Severe interstitial lung disease in connective tissue disease: Rituximab as rescue therapy.

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Introduction

In the context of connective tissue disease (CTD), very severe interstitial lung disease (ILD) unresponsive to traditional treatment is an all too frequent and dispiriting experience. In the absence of lung transplantation, there is little to offer patients other than symptom palliation. In the idiopathic interstitial pneumonias (IIPs), it has been observed that a palliative approach is appropriate once disease severity has reached a critical tipping point: despite a much lower mortality in earlier disease, idiopathic fibrotic nonspecific interstitial pneumonia (NSIP) has the same poor treated outcome as idiopathic pulmonary fibrosis (IPF) in patients with DLco <35% predicted. (ref 1). Clinical experience indicates that in the subgroup of patients with very severe, progressive CTD-ILD, prognosis is similarly bleak.

The pathogenesis of CTD-ILD is complex, and it is broadly accepted that underlying immune system dysfunction and immune-mediated pulmonary inflammation are critical to CTD-ILD development and progression. Abnormalities of cellular and humoral immune function have been described in ILD associated with systemic sclerosis (ref 2-4), idiopathic inflammatory myopathy (ref 5, 6) and several other CTDs (ref 7, 8). The success of anti-inflammatory and immunosuppressive therapy in these conditions supports the notion that immunological over-activity is a key process in progressive lung fibrosis.

Rituximab is a chimeric (human/mouse) monoclonal antibody with a high affinity for the CD20 surface antigen expressed on pre-B and B-lymphocytes. Rituximab results in rapid depletion of B cells from the peripheral circulation (ref 9), before B cell reconstitution begins six to nine months later (ref 10). Evidence for the effectiveness of B cell depletion exists in a number of immune-mediated conditions, including rheumatoid arthritis (ref 11-13), ANCA-
associated vasculitis (ref 14, 15), pulmonary alveolar proteinosis (ref 16) and immune thrombocytopenic purpura (ref 17). A few case series suggest rituximab may also be effective in ILD occurring in the context of immunological over-activity, with favourable responses reported in anti-synthetase (ASS) associated ILD (ref 18) and SSc-ILD (ref 19). However, patients in these series had interstitial lung involvement of predominantly mild to moderate severity.

Evidence for the effectiveness of rituximab as ‘rescue’ therapy in patients with severe, life-threatening ILD is limited (ref 20, 21). We report the use of rituximab as rescue therapy in eight patients with underlying features of connective tissue disease, and exceedingly severe fibrotic lung disease, progressing in spite of vigorous conventional immunosuppression.

**Methods**

*Patient groups*

Review of our medical records and hospital pharmacy prescribing database identified all patients treated with rituximab between December 2007 and December 2010. All consecutive patients with severe, progressive CTD-ILD were included in our analysis, with a total of eight patients. No patients with CTD-ILD were excluded due to poor outcome or early death. A minimum of nine months post treatment follow-up was available for all patients. ILD occurred in association with polymyositis or dermatomyositis (PM/DM) in five patients, of whom four had anti-synthetase Jo-1 antibody. In two patients, ILD occurred in association with undifferentiated connective tissue disease, and in one with systemic sclerosis (SSc). All patients had failed to respond to conventional immunosuppressive therapy, with ongoing deterioration in pulmonary function tests (PFTs) and/or worsening respiratory failure. At the time of referral, two patients were mechanically ventilated and transferred directly to the
intensive care unit (ITU) of our hospital. Table 1 lists demographic information and immunosuppressive therapy in the nine to twelve months prior to rituximab therapy.

Statistical analysis

All patients had PFT follow up of at least nine months following rituximab. In the six patients with PFT data prior to rituximab treatment, the significance of median DLco and FVC percentage change before and after treatment was assessed by Wilcoxon signed rank test. To evaluate statistical significance of response to treatment in all patients, categorical variables of change (worse, stable, improved) were generated by combining significant changes in pulmonary function tests (defined as a change in FVC of ≥10% and/or a change in DLco of ≥15%) and/or clinical status (for the two patients requiring mechanical ventilation, the requirement for mechanical ventilation was classified as a significant deterioration). Change was assessed nine to twelve months before and after rituximab, and analyzed using the Wilcoxon signed-rank test. \( P \) values of ≤ 0.05 were considered statistically significant. Analysis of follow-up data at nine to 12 months was chosen based upon previously reported responses of CTD-ILD to rituximab (ref 18, 19), and the expected duration of B cell ablation following rituximab (ref 10-15).

