstitial abnormalities, inferring the development of new abnormalities related to the ILD.

Data collection form

Name	Age	Sex	1º Dx (date)	Antibody profile	Co-Morbidities	RTX start date	HRCT (Baseline) date	HRCT 2 date	HRCT Post date	Therapy (Pre-RTX)	Therapy (on RTX)	PFT (Baseline)	PFT 2 Date	PFT 3 Date	PFT 4 Date	

- Continued

Echo Baseline Date	Echo end Date	FC Year	6MWT	Pro-BNP	31/12/20 Status

Ethics

Approval will be obtained from the University of the Witwatersrand Human Research Ethics Committee. However, as this is a retrospective study, treatment decisions were made prior to the analysis of data and the study had no influence on patient management. Consent for the use of patient records will be obtained from the Wits Donald Gordan Medical Centre CEO and the treating physicians. No identifying information will be utilised to maintain patient confidentiality, and access of such information will be limited to the co-authors. All information will be stored on the primary investigators and researcher's computers which are protected with the latest anti-virus and anti-malware systems, in compliance with the Protection of Personal Information Act no. 4 of 2013, commencement date 1st July 2020.

Funding

None to disclose.

Proposed timeline

Task	September 2021	October 2021	November 2021	December 2021	January 2022	February 2022	March 2022	April 2022	May 2022	June 2022
Protocol formulation and literature review										
Protocol submission and assessment										
HREC application										
Data collection										
Data Analysis										
Write up and submission										

Delays occurred primarily during the data collection phase due to the Covid-19 pandemic, whilst delays in data analysis and write up also occurred due to concomitant clinical duties.

References

1. Mittoo S, Gelber AC, Christopher-Stine L, Horton MR, Lechtzin N, Danoff SK. Ascertainment of collagen vascular disease in patients presenting with interstitial lung disease. Respir Med. 2009 Aug;103(8):1152-8. doi: 10.1016/j.rmed.2009.02.009. Epub 2009 Mar 21. PMID: 19304475.

2. Oliveira RP, Ribeiro R, Melo L, Grima B, Oliveira S, Alves JD. Connective tissue disease-associated interstitial lung disease. Pulmonology. 2022 Mar-Apr;28(2):113-118. doi: 10.1016/j.pulmoe.2020.01.004. Epub 2020 Feb 7. PMID: 32044296.

3. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, Newman RA, Hanna N, Anderson DR. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood. 1994 Jan 15;83(2):435-45. PMID: 7506951.

4. Keir GJ, Maher TM, Hansell DM, Denton CP, Ong VH, Singh S, Wells AU, Renzoni EA. Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy. Eur Respir J. 2012 Sep;40(3):641-8. doi: 10.1183/09031936.00163911. Epub 2012 Jan 26. PMID: 22282550.

5. Lake FR, February 2023, Interstitial lung disease in rheumatoid arthritis UpToDate, accessed January 2023 https://www.uptodate.com/contents/interstitial-lung-disease-in-rheumatoid-arthritis

6. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE Jr, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schünemann HJ; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011 Mar 15;183(6):788-824. doi: 10.1164/rccm.2009-040GL. PMID: 21471066; PMCID: PMC5450933

7. Behr J, Prasse A, Kreuter M, Johow J, Rabe KF, Bonella F, Bonnet R, Grohe C, Held M, Wilkens H, Hammerl P, Koschel D, Blaas S, Wirtz H, Ficker JH, Neumeister W, Schönfeld N, Claussen M, Kneidinger N, Frankenberger M, Hummler S, Kahn N, Tello S, Freise J, Welte T, Neuser P, Günther A; RELIEF investigators. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase

2b trial. Lancet Respir Med. 2021 May;9(5):476-486. doi: 10.1016/S2213-2600(20)30554-3. Epub 2021 Mar 30. PMID: 33798455.

8. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, Moua T, Crestani B, Wuyts WA, Stowasser S, Quaresma M, Goeldner RG, Schlenker-Herceg R, Kolb M; INBUILD trial investigators. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med. 2020 May;8(5):453-460. doi: 10.1016/S2213-2600(20)30036-9. Epub 2020 Mar 5. PMID: 32145830.

9. Erre GL, Sebastiani M, Manfredi A, Gerratana E, Atzeni F, Passiu G, Mangoni AA. Antifibrotic drugs in connective tissue disease-related interstitial lung disease (CTD-ILD): from mechanistic insights to therapeutic applications. Drugs Context. 2021 Jan 15;10:2020-8-6. doi: 10.7573/dic.2020-8-6. PMID: 33505482; PMCID: PMC7813437.

10. Kolahian S, Fernandez IE, Eickelberg O, Hartl D. Immune Mechanisms in Pulmonary Fibrosis. Am J Respir Cell Mol Biol. 2016 Sep;55(3):309-22. doi: 10.1165/rcmb.2016-0121TR. PMID: 27149613.

11. Sharp C, McCabe M, Dodds N, Edey A, Mayers L, Adamali H, Millar AB, Gunawardena H. Rituximab in autoimmune connective tissue disease-associated interstitial lung disease. Rheumatology (Oxford). 2016 Jul;55(7):1318-24. doi: 10.1093/rheumatology/kew195. Epub 2016 Apr 8. PMID: 27060110

12. Atienza-Mateo B, Remuzgo-Martínez S, Prieto-Peña D, Mora Cuesta VM, Iturbe-Fernández D, Llorca J, Sánchez-Bilbao L, Corrales A, Blanco Rodríguez G, Gómez-Román JJ, Cifrián JM, González-Gay MÁ. Rituximab in the Treatment of Interstitial Lung Disease Associated with Autoimmune Diseases: Experience from a Single Referral Center and Literature Review. J Clin Med. 2020 Sep 23;9(10):3070. doi: 10.3390/jcm9103070. PMID: 32977717; PMCID: PMC7598697.

13. Duarte AC, Cordeiro A, Fernandes BM, Bernardes M, Martins P, Cordeiro I, Santiago T, Seixas MI, Ribeiro AR, Santos MJ. Rituximab in connective tissue disease-associated interstitial lung disease. Clin Rheumatol. 2019 Jul;38(7):2001-2009. doi: 10.1007/s10067-019-04557-7. Epub 2019 Apr 23. PMID: 31016581.

14. Goswami RP, Ray A, Chatterjee M, Mukherjee A, Sircar G, Ghosh P. Rituximab in the treatment of systemic sclerosis-related interstitial lung disease: a systematic review and meta-analysis. Rheumatology (Oxford). 2021 Feb 1;60(2):557-567. doi: 10.1093/rheumatology/keaa550. PMID: 33164098.

15. Md Yusof MY, Kabia A, Darby M, Lettieri G, Beirne P, Vital EM, Dass S, Emery P. Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single centre. Rheumatology (Oxford). 2017 Aug 1;56(8):1348-1357. doi: 10.1093/rheumatology/kex072. PMID: 28444364; PMCID: PMC5850796.

