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1 **Rituximab in autoimmune connective tissue disease-associated interstitial lung disease**

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- 8

1 **Abstract**

2 Background – Connective tissue disease (CTDs) associated interstitial lung disease (ILD) often fails to
3 respond to conventional immuno-modulatory agents. This has led to the exploration of Rituximab, which
4 has shown benefit for other aspects of these diseases, in patients refractory to standard treatments.

5 Methods – We conducted a retrospective analysis of all patients who received Rituximab under the Bristol
6 ILD service, having failed to respond to other immuno-modulatory treatments. Results were collated for
7 pulmonary function and radiological outcomes before and after treatment.

8 Results – 24 patients were managed with Rituximab. Their physiological parameters had failed to improve
9 despite other immuno-modulatory agents with a mean change in FVC prior to therapy of -3.3% (95% CI, -
10 5.6 to -1.1%) and mean DL_{CO} change of -4.3% (95% CI, -7.7 to -0.9%). After Rituximab, radiology remained
11 stable or improved for 11, while worsening was observed in 9 patients. The decline in FVC was reversed
12 following treatment, with a mean change of +4.1% (95% CI, 0.9 to 7.2%), while DL_{CO} was stable (mean
13 change +2.1% (95% CI, -1.0 to 5.2%). Patients with myositis or anti-synthetase syndrome appeared to
14 respond well to treatment, with 4 patients showing clinically significant improvement in FVC >10%.

15 Conclusions – Rituximab is a therapeutic option in treatment refractory CTD-associated ILD. Some disease
16 subgroups may respond better than others, however more work is needed to define its role in managing
17 these patients.

18

Rituximab in autoimmune connective tissue disease-associated interstitial lung disease

Introduction

An increased understanding of the molecular pathways of inflammation and autoimmunity has led to the development of targeted biological agents and expanded the repertoire of treatment options in the autoimmune connective tissue diseases (CTDs). Lymphocyte-targeted therapies, including the anti-CD20 B-cell depleting monoclonal antibody, Rituximab are now used in clinical practice for diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE) and refractory anti-neutrophil cytoplasmic antibody-associated (ANCA +ve) vasculitis[1-3]. This has led to exploration of its use in CTD-associated interstitial lung diseases (ILD) in patients deteriorating despite other immunosuppressive therapy. Evidence for this approach is based on institutional experiences, with no randomised, controlled trials yet published.

The CTDs are heterogeneous processes characterised by autoimmune-mediated inflammation targeting various organ systems with resultant end-organ damage [4]. A more detailed description of CTDs is beyond the scope of this introduction, readers are directed to the cited reviews[5, 4]. One mechanism of action of Rituximab is thought to be through depletion of CD20 +ve B-lymphocytes, thereby inhibiting their differentiation into antibody producing cells and T-cell co-stimulation. Translational studies have highlighted other mechanisms, which are being further investigated[6].

It is recognised that all patients with CTDs are at risk of ILD, some more so than others[5]. While this ILD may be subclinical, having been identified through both radiological appearances and lung function abnormalities in 33-57% of CTD patients with no respiratory symptoms[7-10], 5-80% of patients go on to develop clinically significant lung disease within 3 years, with variation depending on the specific CTD. The radiological and histological pattern of ILD described varies depending on the underlying CTD (Table 1), reflecting the heterogeneity of these conditions.

The Bristol Interstitial Lung Disease service runs a combined service with the Rheumatology CTD team to manage patients with progressive lung disease and over the last 5 years has developed extensive experience

1 managing these patients with immunosuppression; typically including oral immuno-modulatory agents,
2 intravenous (IV) Methylprednisolone and IV Cyclophosphamide. The aims of management in this population
3 of patients are, where possible, to reverse disease progression and decisions to initiate B-cell depletion with
4 Rituximab are implemented through a defined pathway. These decisions are based on a combination of
5 clinical or radiological deterioration, or attenuation of a previous improvement with immune-modulatory
6 treatment. This is a report of our experience.

