RHEUMATOLOGY

Rheumatology 2016;55:1318–1324
doi:10.1093/rheumatology/kew195
Advance Access publication 8 April 2016

Original article

Rituximab in autoimmune connective tissue disease–associated interstitial lung disease

Charles Sharp[1], Melanie McCabe[2], Nick Dodds[3], Anthony Edey[3], Lloyd Mayers[3], Huzaifa Adamali[3], Ann B. Millar[1] and Harsha Gunawardena[3,4]

Abstract

Objective. 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. The aim of this study was 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. Twenty-four patients were treated with rituximab. Their physiological parameters had failed to improve despite other immunomodulatory agents, with a mean change in forced vital capacity (FVC) prior to therapy of −3.3% (95% CI −5.6, −1.1) and mean change in diffusing capacity of carbon monoxide of −4.3% (95% CI −7.7, −0.9). After rituximab, radiology remained stable or improved for 11 patients, 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, 7.2), while diffusing capacity of carbon monoxide was stable [mean change +2.1% (95% CI −1.0, 5.2)]. Patients with myositis overlap or antisynthetase syndrome appeared to respond well to treatment, with four patients showing clinically significant improvement in FVC >10%.

Conclusion. 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.

Key words: interstitial lung disease, connective tissue disease, rituximab, treatment

CLINICAL SCIENCE

Rheumatology key messages

- Rituximab appears to stabilise disease in patients with connective tissue disease–associated interstitial lung disease.
- Patients with myositis overlap syndromes, including the antisynthetase syndrome appeared to respond well to rituximab.
- Further research is needed to identify which patient groups will benefit from rituximab.

Introduction

An increased understanding of the molecular pathways of inflammation and autoimmunity has led to the development of targeted biologic agents and expanded the repertoire of treatment options in the autoimmune CTDs. Lymphocyte-targeted therapies, including rituximab, an anti-CD20 B cell–depleting monoclonal antibody, are now used in clinical practice for diseases such as RA,

[1]Southmead Hospital, Academic Respiratory Unit, University of Bristol, Bristol, [2]Department of Geography, London School of Economics, Houghton Street, London, [3]Bristol Interstitial Lung Disease Service and [4]Academic Rheumatology, North Bristol NHS Trust, Southmead Hospital, Bristol, UK

Submitted 11 November 2015; revised version accepted 8 March 2016

Correspondence to: Harsha Gunawardena, Academic Rheumatology, North Bristol NHS Trust, Southmead Hospital, Bristol, BS10 5NB, UK. E-mail: harsha.gunawardena@nbt.nhs.uk

SLE and refractory 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 randomized, controlled trials yet published.

The CTDs are heterogeneous processes characterized 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, and 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 inhibiting T cell co-stimulation. Translational studies have highlighted other mechanisms, which are being further investigated [6].

It is recognized that all patients with CTDs are at risk of ILD, some more so than others [5]. While the 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, available at *Rheumatology* Online), 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, i.v. methylprednisolone and i.v. CYC. The aim of management in this population of patients is, 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 and radiological deterioration or attenuation of a previous improvement with immunomodulatory treatment. This is a report of our experience.

Methods and materials

Patient selection

A review of our clinical database identified 24 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 for separate analysis was identified with myositis or the antisynthetase syndrome (ASS). Patients with RA were excluded due to the distinct pattern of ILD observed in this group.

Hospital records were reviewed to identify pulmonary function tests (PFTs) performed 5–7 months prior to rituximab treatment, in the 4 weeks immediately before treatment and 6–12 months following treatment. Where relevant, the same approach was used for PFTs prior to, at treatment with and following CYC therapy. High-resolution computed tomography (HRCT) of the chest was identified from the time of treatment and during follow-up. Patients were followed for a median of 29.6 months (S.D. 16.7). All PFT measurements were performed within the same respiratory physiology laboratory. This clinical review was performed with full ethical approval from the Cambridge South Ethics Committee (reference 15/EE/0023).

Imaging

HRCTs were performed for clinical reasons. Images were reconstructed on a standard HRCT algorithm and interspaced 1 mm 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. The 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 intrarater agreement for the extent of disease was 0.55, with a value of 0.92 for interval change.

Statistical analysis

Values are shown as mean (S.D.) and mean difference with confidence intervals or frequencies as appropriate. Changes in PFTs and radiological extent are expressed as the percentage change from start of therapy. Changes in values before, at the time of and after treatment were assessed for normality and analysed with a 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 <0.05 as the threshold for statistical significance. Analyses were performed using SPSS software (version 21.0.0; IBM, Armonk, NY, USA).