16. Maher TM, Tudor VA, Saunders P, Gibbons MA, Fletcher SV, Denton CP, Hoyles RK, Parfrey H, Renzoni EA, Kokosi M, Wells AU, Ashby D, Szigeti M, Molyneaux PL; RECITAL Investigators. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. Lancet Respir Med. 2023 Jan;11(1):45-54. doi: 10.1016/S2213-2600(22)00359-9. Epub 2022 Nov 11. PMID: 36375479.

17. Weill D. Lung transplantation: indications and contraindications. J Thorac Dis. 2018 Jul;10(7):4574-4587. doi: 10.21037/jtd.2018.06.141. PMID: 30174910; PMCID: PMC6105990.

18. Mesa C, Yadlapti S, Guevara M. The Use and Safety of Rituximab in Connective Tissue Disease Associated Interstitial Lung Disease. *Arthritis Rheumatol*. 2019;71 (suppl 10.)
https://acrabstarcts.org/abstarct/the-use-and-safety-of-rituximab-in-connective-tissue-disease-associated-interstitial-lung-disease/.
Accessed 08/2021

19. World Health Organisation Global Alliance against Chronic Respiratory Diseases. Pulmonary Hypertension Functional class.

20. EULAR, The European Alliance of Associations for Rheumatology, ARA, American College of Rheumatology, collaborative projects and classification criteria.

21. Roche Pharma, MabThera/ Rituxin (rituximab),
MabThera / Rituxan (rituximab). (2021).

- https://www.roche.com/products/product-details.htm?productId=b0eb216f-addf-4ed1-b01e-0b12fe0b1ef6
- Accessed 20/09/2021.

22. South African Health Products Regulatory Authority
    - Mabthera (rituximab), proposed package insert.
    - https://www.sahpra.org.za/wp-content/uploads/2020/02/MabThera_PI_Roche-Products_MCC-format-02-October-2015.pdf
    - Accessed 20/09/2021.

Submissible text

Authors

Seedat UF[1], Christian B[1], Schleicher GK[1]

1. Wits Donald Gordon Medical Centre (WDGMC), University of the Witwatersrand, Johannesburg, South Africa.

Affiliations

University of the Witwatersrand

Wits Donald Gordan Medical Centre

Titles

Rituximab therapy in connective tissue disease associated interstitial lung disease - a retrospective single centre observational study.

Declarations

None

Corresponding author

Dr UF Seedat

ubaidseedat@gmail.com

Abbreviations

CTD: connective tissue disease

ILD: interstitial lung disease

CTD-ILD: connective tissue disease associated interstitial lung disease.

WHO: World Health Organization

MDT: multi-disciplinary team

EULAR/ ACR: European League Against Rheumatism/ American College of Rheumatology

RTX: rituximab

SLE: systemic lupus erythematosus

RA: rheumatoid arthritis

SSC: systemic sclerosis

ANA: anti-nuclear antibody

RF: rheumatoid factor

ACCP: anti–cyclic citrullinated peptide

IPF: idiopathic pulmonary fibrosis

PFT: pulmonary function tests

FEV1: forced expiratory volume within 1 second.

FVC: forced vital capacity.

DLCO: diffusing capacity of the lungs for carbon monoxide

HRCT: high-resolution computed tomography

UIP: usual interstitial pneumonia

NSIP: nonspecific interstitial pneumonia

Wits DGMC: Wits Donald Gordon Medical Centre

CHQ: chloroquine

CYC: cyclophosphamide

AZA: azathioprine

MTX: methotrexate

SZP: salazopyrin

MMF: mycophenolate mofetil

LFL: leflunomide

Introduction

Connective tissue disease associated interstitial lung disease (CTD-ILD) is a complex and heterogenous clinical entity. The presence of interstitial lung disease (ILD) in connective tissue disease (CTD) is associated with significant morbidity and mortality.[1] Anti-inflammatory and immuno-modulatory therapy has remained the cornerstone of treatment and highlight the immunological dysfunction critical to its underlying pathophysiology. Rituximab (RTX) is a chimeric monoclonal antibody targeted to CD20+ B-cells, resulting in B-cell depletion.[2] This drug has been utilised as salvage therapy in refractory CTD-ILD and has demonstrated improved outcomes in observational studies.[3]

CTD-ILD may manifest with severe and progressive disease despite maximal conventional therapy. Corticosteroids and immunosuppressives have remained the conventional backbone of care, but severe and progressive CTD-ILD, and its associated morbidity and mortality, remain a challenging clinical scenario. The use and efficacy of anti-fibrotics drugs, originally utilised in idiopathic pulmonary fibrosis in this clinical scenario has emerged with promising results. [4,5,6]However, pricing and availability has limited extensive use in our setting. Lung transplantation remains an option, however advanced multi-system disease, selection criteria and organ availability result in an option feasible only in a very selective patient group. Furthermore, data regarding specific predictors of prognosis in this setting are limited.[7]

The use of RTX in CTD-ILD has evolved over the preceding 12 years. [3,8,9,10] Its use, albeit limited, has showed potential as a treatment modality in slowing disease progression. Conventional immunosuppressive drugs have remained the cornerstone of care, however in certain subgroups and disease profiles further drug therapy may be warranted. This retrospective case series analysis identifies 19 patients treated at the Wits Donald Gordon Medical Centre (DGMC) over a 10-year period (January 2010 to December 2020) with CTD-ILD treated with RTX and analyses its efficacy. Parameters utilised to analyse drug response include pulmonary function tests (PFTs), high resolution computed tomography (HRCT) of the chest and the World Health Organisation (WHO) Functional Class assessment.[11]

Methodology

Patient selection

A review of the available clinical database was performed. Fifty patients were screened at the Wits DGMC between January 2010 and December 2020 under the care of two specialist physicians. Nineteen patients were identified, all over the age of 18 years diagnosed with CTD-ILD by a multidisciplinary team (MDT) consensus based on standardised criteria of the European League Against Rheumatism/ American College of Rheumatology (EULAR/ACR).[12] All patients had received at least one dose of RTX. Over the 24-month period, 16 of the 19 patients received every scheduled dose (4 doses in total, 8gr in total) while 3 patients received less due to non-compliance (one patient receiving 3 doses at 6gr in total and two receiving 2 doses at a total of 4gr). Patients on anti-fibrotic agents and those with inadequate data were excluded. The MDT comprised of a specialist pulmonologist, a specialist rheumatologist and two radiologists practicing at the Wits DGMC during the identified study period.

Data collection

Pulmonary function test indices extracted from hospital records, included the forced vital capacity (FVC), forced expiratory volume within the first second (FEV1), and diffusion capacity for carbon monoxide (DLCO). Periods of assessment were at baseline (within 12 months prior to RTX therapy), and then at interval periods of 3-9 months, 9-15 months, 15-21 months, and 21-27 months from initiation of RTX therapy. High resolution computed tomography of the chest was performed, and findings were standardised based on radiological criteria of CTD-ILD and MDT consensus. Radiological ILD subtype was ascertained prior to RTX therapy (within 18 months prior to RTX initiation) and then monitored at set intervals of 6-9 months, 12-18 months, and 22-28 months from onset of RTX therapy. A qualitative descriptive assessment was performed based on an MDT discussion, and terms ‘stabilisation’, ‘improvement’ or ‘progression’ of disease based on HRCT findings were utilised. A subjective patient assessment was performed based on the WHO Functional Class assessment (I-IV).[11] Changes were recorded at baseline and then at 12 and 24 months. Functional class (FC) 1 indicating no limitation on ordinary activity, FC 2 indicating slight limitation (breathlessness) on ordinary activity, FC 3 indicating marked limitation on ordinary activity and FC 4 indicating discomfort at rest.