Patient assessment

All patients were discussed at our Interstitial Lung Disease multidisciplinary meeting and underwent a full clinical assessment, including high resolution computed tomography (HRCT) and PFTs.

Rituximab treatment

Rituximab was administered in accordance with our hospital New Drugs and Clinical Guidelines Group recommendations. The treatment protocol consists of rituximab 1000 mg administered on day zero and day fourteen (preceded by treatment with intravenous
hydrocortisone and chlorphenamine), the dosing regimen approved for rheumatoid arthritis
treatment (ref 12). Patient 5 received rituximab 375 mg/m² weekly for 4 weeks, administered
before our hospital guidelines were finalized. Following rituximab administration,
requirements for ongoing immunosuppression were assessed on an individual patient basis.

Results

At the time of rituximab treatment, all patients had extremely severe ILD, with a median
DLco of 25% (range 16-32%) and FVC of 45% (range 37-59%), and an anticipated survival
of less than six to twelve months (based on clinical experience, and survival data in patients
with idiopathic fibrotic ILD of similar severity) (ref 1). Following rituximab, we observed a
significant categorical improvement in clinical status and/or PFTs (DLco and/or FVC) in
seven out of eight patients (p=0.008) according to the criteria outlined in the methods section.
In one patient (patient 8), disease severity did not appear to change following treatment, other
than mild symptomatic improvement. In six patients with serial PFTs, there was a median
improvement in DLco of 22% (range 0-119%, p=0.04) and FVC of 18% (range 0-100%,
p=0.03) within nine to twelve months of rituximab administration. This improvement
occurred following a median decline in DLco of 16% (range 8-67%) and in FVC of 29%
(range 3-45%) in the nine to twelve months preceding rituximab treatment (figure 1a, 1b).
Improvements in PFTs and/or clinical status tended to occur rapidly (within two to three
months in most patients), and were also statistically significant (p<0.05) when analyzed at the
earlier time point of six months (± 1) post rituximab treatment.

Five patients had a striking response to rituximab, with dramatic improvements in lung
function (patients 3,4,5) and/or successful extubation (patients 1 and 7). Change in clinical
status and PFTs are summarized in table 2. Supplementary figures 1a-f show lung function
responses to treatment in individual patients. Additional clinical information can be found in the online supplement, including complete functional follow up.

**Polymyositis/Dermatomyositis-associated ILD**

**Patient 1**

This 45 year old male was transferred to the ITU at our hospital after failed extubation following a quadriceps muscle biopsy procedure. Recently diagnosed dermatomyositis with associated organizing pneumonia had deteriorated despite IV methylprednisolone, and at transfer, HRCT demonstrated a pattern of organizing pneumonia with admixed fibrosis and diffuse alveolar damage (figure 2a). The combination of life-threatening respiratory failure, HRCT findings and the underlying autoimmune process resulted in the decision to treat concurrently with IV cyclophosphamide 750 mg and rituximab. A dramatic improvement in HRCT appearances occurred over the following six weeks (figure 2a, b), and improvements in PFTs have continued during follow-up (with a DLco of 50% and FVC 99% predicted at most recent review).

**Patient 2**

This 60 year old male with longstanding PM (Jo-1 antibody positive) associated fibrotic NSIP, experienced gradual respiratory deterioration and persisting myositis activity despite concurrent mycophenylate, cyclosporine and prednisolone. Within nine months of rituximab, serum creatine kinase had decreased from 4500 to 370, and there was a significant subjective improvement in muscle strength and dyspnoea, with a 19% improvement in DLco (table 2).