7

8 **Methods and materials**

9 ***Patient selection***

10 Review of our clinical database identified twenty four patients managed in the combined ILD-Rheumatology
11 / CTD clinic treated with Rituximab. Diagnosis of diffuse parenchymal lung disease was in accordance with
12 British Thoracic Society Interstitial Lung Disease guidelines[11], with biopsies used where clinically indicated.
13 CTDs were diagnosed based on accepted international criteria. A subgroup of patients were identified with
14 myositis or the anti-synthetase syndrome for separate analysis. Patients with Rheumatoid arthritis were
15 excluded due to the distinct pattern of ILD observed in this group.

16 Hospital records were reviewed to identify, pulmonary function tests (PFT) performed 5 to 7 months prior
17 to Rituximab, in the 4 weeks immediately before treatment and 6 to 12 months following treatment. Where
18 relevant, the same approach was taken to PFTs prior to, at treatment with and following cyclophosphamide
19 therapy. High resolution computed tomograms (HRCT) of the chest were identified from time of treatment
20 and during follow-up. Patients were followed for a median of 29.6 months (16.7). All PFT measurements
21 were performed within the same respiratory physiology laboratory.

22 This clinical review was performed with full ethical approval (Reference 15/EE/0023).

23 ***Imaging***

1 HRCTs were performed for clinical reasons. Images were reconstructed on a standard HRCT algorithm and
2 interspaced 1mm slices reviewed on lung window settings were assessed on two separate occasions, 6
3 months apart, by an experienced ILD Thoracic Radiologist blinded to treatment and therapy. Overall extent
4 of interstitial pathology, in addition to the ground glass component, was evaluated and quantified according
5 to the visual estimation of extent of involvement described by Oda et al[12]. Change, compared with
6 baseline imaging, after treatment was assessed and categorised as: improved, stable or worsened. The κ
7 value for intra-rater agreement for extent of disease was 0.55, with a value of 0.92 for interval change.

8 ***Statistical analysis***

9 Values are shown as mean with standard deviation (SD), mean difference with confidence intervals or
10 frequencies as appropriate. Changes in PFTs and radiological extent are expressed as percentage change
11 from start of therapy. Changes in values before, at the time of, and after treatment were assessed for
12 normality and analysed with one-sample t-test using a test value of 0 or paired t-test as appropriate.
13 Categorical variables were analysed using Chi-square testing. All analyses used a p-value of <0.05 as the
14 threshold for statistical significance. Analyses were performed using SPSS software (v21.0.0; IBM Corp.;
15 Armonk, NY, USA).

16 **Results**

17
18 Twenty four patients (16 female), with a mean age of 51.4 yrs (SD 14.9), were treated with Rituximab
19 between October 2009 and January 2015. 12/24 patients were former smokers. The mean duration of
20 follow-up after treatment was 29.6 months (16.7). Biopsy had been performed in 11/24 patients. Patient
21 characteristics are shown in Table 2.

22
23 These patients were all managed under the ILD-Rheumatology/CTD service and all had a diagnosis of CTD-
24 ILD. Twenty two patients had positive serology for autoimmune markers (Table 3). The diagnoses were

1 reached through correlation of clinical, serological, radiological and histopathological data, with diagnoses
2 confirmed through consensus in a multidisciplinary ILD-CTD forum involving Clinicians, Radiologists and
3 Pathologists.

4 5 ***Pre-Rituximab Disease course and treatment (Figure 1)***

6
7 All patients had failed to respond adequately to prior immunosuppressive therapies, including induction with
8 pulsed intravenous Cyclophosphamide in 16 patients (at a dose of 15mg/kg, capped at 1 gram, for 6 cycles,
9 at 3 week intervals) with IV methylprednisolone (500mg-1g prior to each dose of Cyclophosphamide) and
10 Mycophenolate mofetil in 10 patients. Details of the treatments given and the interval to rituximab are given
11 in table 4.

12
13 FVC and DL_{CO} had failed to improve despite treatment prior to Rituximab. Mean change in FVC was -3.3%
14 (p=0.005, 95% CI, -5.6 to -1.1%), with mean DL_{CO} change of -4.3% (p=0.02, 95% CI, -7.7 to -0.9%). Of those
15 treated with Cyclophosphamide, this did not reverse disease trajectory; mean change in FVC following pulsed
16 intravenous treatment was -1.2% (p=0.51, 95% CI, -5.2 to +2.7%), mean change in DL_{CO} was +1.3% (p=0.54,
17 95% CI, -3.1 to +5.7%).