Statistical analysis

The extent of the change in each PFT outcome at follow-up (from baseline) was determined by repeated measures one-way Analysis of Variance (ANOVA). The change in functional class at follow-up (from baseline) was determined by the Stuart-Maxwell test for paired categorical data. High resolution CT findings of the chest could not be analysed statistically due to limited data points; however, they were plotted to investigate trends.

Data analysis was carried out using SAS version 9.4 for Windows. The 5% significance level was used.

Ethical clearance

Ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee. Approval was granted on the 11th of February 2022, Code: M 220104.

Results

Nineteen patients, with a median age of 54 years (Range: 22-77) were treated with RTX between the period of January 2010 and December 2019 under the care of the attending specialist physicians at the Wits DGMC. Patient's CTD diagnosis and ILD pattern was reached through an MDT consensus based on most recent standardised international criteria (EULAR/ACR). Included were baseline demographics, connective tissue disease and antibody profiles, as well as co-morbidities (Table 1)

Table 1: Baseline Demographics and Disease Profile		
Total no.	19	
Age (Baseline)	Median (IQR); 54 (40-60); Range 22-77	
Gender	Female: 14 (74%)	Male: 5 (26%)
CTD Profile	Rheumatoid Arthritis (RA)	9 (47%)
	Systemic Sclerosis (SSC)	4 (21%)
	Systemic Lupus Erythematosus (SLE)	3 (16%)

	Anti-Synthetase Syndrome (ASS)	1 (5%)
	Dermatomyositis (DM)	1 (5%)
	Mixed CTD	1 (5%)
Antibody Profile	ANA+ 1:80	1
	ANA+ 1:160	4
	ANA+ 1:320	2
	ANA+ 1:640	3
	ANA+ 1:1280	1
	ANA+ 1:2560	3
	RF	11
	Anti-CCP	4
	Anti-centromere	2
	Anti-Ro/SSA	2
	Anti-SC-70	2
	Anti-JO-1	1

Figure 1: Connective Tissue Disease Profile

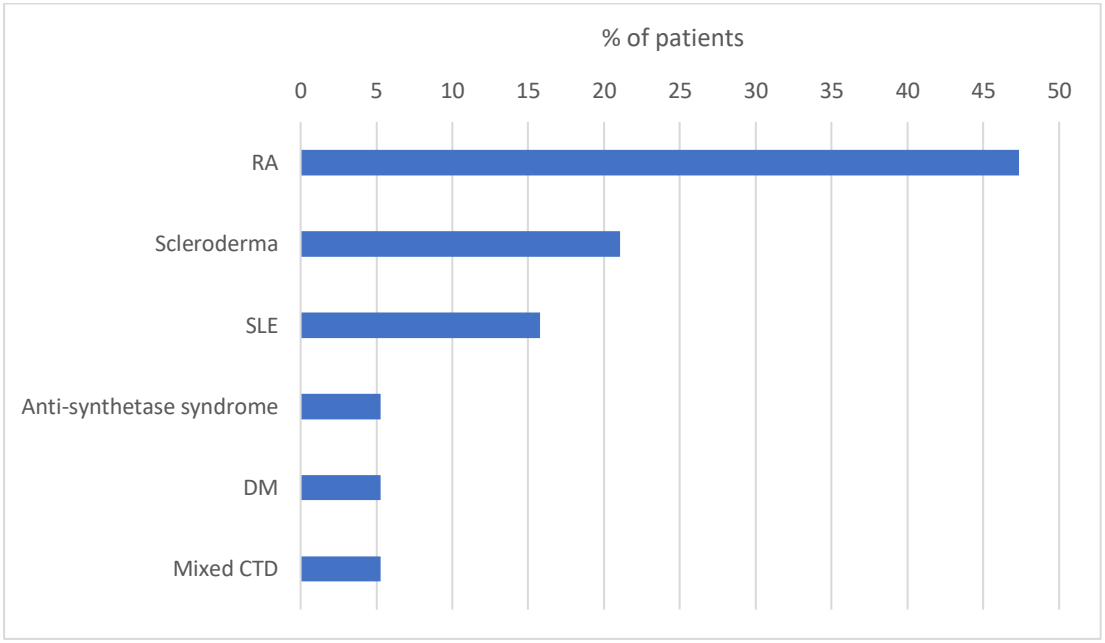
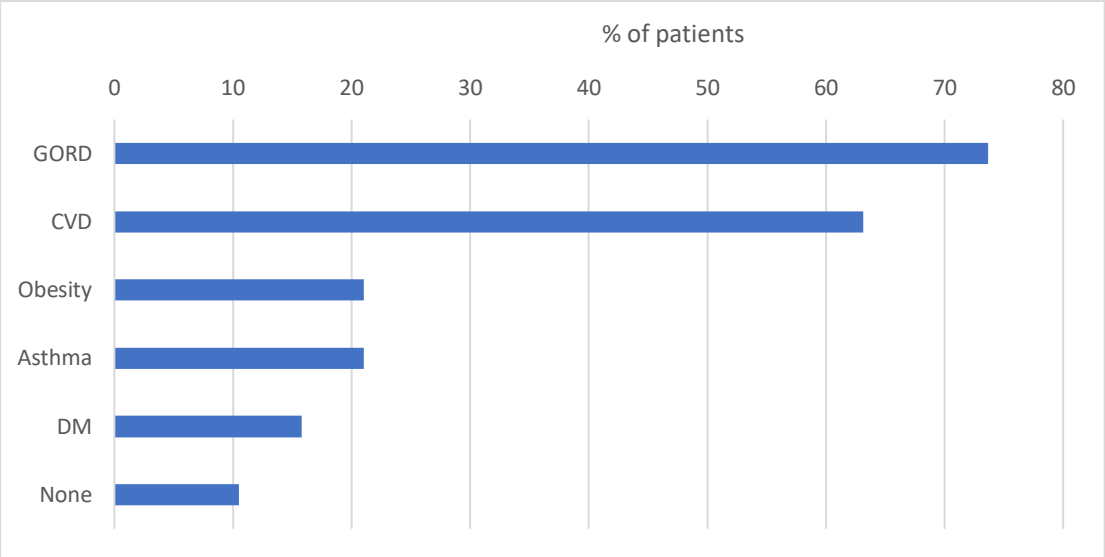


Figure 2: Co-Morbidity Disease Profile



Pre-Rituximab therapy

Immunosuppressive therapy administered in the preceding 5 years to RTX therapy was recorded and compared with therapy given concurrently with RTX, during the observed period from initiation of RTX therapy.