**Patient 3**

This 60 year old female with anti-synthetase antibody (Jo-1) associated fibrotic NSIP experienced a 12 month history of worsening symptoms and deteriorating PFTs despite IV cyclophosphamide. Following rituximab, there was a striking improvement in respiratory and
extra-pulmonary symptoms within three months, coupled with improvements in PFTs (table 2).

Patient 4.
This 29 year old female was referred with rapidly progressive fibrotic NSIP associated with anti-synthetase syndrome (Jo-1), and deterioration despite prednisolone and mycophenylate, followed by IV cyclophosphamide. Rituximab resulted in major improvements in symptoms and PFTs within two to three months of administration, with improvements continuing over the subsequent 12 months of follow-up.

Patient 5.
This 51 year old male was referred with very rapidly progressive fibrotic NSIP, associated with anti-synthetase syndrome (Jo-1), and deteriorating interstitial lung involvement despite prednisolone, mycophenylate and ultimately IV cyclophosphamide. Treatment with rituximab resulted in rapid and striking improvements in symptoms and PFTs (supplementary figure 1d), however he died in his local hospital 18 months following rituximab therapy (with the cause of death reported as a lower respiratory tract infection). During follow-up at our hospital eight days before death, he remained well with stable PFTs (DLco of 38% and FVC of 68%) and normal inflammatory markers. The most recent lymphocyte subset analysis performed 12 months following rituximab (and six months prior to death) revealed persisting B cell depletion although infections had not been problematic over this time. Cyclosporine had recently been commenced (in addition to a long-standing mycophenolate and prednisolone regimen), due to persisting myositis activity, and to allow further steroid reduction.

*Undifferentiated CTD*
Two patients in our cohort had a confirmed CTD with positive autoimmune serology and systemic symptoms (table 1), but did not fulfill the classification criteria for a defined CTD. Their clinical history is as follows:

Patient 6.
This 49 year old man was diagnosed with an undifferentiated CTD in 2006, with HRCT appearances of fibrotic NSIP. Interstitial lung disease progressed despite intravenous cyclophosphamide, followed by mycophenolate and prednisolone. Rituximab was administered in December 2007, with a marked improvement in symptoms and lung function (22% improvement in DLco) over the next nine months, before deterioration recurred (despite continued oral immunosuppression). He was declined for lung transplantation, and a therapeutic approach of cyclical rituximab infusions has been associated with stability of his very severe CTD associated ILD over the last 12 months.

Patient 7.
This 37 year old lady presented with widespread consolidation on HRCT and was managed initially as non-resolving pneumonia. Worsening respiratory failure resulted in the initiation of mechanical ventilation and treatment with IV methylprednisolone (one gram daily for three days; without clinical improvement), and the patient was transferred to our ITU. Positive autoimmune serology (rheumatoid factor 1:1720, anti-Ro antibodies), HRCT appearances of organizing pneumonia with diffuse alveolar damage, and negative microbiology (including virology) on bronchoalveolar lavage (BAL), resulted in the decision to treat with rituximab and reduced dose IV cyclophosphamide (750 mg). Following rituximab, an episode of suspected CMV pneumonitis was successfully treated with aciclovir (more details can be found in the online supplement), and HRCT appearances improved significantly in the subsequent four weeks. The patient was discharged home after
nine weeks. Eight months following the initial rituximab dose, widespread consolidation re-appeared on HRCT on a background of fibrotic changes, and following BAL to exclude infection, a second cycle of rituximab was administered. Dyspnoea gradually improved over the subsequent three months, although significant residual disability remains.

**Systemic sclerosis**

**Patient 8**

This 63 year old man had longstanding SSc associated NSIP, experienced deteriorating symptoms and HRCT imaging despite mycophenylate and prednisolone. Significant haematuria with cyclophosphamide precluded the further use of this agent. Although there was symptomatic improvement and improved six minute walk distance following rituximab (from 198 to 264 meters), there was no significant change in PFTs at 9 months follow-up.

**Discussion**

The observation that rituximab is an effective rescue therapy in some patients with severe CTD-ILD has important clinical implications. If these findings are validated by further experience, it can no longer be assumed that patients with severe progressive CTD-ILD have the same bleak treated outcome as those with end-stage fibrotic idiopathic interstitial pneumonia. We report objective improvement in seven of eight patients (with very striking improvements in five patients) in whom the only realistic outcomes appeared to be lung transplantation or early death.