18
19 CTs were available for review for all patients prior to treatment. On HRCT, mean disease extent was 40.8%
20 (SD 20.3%) of the lung, with ground glass change representing a mean 55.6% (SD 36.3%) of affected areas.
21 The radiological patterns for each patient are shown in Table 5. 21 patients had more than one CT available,
22 enabling assessment of interval change prior to treatment. Radiological appearances were deteriorating for
23 8 patients, had failed to improve for 11 patients. For the two patients whose imaging had improved, the
24 MDT assessment was that there was further scope for improvement.

1 **Decision to treat**

2

3 The decision to commence Rituximab treatment was based on multidisciplinary discussion and a synthesis
4 of features including:

- 5 • Progressive lung function decline
- 6 • Progression or lack of improvement in rheumatological features despite treatment
- 7 • Radiological changes; either progressive changes or a failure of disease adjudged as reversible to
8 improve or resolve (for example ground glass changes)

9

10 **Rituximab administration**

11

12 Rituximab was administered according to rheumatology/CTD protocol, at a dose of 1 gram intravenously
13 infused at days 0 and 14. Following treatment, oral immunosuppression was continued in all patients.

14

15 **Post-treatment disease course (Figure 1)**

16 Pulmonary function testing data both before and after treatment were available for all patients. FVC
17 improved following treatment, with a mean change of 4.1% (p=0.01, 95% CI, 0.9 to 7.2%). DL_{CO} remained
18 stable with a mean change of 2.1% (p=0.18, 95% CI, -1.0 to 5.2%). Four patients demonstrated clinically
19 meaningful improvements of >10% in their FVC following treatment (Figure 1). When comparing pre- and
20 post-treatment disease trajectory, Rituximab reversed previous trends in lung function change for both FVC
21 (p=0.001) and DL_{CO} (p=0.02).

22

23 HRCT imaging following treatment was available for 22 patients. One patient died before interval imaging
24 was completed and one patient with myositis-related lung disease has insufficient followup to merit interval
25 imaging. The mean change in disease extent was -3.75% (p=0.33, 95% CI -11.6 to 4.1). By radiological

1 criteria, the imaging had deteriorated for 9/22 patients, with 13/22 showing disease stability or
2 improvement following treatment. Chi-square analysis comparing the trend in radiological appearances
3 before and after treatment demonstrated no significant differences (χ^2 5.695, $p=0.223$).

4 5 ***Myositis and anti-synthetase subgroup (Figure 2, Table 6)***

6 Thirteen patients (9 female) were identified with myositis or the anti-synthetase syndrome, with a mean age
7 of 53.5 yrs (SD 13.2). Seven of these were former smokers. They had physiological impairment at baseline
8 with a mean FVC of 75.3% predicted (SD 17.0%) and mean DL_{CO} 55.9% predicted (SD 16.4%). On initial HRCT
9 imaging, mean extent of disease was 37.3% (SD 19.2%) with ground glass representing 52.7% (SD 34.4%) of
10 this disease. Treatment prior to Rituximab did not arrest deterioration in physiological parameters. These
11 trends were not significantly different to those with other diagnoses.

12
13 Following treatment, FVC and DL_{CO} both improved statistically by a significantly greater extent than in those
14 patients with alternative diagnoses. Four patients in the myositis group demonstrated improvement in their
15 FVC >10%, showing a clinically meaningful improvement. Radiological appearances were assessed as
16 improved in 3/11 patients, with worsening of disease only adjudged in one patient.

17
18 When comparing patients with myositis or anti-synthetase syndrome with the remaining group, there were
19 significant differences in the response to treatment. FVC change after treatment was greater in the myositis
20 sub-group ($p=0.002$), as was improvement in DL_{CO} ($p=0.009$). There were no other significant between group
21 differences.