Table 2: Pre-RTX Drug therapy	
No. of drugs	**No. of patients**
4	6 (31.5%)
5	8 (42.1%)
6	4 (21%)
7	1 (5%)

Table 3: Drugs pre-RTX therapy			
Drug	**No. of patients**	**Drug dosing and duration**	**Drug dosing and duration Median (IQR); range)**
Corticosteroids (Prednisone)	19 (100%)	Corticosteroid dose (mg/day) (n=19)	10 (10-20); 5-30
		Corticosteroid duration (months) (n=19)	36 (20-60); 17-60
Chloroquine (CHQ)	19 (100%)	CHQ dose (mg/day) (n=19)	200 throughout
		CHQ duration (months) (n=19)	24 (17-60); 10-60
Cyclophosphamide (CYC)	17 (89.5%)	CYC dose (mg/cycle) (n=17)	750 (500-750); 500-1000
		CYC cycles (n=17)	5 (4-6); 3-18
		CYC duration (months) (n=17)	5 (4-6); 3-18
Azathioprine (AZA)	14 (74%)	AZA dose (mg/day) (n=14)	100 (75-150); 50-150
		AZA duration (months) (n=14)	12 (9-27); 2-60
Methotrexate (MTX)	13 (68%)	MTX dose (mg/week) (n=13)	17.5 (15-20); 12.5-25
		MTX duration (months) (n=13)	24 (12-42); 5-60
Salazopyrin (SZP)	6 (32%)	SZP dose (g twice daily) (n=6)	1 throughout
		SZP duration (months) (n=6)	12 (10-24); 9-25
Mycophenolate mofetil (MMF)	5 (26%)	MMF dose (mg twice daily) (n=5)	1000 (500-1000); 500-1000
		MMF duration (months) (n=5)	12 (4-18); 3-24
Leflunomide (LFL)	2 (11%)		

- LFL dose and duration omitted due to insufficient data.

Table 4: Drug therapy concurrent with RTX	
No. of drugs	**No. of patients**
0	1(5%)
1	1 (5%)
2	4 (21%)
3	6 (32%)
4	7 (37%)

Table 5: Drugs concurrent with RTX therapy			
Drug	**No. of patients**	**Drug dosing and duration**	**Drug dosing and duration (Median (IQR); range)**
Corticosteroids (Prednisone)	15 (79%)	Corticosteroid dose (mg/day) (n=15)	10 (5-10); 2.5-20
		Corticosteroid duration (months) (n=15)	24 (24-24); 12-24
Chloroquine (CHQ)	17 (89%)	CHQ dose (mg/day) (n=17)	200 throughout
		CHQ duration (months) (n=17)	24 (24-24); 7-24
Cyclophosphamide (CYC)	0		
Azathioprine (AZA)	10 (53%)	AZA dose (mg/day) (n=10)	100 (100-150); 50-150
		AZA duration (months) (n=10)	24 (24-24); 7-24
Methotrexate (MTX)	5 (26%)	MTX dose (mg/week) (n=5)	20 (15-20); 12.5-25
		MTX duration (months) (n=5)	24 (24-24); 12-24
Salazopyrin (SZP)	4 (21%)		
Mycophenolate mofetil (MMF)	4 (21%)		
Leflunomide (LFL)	0		

- SZP and MMF dose and duration omitted due to insufficient data.

Figure 3: Drug therapy prior to and concurrent with RTX

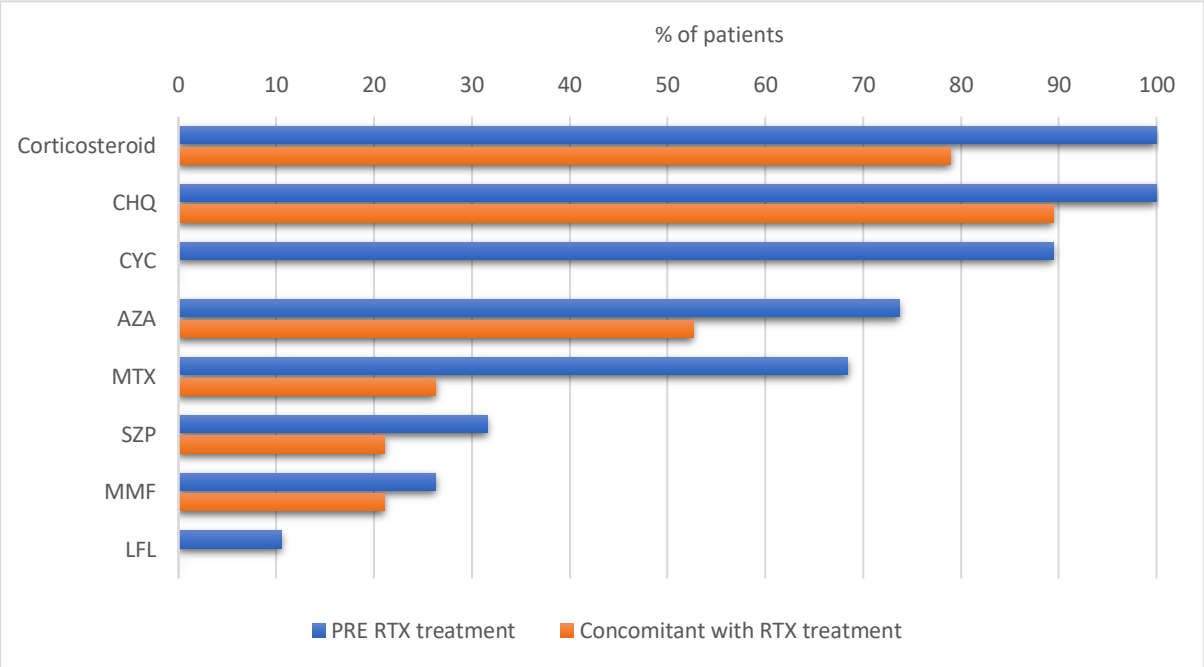


Table 6: Baseline PFT Indices	Median (IQR); range
FVC (L)	2.2, (1.4-2.8); 0.52-3.6
FEV1 (L)	1.73, 1.7 (1.3-2.2); 0.49-3.0
DLCO (mL/min/mm Hg) (17 patients only)	3.31, 3.5 (2.5-4.4); 0.75-6.1
DLCO (%):	44 (25-50); 5-67

Table 7: Baseline HRCT Pattern	
NSIP	15 (78.9%)
UIP	4 (21.1%)

Decision to treat

The decision to treat with RTX was made by the attending clinicians' judgement based on pertinent factors. Patient factors such as disease progression despite the current conventional immunosuppressive regimen. Progression was based on subjective and objective measures, including PFT indices, HRCT findings of the chest and/or patient subjective assessment. Despite a paucity of data due to patients being referred from other clinicians or centres which limited plotting of a trend of disease prior to RTX therapy, the baseline indices of the cohort were comparable to other observed studies.[8,9] Furthermore, the clinical evidence available

regarding the availability and safety profile of RTX has determined it to be an additional therapeutic modality.

Drug administration

Rituximab administration was in accordance with product information under the rheumatology practice protocol, at a dose of 1000mg intravenously and then the dose was repeated at 2 weeks from the first dose.[13, 14] This dosing protocol was thereafter repeated at 6 monthly intervals.