Although this study can be criticized as observational, it appears highly unlikely that a placebo-controlled evaluation could be performed in this context. In the first instance, patients and many clinicians will find a placebo-controlled trial unacceptable in the setting of life-threatening disease for which there is open therapy available with a good conceptual basis for its use. The selective bias against patients with more severe disease, when open
treatment is accessible, has been highlighted as one of the key obstacles to observing clear-cut benefits in placebo-controlled trials in SSc-ILD (ref 22), and in chronic pulmonary sarcoidosis (ref 23). Secondly, careful clinical observational studies based on treatment by proof of concept, rather than evidence base, may be the only feasible option in rare and/or clinically heterogeneous ILDs as those described here. Finally, severe end-stage disease is less attractive to pharmaceutical and other funding bodies, in view of a greater risk of non-efficacy and applicability only to a small patient subset, as highlighted by the exclusion of patients with more severe disease in most of the large recently completed clinical trials in IPF (ref 24-29).

While our report is observational (with the inherent limitations), our analysis was a crossover design, and thus the treatment effect was intrinsically more convincing than an evaluation of de novo therapy with no reference to previous lung function trends. Two series have previously reported the efficacy of rituximab in CTD-ILD (ref 18, 19). Importantly, both series included patients with much less severe interstitial lung involvement than our own cohort. Sem and colleagues reported a positive effect of rituximab in seven of 11 patients with anti-synthetase syndrome associated ILD, the majority of whom had failed conventional immunosuppression (ref 18). Although complete lung function data is not reported, graphical representation of available baseline measurements suggest that DLco and FVC were only mildly to moderately impaired (DLco ≥ 60% predicted in eight of nine patients, FVC ≥ 50% in six), in contrast with the markedly more severe lung disease in our PM/DM cohort (Table 2). In SSc associated ILD, Daoussis and colleagues reported a significant improvement in PFTs following rituximab treatment (compared to standard therapy) (ref 19). Again, rituximab treated patients in this cohort had less severe ILD (mean % predicted DLco of 52 ± 21%, and FVC of 68 ± 20%).
While little prognostic data exists for very severe and progressive CTD-ILD, clinical experience suggests an expected survival of six to twelve months in patients with similar disease severity as those described in our cohort. Our results suggest that, in the context of underlying autoimmunity, even patients with very severe ILD (for whom we would usually plan palliative treatment) may be rescued with rituximab, despite disease that is unresponsive to all traditional treatments. Immunological over-activity appears to be a key process in progressive lung fibrosis, even when fibrosis is severe, and the effectiveness of rituximab suggests that B lymphocytes are key protagonists in disease progression.

Several important caveats should be highlighted in this report. Life-threatening disease severity in patients 1 and 7 (both of whom were mechanically ventilated at the time of referral), resulted in the decision to administer rituximab and IV cyclophosphamide concurrently. This does make an accurate assessment of the stand alone effects of rituximab difficult to ascertain. However, cyclophosphamide was administered only twice, at a reduced dose (50-75% of the dose routinely used), whereas the standard regimen for ILD-CTD would have included six monthly doses (at 600 mg/m² each) (ref 30). It therefore seems unlikely that the small dose of cyclophosphamide was effective on its own in controlling devastating ILD, although an additive effect cannot be excluded. In the other patients, the effect of concomitant or preceding immunosuppression needs to be considered as a potential confounding factor. Three received treatment with IV cyclophosphamide before switching to Rituximab. Although a delayed effect of IV cyclophosphamide cannot be excluded with absolute certainty, stabilization and/or improvement in lung function was observed in responders within six months of initiation of cyclophosphamide in a large retrospective cohort of patients with progressive fibrotic lung disease (ref 31). The remaining three patients had continued to progress while on mycophenolate, and response to rituximab seems the most plausible explanation for the observed improvement.
A negligible treatment effect was observed in one patient (patient 8) following rituximab. As described, this 60 year old male had SSc-associated fibrotic NSIP of over 10 years duration, and while there was a definite improvement in symptoms and exercise capacity at nine months, there was no significant change in PFTs.