22 23 ***Adverse events***

24 There were no complications observed associated with treatment. One patient died due to disease
25 progression four months after treatment.

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Discussion

We report here our experience of Rituximab in CTD-ILD in a significant number of patients, including an identified cohort with myositis/overlap syndromes. This report adds to very limited published data for use of B-cell depletion as treatment in this difficult disease group.

The decision to treat is multi-factorial, guided by a combination of respiratory parameters and also rheumatological considerations. One unanswered question, and one which will prove challenging in the context of clinical trials, is the means of defining treatment success. In some patients the aim of treatment is to arrest or slow decline, whilst in others the aim is to reverse disease. In patients with CTD-ILD, namely SSc and overlap myositis, one could debate that disease stability or lack of progression is a marker of treatment response.

Also a consideration is the natural history of disease. Where endothelial injury has occurred, resulting in the beginnings of fibrosis, the mesenchymal cells within later fibroblastic foci may begin to drive progressive fibrosis. Treatment aimed at arresting the autoimmune injury prior to this is the rationale behind aggressive treatment in early disease. The clinical data for disease course and natural history of CTD-ILD is lacking however.

Our data demonstrates, consistent with previously published series, a numerical improvement in FVC, with stability of DL_{CO}, however no impact was seen on radiological appearances. It is important to highlight that these improvements were only clinically significant in four patients. These “responders” were patients with myositis or anti-synthetase syndrome-related lung disease and this group appear to respond particularly well to treatment, with greater improvement in FVC and DL_{CO} compared to the non-myositis group.

The limitations to our data are their observational nature, and the heterogeneity of data captured in the course of disease. Despite this, we have observed statistically significant benefit in these patients and clinically relevant benefit in a subgroup.

1 Preliminary reports including case reports and series have suggested that B cell depletion is a potential
2 therapeutic target in CTD-ILD. The first report of successful treatment of Systemic Sclerosis (SSc)-associated
3 ILD with Rituximab was in 2008[13], with further experience reported in a cohort of 8 patients, in whom the
4 FVC and diffusing capacity of carbon monoxide (DL_{CO}) increased significantly more than a matched cohort
5 receiving standard treatment[14]. In addition, a further study has highlighted the potential role of Rituximab
6 in the anti-synthetase syndrome; 11 patients with severe and progressive ILD, who had failed to improve
7 with Cyclophosphamide, demonstrated stabilisation of their lung disease based on forced vital capacity
8 (FVC), DL_{CO} and high resolution computed tomography appearances[15].

9 Keir and colleagues have reported their experience of Rituximab in a more diverse cohort of 50 patients with
10 ILD of various aetiologies, including CTD-ILD and also hypersensitivity pneumonitis and smoking-related
11 ILDs[16]. They reported a median improvement in FVC in the 6-12 months following treatment of 6.7%, with
12 stability of DL_{CO}. The FVC in a subgroup of 33 patients with CTD-ILD, improved by 8.9%. Their results
13 suggested a role for anti-CD20 B cell therapies in CTD-ILD and possibly a wider role in other ILDs.

14 A subset of CTD patients with inflammatory myositis have been recognised to have a high risk of ILD. This
15 group of diseases includes the anti-synthetase syndrome (ASS), which is characterised by auto-antibodies
16 against the aminoacyl-tRNA synthetases, including anti-Jo1, anti-PL7 and anti-PL12. This clinical syndrome
17 is characterised by prominent ILD, with accompanying myositis, cutaneous changes including “mechanic’s
18 hands”, fevers and non-erosive arthritis[17]. A number of factors in this group have been linked with the
19 development and severity of ILD, including Asian ethnicity, those with severe skin involvement, minimal or
20 no clinical muscle weakness and pyrexia. This group of patients may also manifest ILD as their first
21 presentation of CTD. In one cohort, 15% of new patients referred to a tertiary referral centre met diagnostic
22 criteria for CTDs[18].