Post RTX treatment course

Pulmonary function testing

The available pulmonary function testing was analysed. In view of the sample size, the following observations were made. At the 3–9-month follow-up from baseline, the mean change in FVC (0.09L; 95% CI -0.14 to 0.32L) was not significantly different to baseline values (p=0.41). At the 21-27-month follow up from baseline, the mean change in FVC (0.01L; 95% CI -0.13 to 0.14L) was not significantly different to baseline values (p=0.91). The mean change in FEV1 from baseline to 3-9-months (0.09L; 95% CI -0.10 to 0.28) was not significantly different to baseline values (p=0.34). The mean change in FEV1 from baseline to 21-27-months (-0.03L; 95% CI -0.13 to 0.06L) was not significantly different to baseline values (p=0.50). Due to incomplete data, DLCO values could not be analysed statistically, however the data was plotted to investigate trends throughout drug therapy. For all 19 patients, individual PFT indices were plotted to ascertain a trend throughout drug therapy in the study period. (Figures 4,5,6,7)

Figure 4: FVC (L) changes over time (21-27 months)

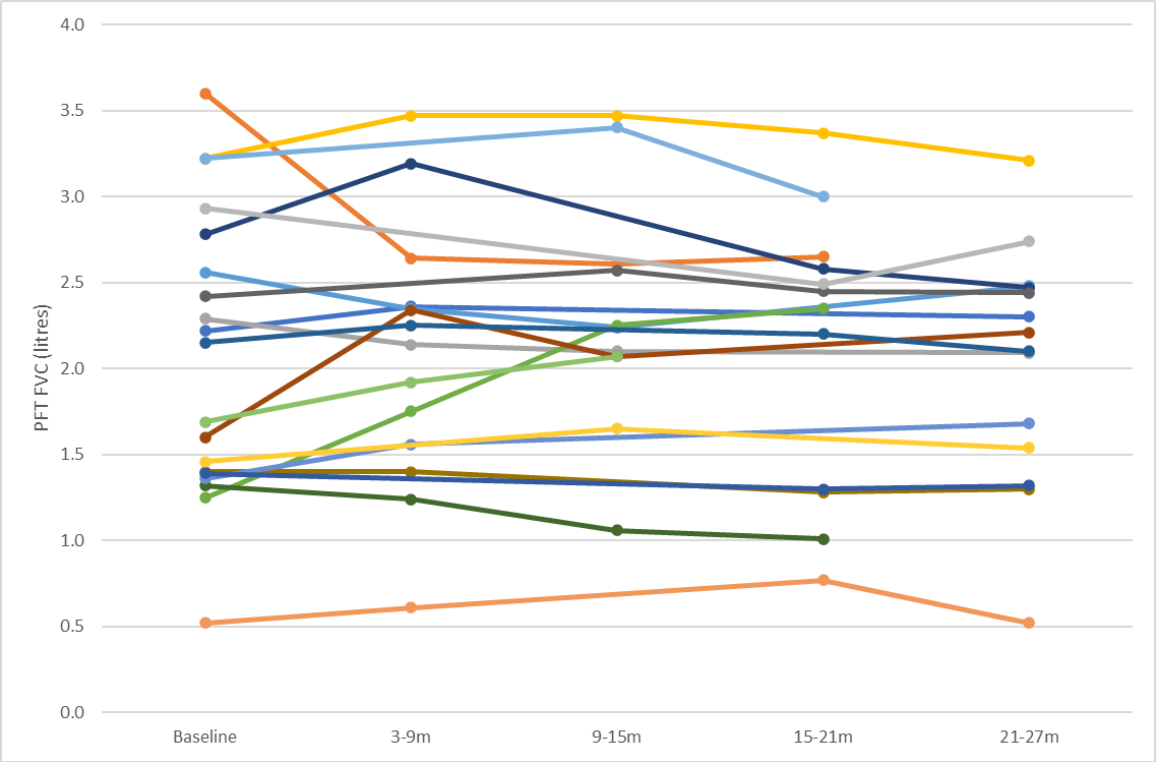


Figure 5: FEV1 (L) changes over time (21-27 months)

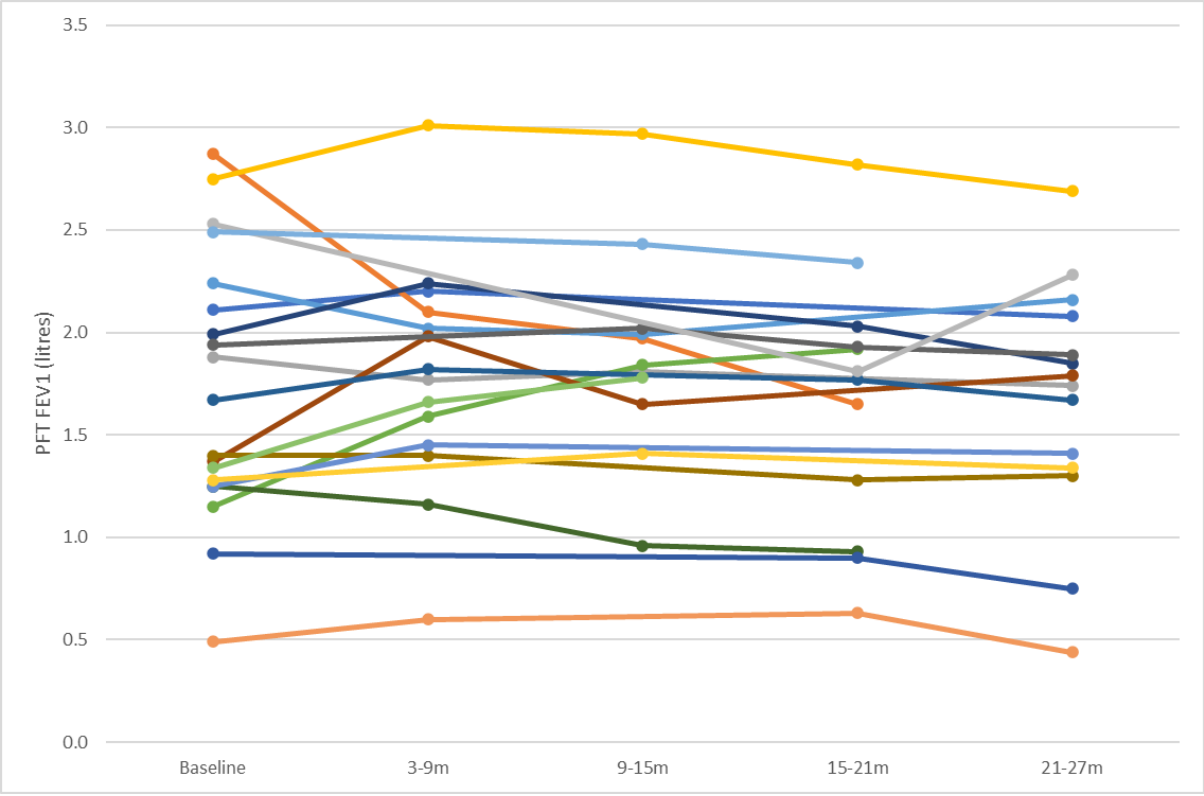


Figure 6: DLCO (L) changes over time (21-27 months)