Results

Twenty-four patients (16 females), with a mean age of 51.4 years (S.D. 14.9), were treated with rituximab between October 2009 and January 2015. Twelve of the 24 patients were former smokers. The mean duration of follow-up after treatment was 29.6 months (S.D. 16.7). A 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, available at *Rheumatology* Online). The diagnoses were reached through correlation of clinical, serological, radiological and histopathological data, with diagnoses confirmed through

Table 1 Baseline characteristics of patients

Variable	Value
Demographics	
Age, mean (s.d.), years	51.4 (14.9)
Female, ***n*** (%)	16 (66.7)
Ex-smokers, ***n*** (%)	12 (50)
Oxygen use, ***n*** (%)	5 (20.8)
Diagnosis, ***n***	
Antisynthetase syndrome (ASS)	10
DM (other/non-ASS)	3
SSc	3
SS	2
SLE	2
Unclassifiable CTD-ILD	4
Biopsy, ***n*** (%)	11 (45.8)
Histopathological pattern, ***n***	
NSIP	9
LIP	1
Hypersensitivity pneumonitis	1
Identified autoantibodies, ***n*** (%)[a]	**22 (91.7)**
Treatment, ***n***	
CYC	**16**
I.v. methylprednisolone	**16**
MMF	**9**
HCQ	**2**
AZA	**4**
MTX	**1**
Physiology, mean (s.d.)	
FVC, % predicted	78.4 (21.4)
FEV1, % predicted	75.4 (18.6)
FEV1:FVC ratio	0.81 (0.06)
DLCO, % predicted	50.9 (18.0)
SO_2, %	96 (1.5)

[a]See Supplementary Table S2, available at *Rheumatology* Online. DL_{CO}: diffusing capacity for carbon monoxide; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; LIP: lymphocytic interstitial pneumonia; n: number of patients; NSIP: non-specific interstitial pneumonia; SO_2: oxygen saturation.

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 i.v. CYC in 16 patients (at a dose of 15 mg/kg, capped at 1 g, for six cycles, at 3 week intervals) with i.v. methylprednisolone (500 mg–1 g prior to each dose of CYC) and MMF in 10 patients. Details of the treatments given and the interval to rituximab are given in Supplementary Table S3, available at *Rheumatology* Online.

Prior to rituximab, the mean change in forced vital capacity (FVC) was −3.3% (95% CI −5.6, −1.1; P = 0.005), with a mean change in the diffusing capacity of carbon monoxide (DLCO) of −4.3% (95% CI −7.7, −0.9; P = 0.02). Of those treated with CYC, this did not reverse disease trajectory; the mean change in FVC following pulsed i.v. treatment was −1.2% (95% CI −5.2, +2.7; P = 0.51) and the mean change in DLCO was +1.3% (95% CI −3.1, +5.7; P = 0.54) (Fig. 1).

CTs were available for review for all patients prior to treatment. On HRCT, the mean disease extent was 40.8% (s.d. 20.3) of the lung, with ground glass change representing a mean 55.6% (s.d. 36.3) of affected areas. The radiological patterns for each patient are shown in Supplementary Table S4, available at *Rheumatology* Online. 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 into account clinical features including progression or lack of improvement in rheumatologic features and/or progressive lung function decline and/or radiological HRCT changes, either progressive changes or a failure of disease adjudged as reversible to improve or resolve (e.g. ground glass changes).

Rituximab administration

Rituximab was administered according to rheumatology/CTD protocol, at a dose of 1 g i.v. infused on 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% (95% CI 0.9, 7.2; P = 0.01). DLCO remained stable, with a mean change of 2.1% (95% CI −1.0, 5.2; P = 0.18). Four patients demonstrated clinically meaningful improvements of >10% in their FVC following treatment (Fig. 1). When comparing pre- and post-treatment disease trajectory, rituximab reversed previous trends in lung function change for both FVC (P = 0.001) and DLCO (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 had insufficient follow-up to merit interval imaging. The mean change in disease extent was −3.75% (95% CI −11.6, 4.1; P = 0.33). 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 antisynthetase subgroup

Thirteen patients (nine females) were identified from their clinico-serological phenotype with myositis or ASS, with a mean age of 53.5 years (s.d. 13.2). Seven of these were