Increased risk of infection following rituximab is a serious concern. In haematological malignancies, repeated doses of rituximab appear to be associated with an increased infection risk (ref 32, 33), although this is not clearly apparent in rheumatological disease. In a recent meta-analysis of 745 patients with rheumatoid arthritis (RA), the rate of serious infections was not significantly different between rituximab and placebo-treated patients (2.3% vs 1.5%) (ref 34). In a long term safety analysis of 2578 patients with RA treated with at least one course of rituximab, the rate of severe infections did not increase with subsequent doses, despite an increased incidence of hypogammaglobulinaemia (ref 35). Progressive multifocal leukoencephalopathy has been described in rituximab treated patients. Although the reported incidence is extremely low (less than 1:20,000 in rituximab-treated RA patients) (ref 36), patients should be monitored closely for the development of new or worsening neurological symptoms. Rituximab induced pulmonary reactions have also been reported, with steroid responsive organizing pneumonia the most common manifestation in one systematic review (ref 37).

Two patients in our cohort had significant infectious complications following rituximab. Patient 7 experienced recurrent lower respiratory tract infections following rituximab and patient 5 died of a respiratory tract infection 18 months after rituximab. Patient 5 had commenced cyclosporine (in addition to longstanding mycophenolate) to better control his myositis, four months prior to the fatal respiratory infection, and the contribution of rituximab in predisposing to infection is difficult to establish. Neither patient experienced reduced immunoglobulin levels during follow-up. The possibility that rituximab-induced
serious lung infections are more frequent in patients with ILD compared to autoimmune
diseases without significant lung involvement will need to be evaluated further.

**Conclusion**

In a selected group of patients with severe, progressive connective tissue disease associated
ILD resistant to conventional immunosuppressive treatment, rituximab therapy was
associated with significant clinical and functional improvements. Further work is needed to
confirm these findings, delineate the pathways through which B cell ablation may inhibit lung
fibrosis and to evaluate best re-treatment regimens and assess longer term outcomes and
safety concerns.
References


22. Wells AU, Latsi P, McCune WJ. Daily cyclophosphamide for scleroderma: are patients with the most to gain underrepresented in this trial? Am J Respir Crit Care Med. 2007;176:952-3.


Table 1.
Baseline characteristics of patients treated with rituximab, including immunosuppressive therapy in the previous 12 months.

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>HRCT pattern</th>
<th>Year of ILD diagnosis</th>
<th>Serum auto-antibody/CTD features</th>
<th>Pre-rituximab immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymyositis/Dermatomyositis</strong></td>
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</tr>
<tr>
<td>1. 45/M</td>
<td>Organizing Pneumonia/DAD</td>
<td>2009</td>
<td>ENA, anti Ro positive DM on muscle biopsy</td>
<td>IV methylprednisolone</td>
</tr>
<tr>
<td>2. 60/M</td>
<td>Fibrotic NSIP*</td>
<td>2003</td>
<td>anti-Jo 1, myositis</td>
<td>MMF, prednisolone, cyclosporine IV cyclophosphamide</td>
</tr>
<tr>
<td>3. 60/F</td>
<td>Fibrotic NSIP</td>
<td>2000</td>
<td>anti-Jo 1, myositis rheumatoid factor</td>
<td>MMF, prednisolone IV cyclophosphamide</td>
</tr>
<tr>
<td>4. 29/F</td>
<td>Fibrotic NSIP</td>
<td>2009</td>
<td>anti-Jo 1, myositis anti-Ro</td>
<td>MMF, prednisolone IV cyclophosphamide</td>
</tr>
<tr>
<td>5. 51/M</td>
<td>Fibrotic NSIP</td>
<td>2005</td>
<td>anti-Jo 1, myositis</td>
<td>MMF, prednisolone IV cyclophosphamide</td>
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<tr>
<td><strong>Undifferentiated CTD</strong></td>
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<tr>
<td>6. 49/M</td>
<td>Fibrotic NSIP</td>
<td>2006</td>
<td>ANA +++ (speckled) Raynaud’s, GORD</td>
<td>IV cyclophosphamide prednisolone, MMF</td>
</tr>
<tr>
<td>7. 37/F</td>
<td>Organizing Pneumonia/DAD</td>
<td>2009</td>
<td>Rheumatoid factor anti-CCP, anti-Ro</td>
<td>IV methylprednisolone</td>
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<td><strong>Systemic sclerosis</strong></td>
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<tr>
<td>8. 63/M</td>
<td>Fibrotic NSIP</td>
<td>1999</td>
<td>ATA</td>
<td>MMF, prednisolone</td>
</tr>
</tbody>
</table>