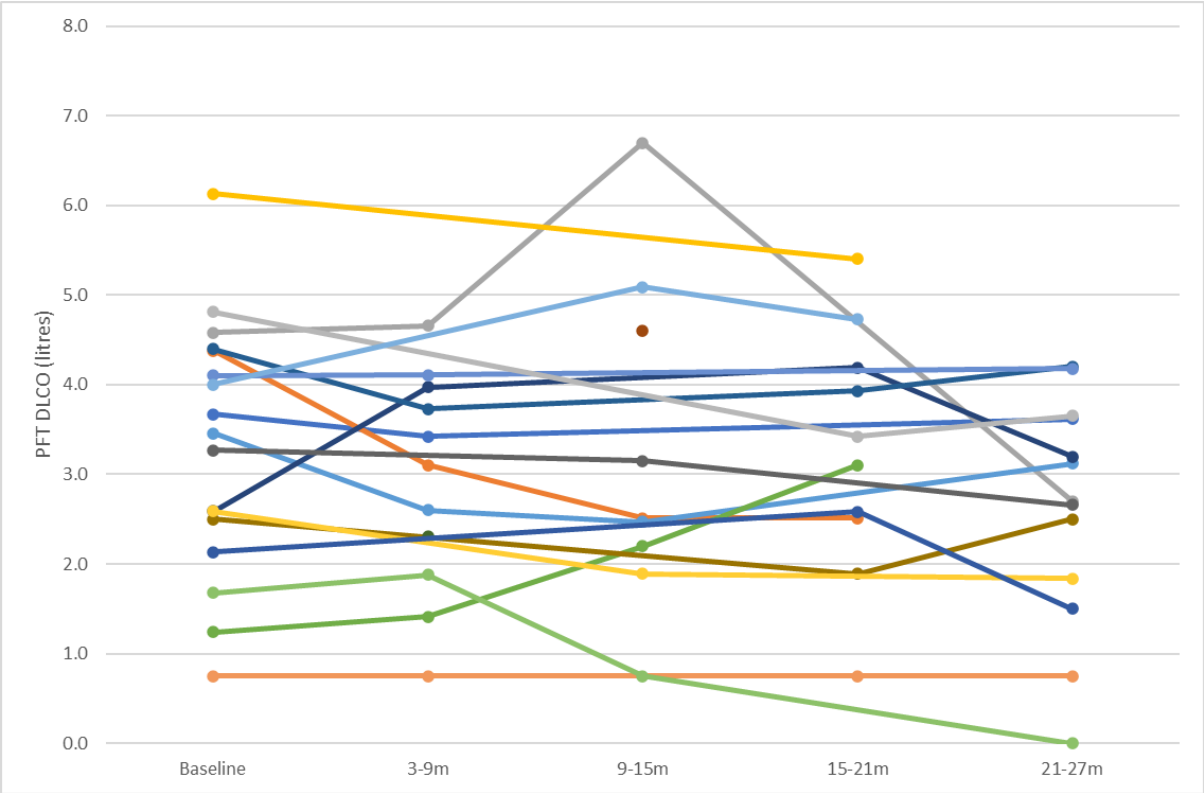
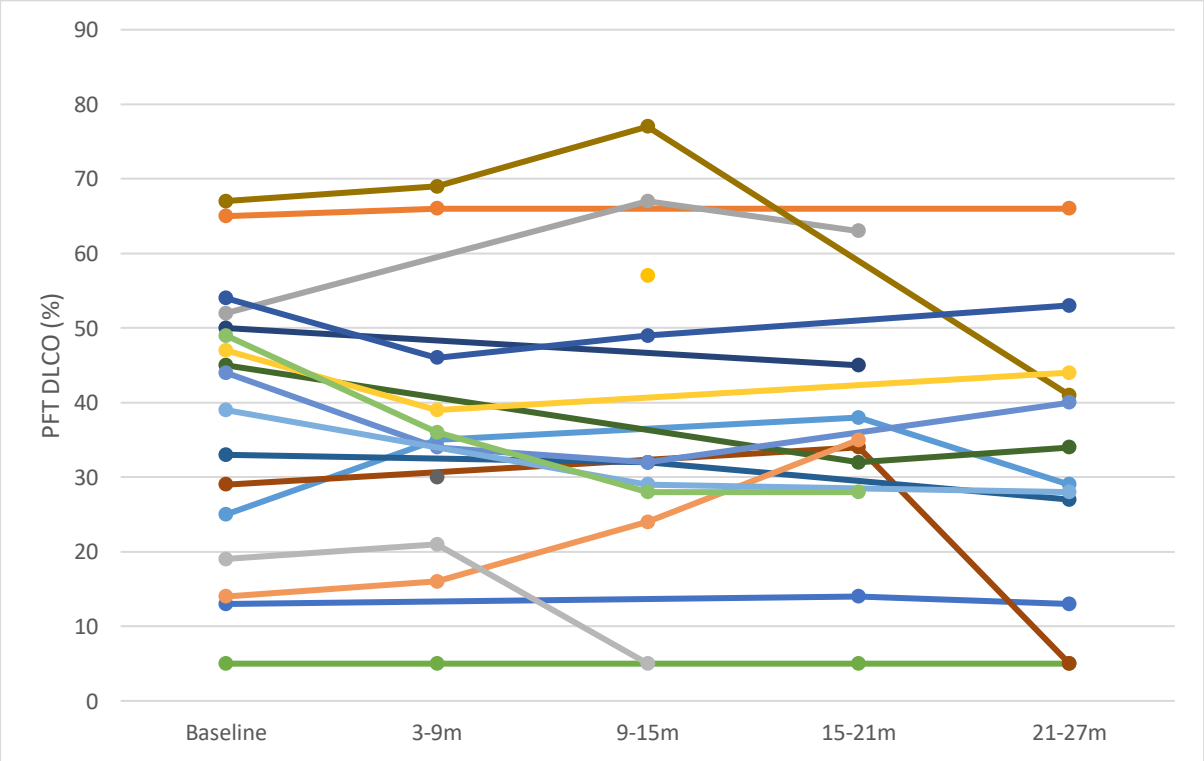