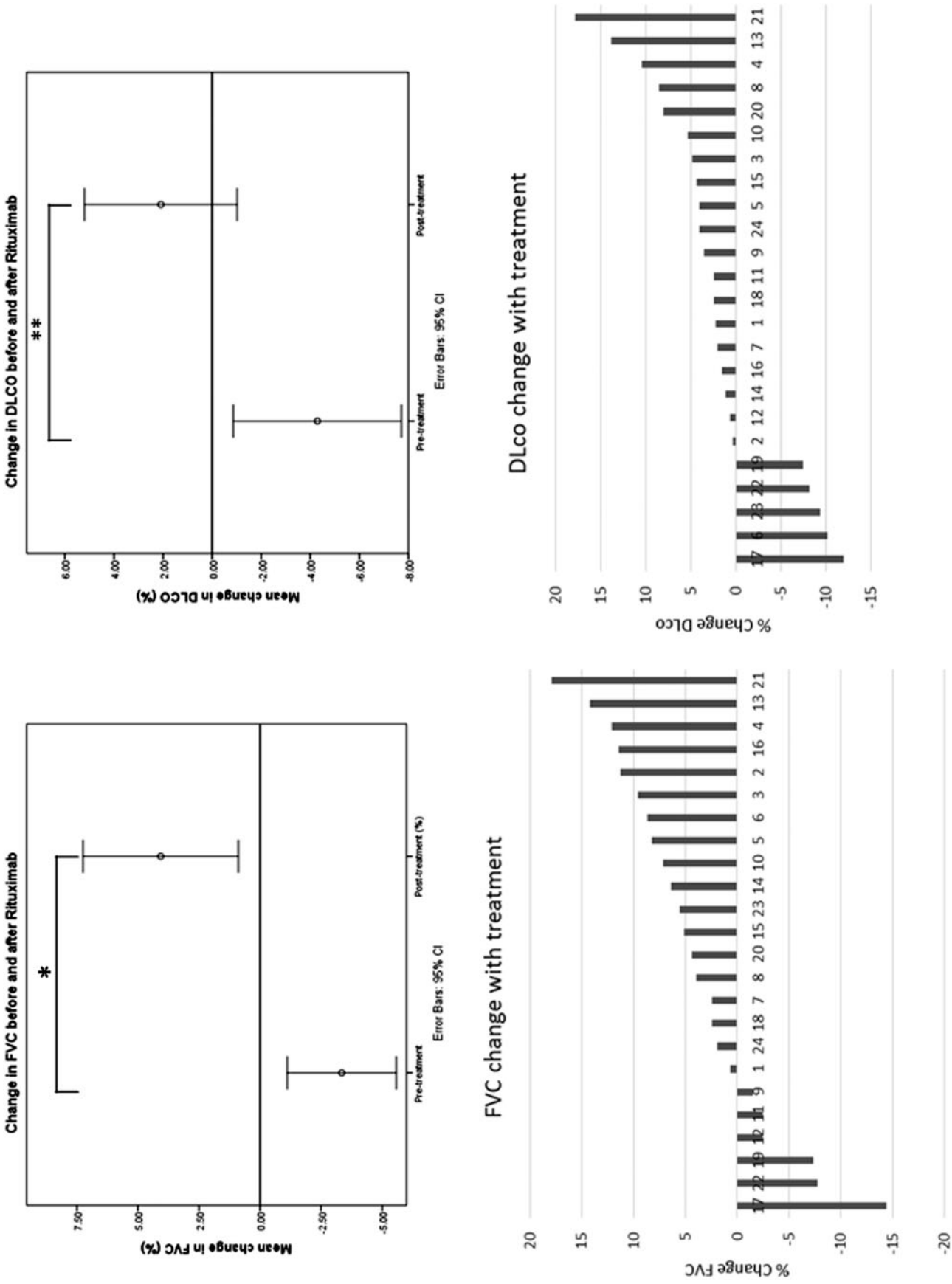
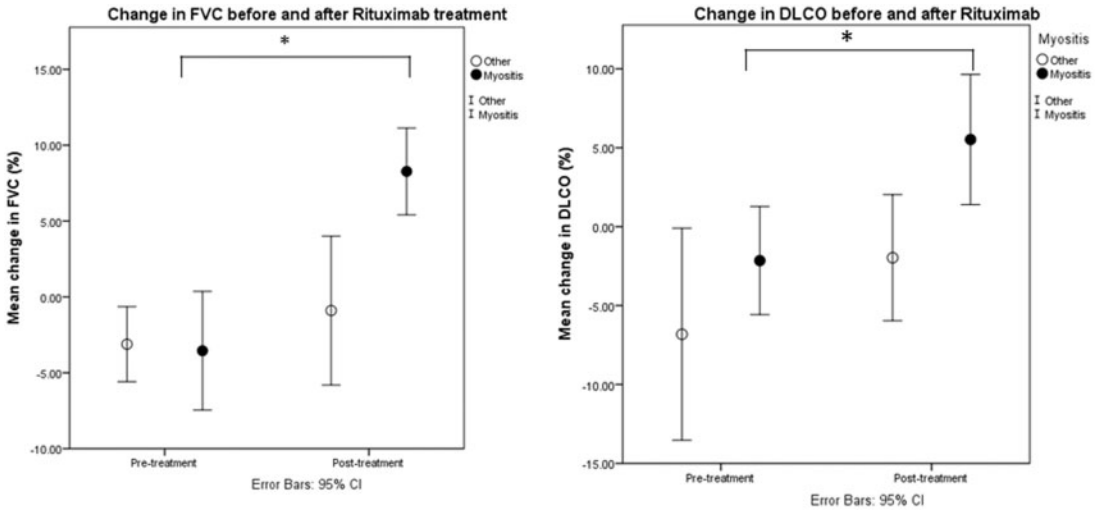