23 Our observed response to Rituximab therapy in a myositis-overlap group complements the findings of the
24 RIM study[19]. This large randomised, controlled trial of early (at weeks 0 and 1), compared to late (at weeks

8 and 9) Rituximab in treatment-refractory myositis found no difference in the primary end point of time to achieve the International Myositis Assessment and Clinical Studies Group preliminary definition of improvement. This is likely to have been due to study design, as 83% of patients had achieved the primary outcome by 20 weeks from randomisation. A subgroup analysis demonstrated that presence of anti-synthetase autoantibodies was a strong predictor of improvement with treatment[20].

This adds to the weight of evidence of the heterogeneity of CTD-ILD, and also further underscores the need for further research in this group of patients for whom there is little robust evidence for treatment. The RECITAL study, a randomised, controlled trial comparing Rituximab to Cyclophosphamide in CTD-ILD (clinicaltrials.gov identifier: NCT01862926) is designed to address this important question. A further resource, which would be of value in this field by pooling data such as ours, would be a registry for CTD-ILD.

Data such as ours remains central to providing evidence to support the decision to use agents such as Rituximab in these patients and in the absence of published clinical trials is vital to support decision making, including those surrounding clinical commissioning within the NHS in England.

In conclusion, we present here our experience using Rituximab for treatment-refractory CTD-ILD. Rituximab has arrested previous decline in lung function in this cohort, with particular benefit seen in a subgroup of patients with myositis-overlap syndromes. The role of Rituximab in CTD-ILD remains to be defined and our data highlights the need for more research to identify those patients who will have the best response to treatment.

Key messages

- Rituximab appeared to reverse previously declining lung function in patients with connective tissue disease-associated interstitial lung disease
- A subgroup of patients with myositis-overlap syndromes, including the anti-synthetase syndrome appeared to respond particularly to Rituximab.
- Further research is needed to identify which patient groups will benefit from Rituximab.

1 **Competing interests**

2 The authors declare no competing interests.

3 **Author Contributions**

4 CS, LM and ND identified cases and collated data. CS and MM conducted the statistical analysis. HA, ABM and HG
5 oversaw patient care. CS, ABM and HG conceived the study and drafted the manuscript. All authors read and
6 approved the final manuscript.

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14

15 **Figure Legends**

16 **Figure 1** – Changes in lung function before and after treatment

17 FVC – Forced vital capacity, DLCO – Diffusing capacity for carbon monoxide. *p=0.001, **p=0.02

18

19 **Figure 2** – Comparison of myositis subgroup and other patients' response to treatment

20 FVC – Forced vital capacity, DLCO – Diffusing capacity for Carbon Monoxide. * p<0.01

21

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1 **Tables**

2 **Table 1 – Incidence of subtypes of ILD in CTD**

	Patients with lung involvement	UIP	NSIP	COP	DAD	LIP	DAH
Systemic sclerosis	20-65%	++	++++	+	+	-	-
Rheumatoid arthritis	~70%	++	+	-	+	-	-
Mixed connective tissue disease	20-80%	++	+++	-	-	+	-
Systemic lupus erythematosus	50-60%	+	+	+	++	-	+++
Inflammatory myositis-CTD overlap*	~75%	++	++++	++	+	-	-
Primary Sjogren's syndrome	10-30%	+	+	+	-	+++	-

(Lowest (-) to highest (++++)).
 UIP (Usual Interstitial Pneumonia), NSIP (Non-specific Interstitial Pneumonia), COP (Cryptogenic Organising Pneumonia), DAD (Diffuse Alveolar Damage), LIP (Lymphocytic Interstitial Pneumonia), DAH (Diffuse Alveolar Haemorrhage).
 *Includes Anti-synthetase syndrome, dermatomyositis and overlap myositis.