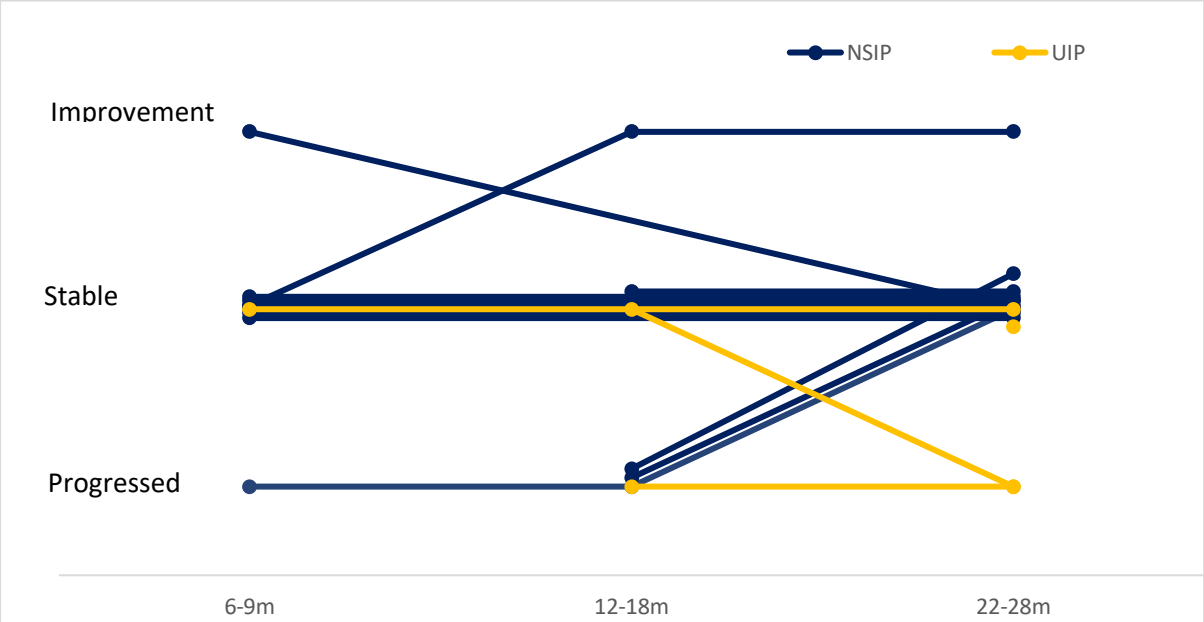
Figure 7: DLCO changes (%) over time (21-27 months)



High resolution computed tomography of the chest.

Findings of HRCT of the chest were recorded at set intervals but due to unavailable data and small sample size, statistical analysis was not feasible. Despite this, available data was plotted below.

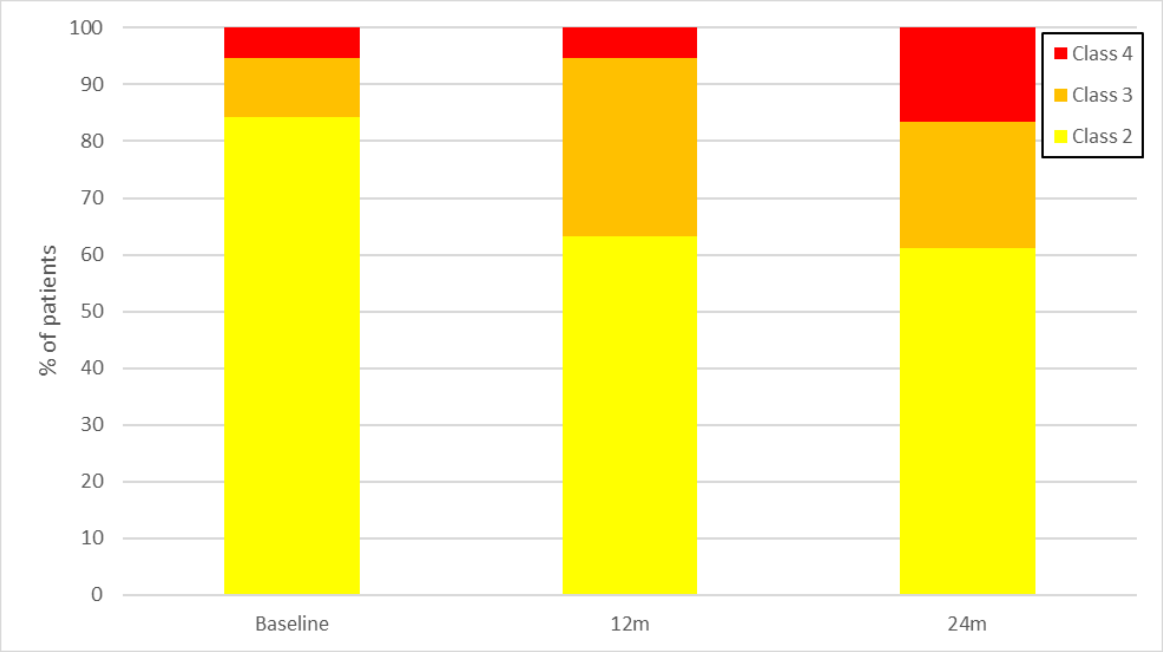
Figure 8: HRCT progression over time (22-28 months)



Functional class assessment

Analysis revealed that functional class worsened significantly from baseline to 12m (p=0.46), but not from baseline to 24m (p=0.083).

Figure 9: Functional class assessment over time (24 months)



Adverse events

No significant or life-threatening adverse events related to drug therapy were noted. No patient deaths were observed during the analysed period.

Discussion

Interstitial lung disease remains a common and important manifestation of inflammatory connective tissue disease. Identifying its presence has important clinical implications regarding therapeutic modalities.

The presence of ILD in CTD is an independent factor associated with decreased survival with five-year mortality rates exceeding 10% (10-39%[15,16,17]). The historical goal of treatment in such a clinical scenario is aimed at halting disease progression by preserving pulmonary function and preventing associated complications and mortality. Current therapies are comprised of corticosteroids and immunomodulatory drugs such as azathioprine, mycophenolate mofetil and cyclophosphamide.[18] The underlying dysregulated immune response to host tissue highlights how modulation of autoimmunity remains key to disease control.[19] Rituximab, a chimeric monoclonal antibody targeted to CD20+ B-cells results in B-Cell depletion, causing a decrease in humoral mediated autoimmunity and associated tissue damage. [3,20]

We report here our experience of RTX use in CTD-ILD in a varied patient cohort at the Wits DGMC, adding to the limited data available regarding its use in our geographical setting. Data emerging in the preceding 12 years has highlighted RTX as a potential drug choice in such a clinical scenario. A retrospective analysis by Kier et al. concluded that 7 out of their 8-patient cohort showed a favourable response to RTX.[3] Parameters utilised to assess the response to RTX included PFTs, HRCT of the chest and clinical symptoms. Furthermore, more recent evidence by Atienza-Mateo B et al. concluded that RTX constitutes a promising therapeutic option to preserve lung function in patients in this clinical scenario, regardless of their underlying pattern of CTD or radiological profile.[9] More recently comparative analysis has emerged, The Recital trial published in late 2022 compared RTX to cyclophosphamide in patients with CTD-ILD and demonstrated non-superiority with fewer adverse events.[10]

Our identified cohort of patients had varied CTD profiles with most patients having been diagnosed with RA (n=9). Patients identified had progressive disease or significantly impaired baseline indices despite prior treatment, with values comparable to baseline indices described in other studies.[8,9] Identified patients required at least 4 immunosuppressive drugs prior to the decision being made to start RTX. Our findings highlighted a similar trend of treatment response in a challenging cohort of patients. Despite limitations to our study noted below, pulmonary function appeared to stabilise with a mean change in FVC of 0.09L (95% CI -0.14 to 0.32L) observed at the 3-9-month follow-up period from baseline. Furthermore, at the 21-27-month follow-up from baseline the mean change in FVC was 0.01L (95% CI -0.13

to 0.14L). In addition to this, the mean change in FEV1 followed a similar trend to FVC values with a mean change in FEV1 from baseline to 3-9-months of 0.09L (95% CI -0.10 to 0.28) and a mean change in FEV1 from baseline to 21-27-months of -0.03 L (95% CI -0.10 to 0.28).