Fig. 1 Changes in lung function before and after treatment

(**A**) Mean change in FVC. (**B**) Mean change in DLCO. (**C**) Fountain plot of individual patient changes in FVC. (**D**) Fountain plot of individual patient changes in DLCO. *P = 0.001, **P = 0.02. FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide.

Fig. 2 Comparison of myositis subgroup and other patients' response to treatment



*P $<$ 0.01. FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide.

former smokers. They had physiological impairment at baseline with a mean FVC of 75.3% predicted (S.D. 17.0) and a mean DLCO of 55.9% predicted (S.D. 16.4). On initial HRCT imaging, the mean extent of disease was 37.3% (S.D. 19.2), with ground glass representing 52.7% (S.D. 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 from those with other diagnoses.

Following treatment, FVC and DLCO both improved statistically by a significantly greater extent than in those patients with alternative diagnoses (Fig. 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 of 11 patients, with worsening of disease seen in only 1 patient (Table 2).

When comparing patients with myositis or ASS with the remaining group, there were significant differences in the response to treatment. The FVC change after treatment was greater in the myositis subgroup (P = 0.002), as was improvement in DLCO (P = 0.009). There were no other significant between-group differences. The four patients in whom no autoantibody was identified demonstrated post-treatment deterioration (Fig. 1, patients 17, 19, 22 and 23).

Adverse events

There were no complications observed associated with treatment. One patient died due to disease progression 4 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 the use of B cell depletion as treatment in this difficult disease group.

The decision to treat is multifactorial, guided by a combination of respiratory parameters and also rheumatologic 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, while 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 the 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. However, the clinical data for disease course and natural history of CTD-ILD are lacking.

Our data demonstrate, consistent with previously published series, a numerical improvement in FVC, with stability of DLCO, 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 ASS-related lung disease and this group appears to respond particularly well to treatment, with greater improvement in FVC and DLCO compared with the non-myositis group.

The limitations of our data are their observational nature and the heterogeneity of data captured in the course of disease. Despite this, we observed a 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

Table 2 Comparison of treatment effects in myositis and non-myositis group of patients

Variable		Myositis group Mean (S.D.)	Non-myositis group Mean (S.D.)	P-value
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
DLCO 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

DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity.

therapeutic target in CTD-ILD. The first report of successful treatment of SSc-associated ILD with rituximab was in 2008 [13], with further experience reported in a cohort of eight patients in whom the FVC and DLCO increased significantly more than a matched cohort receiving standard treatment [14]. In addition, a further study highlighted the potential role of rituximab in ASS; 11 patients with severe and progressive ILD, who had failed to improve with CYC, demonstrated stabilization of their lung disease based on FVC, DLCO and HRCT appearance [15].

