Rituximab in autoimmune connective tissue disease–associated interstitial lung disease

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Abstract

Background – Connective tissue disease (CTD) associated interstitial lung disease (ILD) often fails to respond to conventional immunomodulatory agents. There is now considerable interest in the use of Rituximab in systemic autoimmune CTD, in patients refractory to standard treatments.

Objectives - To review the experience of North Bristol NHS Trust managing patients with CTD-associated ILD with Rituximab and explore possible associations with treatment response.

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

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

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

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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, systemic lupus erythematous (SLE) and refractory anti-neutrophil cytoplasmic antibody-associated (ANCA) 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 (4, 5). One mechanism of action of Rituximab is thought to be through depletion of CD20 positive 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 (Supplementary Table S1), 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 managing these patients with immunosuppression; typically including oral immunomodulatory agents, intravenous (IV) Methylprednisolone and IV Cyclophosphamide. The aims of management in this population of patients are, where possible, to reverse disease progression and decisions to initiate B-cell depletion with Rituximab are implemented through a defined pathway. These decisions are based on a combination of clinical or radiological deterioration, or attenuation of a previous improvement with immunomodulatory treatment. This is a report of our experience.

Methods and materials

Patient selection

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

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

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

Imaging

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

Statistical analysis

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

Results

Twenty four patients (16 female), with a mean age of 51.4 years (SD 14.9), were treated with Rituximab between October 2009 and January 2015. 12 out of 24 patients were former smokers. The mean duration of follow-up after treatment was 29.6 months (16.7). Biopsy had been performed in a total of 11 patients. Patient characteristics are shown in Table 1.

These patients were all managed under the Bristol CTD-ILD service and all had a diagnosis of CTD-ILD. Twenty two patients had positive serology for autoimmune markers (Supplementary Table S2). The diagnoses were reached through correlation of clinical, serological, radiological and histopathological data, with diagnoses confirmed through consensus in a multidisciplinary team (MDT) CTD-ILD forum involving Clinicians, Radiologists and Pathologists.

Pre-Rituximab Disease course and treatment

Following MDT review, it was concluded that all patients had failed to respond adequately to prior immunosuppressive therapies, including induction with pulsed intravenous Cyclophosphamide in 16 patients (at a dose of 15mg/kg, capped at 1 gram, for 6 cycles, at 3 week intervals) with IV methylprednisolone (500mg-1g prior to each dose of Cyclophosphamide) and Mycophenolate mofetil in 10 patients. Details of the treatments given and the interval to rituximab are given in Supplementary Table S3.

Prior to Rituximab, mean change in FVC was -3.3% (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 treated with Cyclophosphamide, this did not reverse disease trajectory; mean change in FVC following pulsed 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, 95% CI, -3.1 to +5.7%) *(Figure 1)*.

CTs were available for review for all patients prior to treatment. On HRCT, mean disease extent was 40.8% (SD 20.3%) of the lung, with ground glass change representing a mean 55.6% (SD 36.3%) of affected areas. The radiological patterns for each patient are shown in Supplementary Table S4. Twenty one patients had more than one CT available, enabling assessment of interval change prior to treatment. Radiological appearances were deteriorating for 8 patients and had failed to improve for 11 patients. For the two

patients whose imaging had improved, the MDT assessment was that there was further scope for improvement.

Decision to treat

The decision to commence Rituximab treatment was based on MDT discussion taking in to account clinical features including:

- Progression or lack of improvement in rheumatological features

and/or

- Progressive lung function decline
- and/orRadiological HRCT changes; either progressive changes or a failure of disease adjudged as reversible to improve or resolve (for example ground glass changes)

Rituximab administration

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

Post-treatment disease course

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

HRCT imaging following treatment was available for 22 patients. One patient died before interval imaging was completed and one patient with myositis-related lung disease has insufficient followup to merit interval imaging. The mean change in disease extent was -3.75% (p=0.33, 95% CI -11.6 to 4.1). By radiological criteria, the imaging had deteriorated for 9/22 patients, with 13/22 showing disease stability or improvement following treatment. Chi-square analysis comparing the trend in radiological appearances before and after treatment demonstrated no significant differences (χ^2 5.695, p=0.223).

CTD-myositis overlap and anti-synthetase subgroup

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

Following treatment, FVC and DL_{CO} both improved statistically by a significantly greater extent than in those patients with alternative diagnoses (Figure 2). Four patients in the myositis overlap group demonstrated improvement in their FVC >10%, showing a clinically meaningful improvement. Radiological appearances were assessed as improved in 3 out of 11 patients, with worsening of disease only adjudged in one patient (Table 2).

When comparing patients with myositis or anti-synthetase syndrome with the remaining group, there were significant differences in the response to treatment. FVC change after treatment was greater in the

myositis sub-group (p=0.002), as was improvement in DL_{CO} (p=0.009) (Table 2). There were no other significant between group differences. The four patients in whom no autoantibody was identified demonstrated post-treatment deterioration (Figure 1, patients 17, 19, 22 and 23).

Adverse events

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

Discussion

We report here our experience of Rituximab in CTD-ILD in a significant number of patients, including an identified cohort with CTD-myositis/overlap syndromes. This report adds to 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 that 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.