3

4

1 **Table 2 – Baseline characteristics of patients**

Demographics	
Age	51.4 (14.9)
Female	16 (66.7%)
Ex-smokers	12 (50%)
Oxygen use	5/24
Diagnosis	
Anti-synthetase syndrome (ASS)	10
Dermatomyositis (other / non-ASS)	3
Systemic sclerosis	3
Sjögren’s syndrome	2
SLE	2
Unclassifiable CTD-ILD	4
Biopsy	11/24
Histopathological pattern	
NSIP	9
LIP	1
Hypersensitivity Pneumonitis	1
Identified auto-antibodies (see Table 3)	22/24
Treatments	
Cyclophosphamide	16
IV Methylprednisolone	16
Mycophenolate mofetil	9
Hydroxychloroquine	2
Azathioprine	4
Methotrexate	1
Physiology	
FVC (% pred)	78.4 (21.4)
FEV1 (% pred)	75.4 (18.6)
FEV1/FVC ratio	0.81 (0.06)
DL _{CO} (% pred)	50.9 (18.0)
SO ₂ (%)	96 (1.5)
SLE – Systemic Lupus Erythematosus, NSIP – Non-specific Interstitial Pneumonia, LIP – Lymphocytic Interstitial Pneumonia, FVC – Forced Vital Capacity, FEV1 – Forced Expiratory Volume in 1 second, DL _{CO} – Diffusing Capacity for Carbon Monoxide, SO ₂ – Oxygen Saturations	

2

3

1 **Table 3 – Patient diagnoses and auto-immune profiles**

Patient	Age	Gender	Diagnosis	Radiological pattern	Histopathological pattern	Extractable Nuclear Antibodies
1	40.2	Male	Scleroderma	NSIP	Fibrotic NSIP	Scl70
2	61.0	Female	Dermatomyositis	NSIP/OP		
3	67.6	Female	Anti-synthetase	NSIP		RNP, Jo1
4	62.0	Male	Anti-synthetase	NSIP/OP	Cellular/Fibrotic NSIP	EJ
5	37.7	Female	Anti-synthetase	NSIP		Jo1
6	73.0	Male	Dermatomyositis	NSIP		PM-Scl
7	49.1	Female	Anti-synthetase	NSIP/OP		Jo1
8	59.5	Female	Anti-synthetase	NSIP/OP		
9	68.4	Female	SLE	NSIP		dsDNA
10	29.7	Female	Dermatomyositis	NSIP		MDA5
11	25.3	Female	Scleroderma	NSIP	Fibrotic NSIP	Ro, Scl70
12	40.7	Female	SLE	OP		
13	48.8	Female	Anti-synthetase	NSIP/OP		Jo1
14	36.8	Female	Sjogrens	LIP	LIP	Ro, La
15	36.2	Female	Anti-synthetase	NSIP/OP	Cellular NSIP	PL-7
16	21.0	Male	Scleroderma	NSIP	Fibrotic NSIP	Scl70
17	51.8	Female	Unclassifiable CTILD	NSIP	Fibrotic NSIP	
18	64.7	Female	Anti-synthetase	NSIP	Fibrotic NSIP	PM-Scl
19	57.0	Female	Unclassifiable CTILD	LIP	Fibrotic NSIP	
20	47.8	Male	Anti-synthetase	NSIP/OP	Fibrotic NSIP	PM-Scl
21	58.8	Male	Anti-synthetase	NSIP		PL-12
22	60.8	Male	Unclassifiable CTILD	Possible UIP		
23	68.3	Male	Unclassifiable CTILD	NSIP		
24	66.4	Female	Sjogrens	NSIP	Hypersensitivity pneumonitis	RNP, Sm, dsDNA

NSIP – Non-specific Interstitial Pneumonia, LIP – Lymphocytic Interstitial Pneumonia, OP, organising pneumonia, SLE – Systemic Lupus Erythematosus

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1 **Table 4 – Patient treatment prior to Rituximab**