DAD= diffuse alveolar damage  
NSIP= non-specific interstitial pneumonia  
MMF= mycophenolate mofetil  
ENA= extractable nuclear antigen  
DM= dermatomyositis  
ANA= anti-nuclear antibody  
GORD= gastro-oesophageal reflux disease  
CCP = cyclic citrullinated peptide  
ATA= anti-topoisomerase antibody  

* Fibrotic NSIP confirmed on surgical lung biopsy
Table 2.
Change in pulmonary function tests and symptoms for individual patients nine to twelve months pre- and post rituximab treatment. Nadir values represent the PFT measurements (or requirement for mechanical ventilation), immediately prior to rituximab administration.

<table>
<thead>
<tr>
<th>Pulmonary function tests</th>
<th>Pre</th>
<th>Nadir</th>
<th>Post</th>
<th>% change post rituximab</th>
<th>Symptoms post rituximab</th>
<th>Categorical response to rituximab</th>
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<tr>
<td><strong>PM/DM</strong></td>
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<tr>
<td>Patient 1</td>
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<tr>
<td></td>
<td>FVC</td>
<td>83%</td>
<td>ventilated</td>
<td>89%</td>
<td>n/a</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>DLco</td>
<td>54%</td>
<td></td>
<td>50%</td>
<td></td>
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<tr>
<td></td>
<td>FVC</td>
<td>57%</td>
<td>54%</td>
<td>51%</td>
<td>+ 2%</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>DLco</td>
<td>32%</td>
<td>27%</td>
<td>33%</td>
<td>+ 19%</td>
<td></td>
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<td>3</td>
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<tr>
<td></td>
<td>FVC</td>
<td>61%</td>
<td>59%</td>
<td>72%</td>
<td>- 2%</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>DLco</td>
<td>26%</td>
<td>22%</td>
<td>31%</td>
<td>- 19%</td>
<td></td>
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<td>4</td>
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<tr>
<td></td>
<td>FVC</td>
<td>n/a</td>
<td>40%</td>
<td>80%</td>
<td>+100%</td>
<td>Improved</td>
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<tr>
<td></td>
<td>DLco</td>
<td>73%</td>
<td>30%</td>
<td>46%</td>
<td>+ 53%</td>
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<td>5</td>
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<tr>
<td></td>
<td>FVC</td>
<td>85%</td>
<td>49%</td>
<td>70%</td>
<td>+ 33%</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>DLco</td>
<td>48%</td>
<td>16%</td>
<td>35%</td>
<td>+ 119%</td>
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<tr>
<td><strong>UCTD</strong></td>
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<tr>
<td></td>
<td>FVC</td>
<td>56%</td>
<td>40%</td>
<td>42%</td>
<td>+ 5%</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>DLco</td>
<td>40%</td>
<td>32%</td>
<td>39%</td>
<td>+ 22%</td>
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<td></td>
<td>FVC</td>
<td>n/a</td>
<td>ventilated</td>
<td>44%</td>
<td>n/a</td>
<td>Improved</td>
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<tr>
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<td>DLco</td>
<td>n/a</td>
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<td>23%</td>
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<tr>
<td><strong>SSc</strong></td>
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<td>FVC</td>
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<td>37%</td>
<td>37%</td>
<td>0%</td>
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<td>24%</td>
<td>22%</td>
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</tr>
</tbody>
</table>

PM/DM = polymyositis/dermatomyositis
UCTD = undifferentiated connective tissue disease
SSc = systemic sclerosis
Figure 1b