Keir *et al.* [16] reported their experience of rituximab in a more diverse cohort of 50 patients with ILD of various aetiologies, including CTD-ILD, hypersensitivity pneumonitis and smoking-related ILDs. They reported a median improvement in FVC in the 6–12 months following treatment of 6.7%, with stability of DLCO. 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 recognized to have a high risk of ILD. This group of diseases includes ASS, which is characterized by autoantibodies against the aminoacyl-tRNA synthetases, including anti-Jo1, anti-PL7 and anti-PL12. This clinical syndrome is characterised by prominent ILD, with some accompanying myositis, cutaneous changes including mechanic's hands, fevers and non-erosive arthritis [17]. 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 the diagnostic criteria for CTDs [18].

Our observed response to rituximab therapy in a myositis-overlap group complements the findings of the Rituximab In Myositis (RIM) study [19]. This large, randomized, controlled trial of early (at weeks 0 and 1), compared with late (at weeks 8 and 9), rituximab in treatment-refractory myositis found no difference in the primary endpoint 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 randomization. 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 the presence of antisynthetase 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 randomized controlled trial comparing rituximab to CYC in CTD-ILD (ClinicalTrials.gov identifier: NCT01862926) is designed to address this important question. A further resource that would be of value in this field by pooling data such as ours would be a registry for CTD-ILD.

Data such as ours remain 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 UK National Health Service.

In conclusion, we present here our experience using rituximab for treatment-refractory CTD-ILD. Rituximab appears to stabilize 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 highlight the need for more research to identify those patients who will have the best response to treatment.

Acknowledgements

C.S., L.M. and N.D. identified cases and collated data. C.S. and M.M. conducted the statistical analysis. H.A., A.B.M. and H.G. oversaw patient care. C.S., A.B.M. and H.G. conceived the study and drafted the manuscript. All authors read and approved the final manuscript.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 Stone JH, Merkel PA, Spiera R *et al*. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32.

2 Cohen SB, Emery P, Greenwald MW *et al*. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54:2793–806.

3 Fernandez-Nebro A, de la Fuente JL, Carreno L *et al*. Multicenter longitudinal study of B-lymphocyte depletion in refractory systemic lupus erythematosus: the LESIMAB study. Lupus 2012;21:1063–76.

4 Fischer A, Brown KK. Interstitial lung disease in undifferentiated forms of connective tissue disease. Arthritis Care Res (Hoboken) 2015;67:4–11.

5 Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders. Lancet 2012;380:689–98.

6 Weiner GJ. Rituximab: mechanism of action. Semin Hematol 2010;47:115–23.

7 Gabbay E, Tarala R, Will R *et al*. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med 1997;156:528–35.

8 Gochuico BR, Avila NA, Chow CK *et al*. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med 2008;168:159–66.

9 Schnabel A, Hellmich B, Gross WL. Interstitial lung disease in polymyositis and dermatomyositis. Curr Rheumatol Rep 2005;7:99–105.

10 White B. Interstitial lung disease in scleroderma. Rheum Dis Clin North Am 2003;29:371–90.

11 Bradley B, Branley HM, Egan JJ *et al*. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008;63(Suppl 5):v1–58.

12 Oda K, Ishimoto H, Yatera K *et al*. High-resolution CT scoring system-based grading scale predicts the clinical outcomes in patients with idiopathic pulmonary fibrosis. Respir Res 2014;15:10.

13 McGonagle D, Tan AL, Madden J *et al*. Successful treatment of resistant scleroderma-associated interstitial lung disease with rituximab. Rheumatology 2008;47:552–3.

14 Daoussis D, Liossis SN, Tsamandas AC *et al*. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology 2010;49:271–80.

15 Sem M, Molberg O, Lund MB, Gran JT. Rituximab treatment of the anti-synthetase syndrome: a retrospective case series. Rheumatology 2009;48:968–71.

16 Keir GJ, Maher TM, Ming D *et al*. Rituximab in severe, treatment-refractory interstitial lung disease. Respirology 2014;19:353–9.

17 Mahler M, Miller FW, Fritzler MJ. Idiopathic inflammatory myopathies and the anti-synthetase syndrome: a comprehensive review. Autoimmun Rev 2014;13:367–71.

18 Mittoo S, Gelber AC, Christopher-Stine L *et al*. Ascertainment of collagen vascular disease in patients presenting with interstitial lung disease. Respir Med 2009;103:1152–8.

19 Oddis CV, Reed AM, Aggarwal R *et al*. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. Arthritis Rheum 2013; 65:314–24.

20 Aggarwal R, Bandos A, Reed AM *et al*. Predictors of clinical improvement in rituximab-treated refractory adult and juvenile dermatomyositis and adult polymyositis. Arthritis Rheumatol 2014;66:740–9.