Patient	Diagnosis	Pre-Rituximab treatment	Duration of treatment	Comments
1	Scleroderma			Patient presented with extremis and urgently
2	Dermatomyositis	Previous oral cyclophosphamide, then MMF*	>2 years	
3	Anti-synthetase	IV cyclophosphamide and methylprednisolone, then azathioprine*	12 months	
4	Anti-synthetase	IV methylprednisolone and cyclophosphamide, then MMF*	10 months	
5	Anti-synthetase	IV cyclophosphamide, then MMF*	24 months	
6	Dermatomyositis	IV cyclophosphamide	6 months	
7	Anti-synthetase	IV cyclophosphamide, then MMF*	9 months	
8	Anti-synthetase	IV cyclophosphamide, then azathioprine* and hydroxychloroquine*	12 months	
9	SLE	Hydroxychloroquine*	>2 years	Unable to tolerate cyclophosphamide
10	Dermatomyositis	IV cyclophosphamide	21 months	
11	Scleroderma	IV cyclophosphamide, then MMF*, with previous hydroxychloroquine and methotrexate	13 months	
12	SLE	MMF* and hydroxychloroquine*	>2 years	
13	Anti-synthetase	IV cyclophosphamide, then MMF*	9 months	
14	Sjogrens	IV cyclophosphamide and methylprednisolone, then azathioprine* and hydroxychloroquine*	10 months	
15	Anti-synthetase	IV cyclophosphamide	20 months	
16	Scleroderma	IV cyclophosphamide, then MMF*	7 months	
17	Unclassifiable CTILD	IV cyclophosphamide, then MMF*	11 months	
18	Anti-synthetase	IV cyclophosphamide	12 months	
19	Unclassifiable CTILD	Methotrexate*	>2 years	
20	Anti-synthetase	IV cyclophosphamide, then MMF*	12 months	
21	Anti-synthetase	IV methylprednisolone, then oral cyclophosphamide	18 months	
22	Unclassifiable CTILD	IV cyclophosphamide	9 months	
23	Unclassifiable CTILD	Methotrexate*	10 months	
24	Sjogrens			Unable to tolerate cyclophosphamide

The ongoing treatment at the time of Rituximab is indicated by *. All patients had received varying doses of oral prednisolone. Where no oral treatment is stated, prednisolone was ongoing.

NSIP – Non-specific Interstitial Pneumonia, LIP – Lymphocytic Interstitial Pneumonia, OP, organising pneumonia, S – Systemic Lupus Erythematosus, MMF – Mycophenolate mofetil, IV - intravenous

1 **Table 5 – Radiological pattern, extent of disease and response to treatment**

Patient	Pattern	Disease Extent (%)	Ground glass (% extent within fibrosis)	Traction change	Improvement /worsening	Change in extent after treatment (%)
1	Cellular NSIP	70	100	None	Worse	5
2	NSIP/OP	15	0	None	No change	5
3	NSIP	25	75	Mild	Better	-10
4	NSIP/OP	40	20	Mild	No change	0
5	NSIP	30	90	None	Worse	0
6	NSIP	10	50	None	No change	0
7	NSIP/OP	50	0	None	No change	0
8	NSIP/OP	20	40	Mild	No change	0
9	NSIP	70	50	Moderate	Worse	10
10	NSIP	25	80	None	No change	0
11	NSIP	75	80	None	Worse	0
12	OP	15	0	None	Worse	0
13	NSIP/OP	70	100	None	Better	-40
14	LIP	30	100	None	Worse	20
15	NSIP/OP	45	40	None		
16	NSIP	40	100	None	Worse	15
17	NSIP	30	90	None	Worse	10
18	NSIP	50	50	Mild		
19	LIP	50	0	None	No change	0
20	NSIP/OP	35	40	None	No change	0
21	NSIP	70	100	None	Better	-40
22	Possible UIP	40	10	Moderate		-40
23	NSIP	60	60	Mild	Worse	20
24	NSIP	15	60	Mild	No change	0

NSIP – Non-specific Interstitial Pneumonia, LIP – Lymphocytic Interstitial Pneumonia, OP, organising pneumonia, UIP – Usual Interstitial Pneumonia

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1 **Table 6 – Comparison of treatment effects in myositis and non-myositis group of patients**

		Myositis group		Non-myositis group		p-value
		Mean	SD	Mean	SD	
FVC change (%)	Before treatment	-3.5	6.5	-3.1	3.7	0.84
	After treatment	8.3	4.7	-0.9	7.3	0.002
DL _{co} change (%)	Before treatment	-2.2	5.7	-6.8	10.0	0.19
	After treatment	5.5	6.8	-2.0	5.9	0.009
Change in disease extent on CT (%)		-10.0	18.4	3.6	16.4	0.068
FVC – Forced Vital Capacity, DL _{co} – Diffusing Capacity for Carbon Monoxide						

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