Radiological measures of disease were difficult to statistically analyse, however patterns of ILD and qualitative assessment were utilised. Of the 11 available HRCT of the chest at 6-9 months, 9 indicated stability, 1 indicated improvement and 1 indicated progression. At the 12-18-month interval, 12 HRCTs were available of which 7 indicated stability, 4 indicated progression and 1 indicated improvement. At 22-28 months, 17 HRCTs were available of which 13 indicated stability, 3 indicated progression and 1 indicated improvement. Most of the benefit appeared in NSIP group, with progressive radiological disease seen in 4 of the 5 patients with UIP.

The WHO Functional Class assessment (I-IV) for pulmonary hypertension was utilised as a subjective measure of disease. Results were varied, with some patients reporting symptomatic improvement while others reporting symptomatic progression. Overall, the functional class worsened significantly from baseline to 12m ($p=0.46$), but not from baseline to 24m ($p=0.083$). Complications of disease including the presence of pulmonary hypertension may have contribute to a deteriorating FC and other modalities such as echocardiography may have been useful. Another observed aspect of our study was analysing drug use prior to, and concurrent with RTX treatment. Rituximab therapy appeared to be associated with the use of less concurrent drugs, possibly mitigating other drug related adverse events and limiting long term exposure to corticosteroids and cyclophosphamide.

Overall, RTX provided an additional therapeutic modality in a challenging clinical entity. Limitations of our study were noted. The small sample size limited statistically significant findings and subgroup analysis could not be achieved. Furthermore, due the nature of the retrospective analysis, immunosuppressive regimens could not be standardised and a control arm to comparatively analyse its effects were not feasible. Insufficient data points also negated plotting a trend of clinical decline prior to RTX use. Despite this, Rituximab remains

a therapeutic option in such a population providing clinical stability in PFT, HRCT and FC assessments. Our data adds to a pool of evidence that RTX in CTD-ILD can be considered when additional therapeutic modalities are required, or other modalities such as anti-fibrotics are limited by cost or availability. Further building on this, is the observed safety profile.

In conclusion, we report here our experience of RTX in CTD-ILD at our centre. Rituximab appears to provide stability to radiological, pulmonary function and subjective measures of disease and adds to the arsenal of therapeutics in this challenging clinical scenario. Despite greater availability and promising data regarding anti-fibrotic drug use in this setting, RTX remains an option as a therapeutic modality.

Acknowledgements

The Wits Donald Gordon Medical Centre and its staff in particular Dr S Tager, the research team, and the radiology department, in particular Dr E Boshoff.

The consulting statistician Dr P Gaylard.

The patients under the care of the attending physicians.

UFS collected and collated data, drew up the protocol and manuscript, GKS served as the primary supervisor. GKS and BC provided the data set.

Word count 2730 (excluding abstract and references)

The above research was accepted and presented in platform format at the South African Thoracic Society Congress hosted in Durban August 2023.

Abstract publication was accepted and published in the African Journal of Thoracic and Critical Care Medicine Vol. 29 no. 2 (SATS Congress Abstracts), Completed research is submitted and awaiting feedback from said journal.

References

1. Oliveira RP, Ribeiro R, Melo L, Grima B, Oliveira S, Alves JD. Connective tissue disease-associated interstitial lung disease. Pulmonology. 2022;28(2):113-8. PMID: 32044296.

2. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood. 1994 Jan 15;83(2):435-45. PMID: 7506951.

3. Keir GJ, Maher TM, Hansell DM, Denton CP, Ong VH, Singh S, et al. Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy. Eur Respir J. 2012 Sep;40(3):641-8. PMID: 22282550.

4. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011 Mar 15;183(6):788-824. PMID: 21471066; PMCID: PMC5450933.

5. Behr J, Prasse A, Kreuter M, Johow J, Rabe KF, Bonella F, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. Lancet Respir Med. 2021 May;9(5):476-86. PMID: 33798455.

6. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med. 2020 May;8(5):453-60. PMID: 32145830.

7. Weill D. Lung transplantation: indications and contraindications. J Thorac Dis. 2018 Jul;10(7):4574-87. PMID: 30174910.

8. Sharp C, McCabe M, Dodds N, Edey A, Mayers L, Adamali H, et al. Rituximab in autoimmune connective tissue disease-associated interstitial lung disease. Rheumatology (Oxford). 2016 Jul;55(7):1318-24. PMID: 27060110.

9. Atienza-Mateo B, Remuzgo-Martínez S, Prieto-Peña D, Mora Cuesta VM, Iturbe-Fernández D, Llorca J, et al. Rituximab in the Treatment of Interstitial Lung Disease Associated with Autoimmune Diseases: Experience from a Single Referral Center and Literature Review. J Clin Med. 2020 Sep 23;9(10):3070. PMID: 32977717.

10. Maher TM, Tudor VA, Saunders P, Gibbons MA, Fletcher SV, Denton CP, et al. Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial. Lancet Respir Med. 2023 Jan;11(1):45-54. PMID: 36375479.

11. World Health Organisation Global Alliance against Chronic Respiratory Diseases. Pulmonary Hypertension Functional class.

12. EULAR, The European Alliance of Associations for Rheumatology, ARA, American College of Rheumatology, collaborative projects and classification criteria.

13. Roche Pharma, MabThera/ Rituxin (rituximab), *MabThera / Rituxan (rituximab)*. (2021).

    - https://www.roche.com/products/product-details.htm?productId=b0eb216f-addf-4ed1-b01e-0b12fe0b1ef6
    - Accessed 20/09/2021.

14. South African Health Products Regulatory Authority
    - Mabthera (rituximab), proposed package insert.
    - https://www.sahpra.org.za/wp-content/uploads/2020/02/MabThera_PI_Roche-Products_MCC-format-02-October-2015.pdf
    - Accessed 20/09/2021.

15. Fischer A, Distler J. Progressive fibrosing interstitial lung disease associated with systemic autoimmune diseases. Clin Rheumatol. 2019 Oct;38(10):2673-81. PMID: 31423560.

16. Hyldgaard C, Hilberg O, Pedersen AB, Ulrichsen SP, Løkke A, Bendstrup E, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis. 2017 Oct;76(10):1700-6. PMID: 28611082.

17. Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med. 2002 Jun 15;165(12):1581-6. PMID: 12070056.

18. Vij R, Strek ME. Diagnosis, and treatment of connective tissue disease-associated interstitial lung disease. Chest. 2013 Mar;143(3):814-24. PMID: 37864077.

19. Kolahian S, Fernandez IE, Eickelberg O, Hartl D. Immune Mechanisms in Pulmonary Fibrosis. Am J Respir Cell Mol Biol. 2016 Sep;55(3):309-22. PMID: 27149613.

20. van der Kolk LE, Baars JW, Prins MH, van Oers MH. Rituximab treatment results in impaired secondary humoral immune responsiveness. Blood. 2002 Sep 15;100(6):2257-9. PMID: 12200395.