Preliminary reports including case reports and series have suggested that B cell depletion is a potential therapeutic target in CTD-ILD. The first report of successful treatment of Systemic Sclerosis (SSc)-associated ILD with Rituximab was in 2008 (14), with further experience reported in a cohort of 8 patients, in whom the FVC and diffusing capacity of carbon monoxide (DL_{CO}) increased significantly more than a matched cohort receiving standard treatment (15). In addition, a further study has highlighted the potential role of Rituximab in the anti-synthetase syndrome; 11 patients with severe and progressive ILD, who had failed to improve with Cyclophosphamide, demonstrated stabilisation of their lung disease based on forced vital capacity (FVC), DL_{CO} and high resolution computed tomography appearances (16).

Keir and colleagues have reported their experience of Rituximab in a more diverse cohort of 50 patients with ILD of various aetiologies, including CTD-ILD and also hypersensitivity pneumonitis and smoking-related ILDs (17). They reported a median improvement in FVC in the 6-12 months following treatment of 6.7%, with stability of DL_{CO}. The FVC in a subgroup of 33 patients with CTD-ILD, improved by 8.9%. Their results suggested a role for anti-CD20 B cell therapies in CTD-ILD and possibly a wider role in other ILDs.

A subset of CTD patients with inflammatory myositis have been recognised to have a high risk of ILD. This group of diseases includes the anti-synthetase syndrome (ASS), which is characterised by auto-antibodies

against the aminoacyl-tRNA synthetases, including anti-Jo1, anti-PL7 and anti-PL12. This clinical syndrome is characterised by prominent ILD, with in some accompanying myositis, cutaneous changes including "mechanic's hands", fevers and non-erosive arthritis (18). A number of factors in this group have been linked with the development and severity of ILD, including Asian ethnicity, those with severe skin involvement, minimal or no clinical muscle weakness and pyrexia. This group of patients may also manifest ILD as their first presentation of CTD. In one cohort, 15% of new patients referred to a tertiary referral centre met diagnostic criteria for CTDs (19).

Our observed response to Rituximab therapy in a myositis-overlap group complements the findings of the RIM study (20). 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. Interestingly, those patients in whom no autoantibody was identified seemed to fail to respond to Rituximab in our cohort. A subgroup analysis in the RIM study demonstrated that presence of anti-synthetase autoantibodies was a strong predictor of improvement with treatment (13).

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 NHS England.

In conclusion, we present here our experience using Rituximab for treatment-refractory CTD-ILD. Rituximab appears to stabilise clinical, physiological and radiological features in this cohort, with particular benefit seen in a subgroup of patients with myositis-overlap syndromes. The role of Rituximab in CTD-ILD is promising but 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 appears to stabilise disease in patients with connective tissue disease-associated interstitial lung disease.
- Patients with myositis-overlap syndromes, including the anti-synthetase syndrome appeared to respond well to Rituximab.
- Further research is needed to identify which patient groups will benefit from Rituximab.

Competing interests

The authors declare no competing interests.

Author Contributions

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

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Figure Legends

Figure 1 – Changes in lung function before and after treatment

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

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

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

Tables

Table 1 – 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 Supplementary table S2)	**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)
SO2 (%)	96 (1.5)
SLE – Systemic Lupus Erythematous, 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, SO2 – Oxygen Saturations	

Table 2 – 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						

Supplementary tables

Table S1 – 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.

Table S2 – Patient diagnoses and autoimmune profiles

Patient	Age	Gender	Diagnosis	Radiological pattern	Histopathological pattern	Antibodies
1	40.2	Male	Scleroderma	NSIP	Fibrotic NSIP	Scl70
2	61.0	Female	Dermatomyositis	NSIP/OP		Jo1
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		PL-12
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		dsDNA
13	48.8	Female	Anti-synthetase	NSIP/OP		Jo1
14	36.8	Female	Sjogren's syndrome	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 CTD-ILD	NSIP	Fibrotic NSIP	pANCA
18	64.7	Female	Anti-synthetase	NSIP	Fibrotic NSIP	PM-Scl
19	57.0	Female	Unclassifiable CTD-ILD	LIP	Fibrotic NSIP	No antibody detected
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 CTD-ILD	Possible UIP		No antibody detected
23	68.3	Male	Unclassifiable CTD-ILD	NSIP		Non-specific ANA
24	66.4	Female	Sjogren's syndrome	NSIP	Hypersenstitivity pneumonitis	RNP, Sm, dsDNA

NSIP – Non-specific Interstitial Pneumonia, LIP – Lymphocytic Interstitial Pneumonia, OP, organising pneumonia, SLE – Systemic Lupus Erythematous, CTD-ILD – Connective Tissue Disease-associated Interstitial Lung Disease

Table S3 – Patient treatment prior to Rituximab

Patient	Diagnosis	Pre-Rituximab treatment	Duration of treatment	Comments
1	Scleroderma	None		Patient present extremis and t 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 t cyclophosphamid
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	None		Unable to t cyclophosphamid

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, SL
Systemic Lupus Erythematous, MMF – Mycophenolate mofetil, IV - intravenous

Table S4 – 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						