# Rituximab for the treatment of systemic sclerosis-interstitial lung disease

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**This editorial refers to 'Rituximab in the treatment of systemic sclerosis related interstitial lung disease: a systematic review and meta-analysis', by Goswami et al.**

Interstitial lung disease (ILD) is a leading cause of disease-related morbidity and mortality in patients with systemic sclerosis (SSc) (1). The majority (~80%) of patients with SSc have evidence of ILD (depending on the method of case ascertainment) and around one-third (25-30%) develop progressive ILD (1). Recently, Nintedanib was approved for management of SSc-ILD, and current therapies have limited efficacy (2). Cyclophosphamide is suggested by expert treatment guidelines and recommendations including those published under the auspices of the British Society of Rheumatology and European Scleroderma Trials and Research (EUSTAR) group (2,3). However, the efficacy of cyclophosphamide is limited, and treatment is often poorly tolerated. Furthermore, there is increasing use of mycophenolate

mofetil (MMF) which has comparable efficacy to cyclophosphamide and is often better tolerated (4). Accordingly, with such a paucity of therapeutic options for SSc-ILD there is significant ongoing international interest (including clinical trials) exploring established e.g. rituximab (RTX) and novel drug therapies (1). There is clear evidence that B-cells play an important (and perhaps) pathogenic role in the pathogenesis of SSc-ILD including through the generation of characteristic autoantibodies e.g. anti-Scl-70 which is associated with a more severe disease course (e.g. ILD) and mortality.

In this issue of *Rheumatology*, Goswami et al (5) conducted a systematic review and meta-analysis which sought to assess the effect of RTX on lung function perimeters in patients with SSc-ILD. The authors identified 20 studies which included 575 patients with SSc and only two of these were randomised controlled trials. RTX was associated with a significant improvement (95% confidence interval) in FVC and DLCO of 4.49% (0.25-8.73) and 3.47% (0.99-5.96) at 6 months, and with similar improvement at 12 months of 7.03% (4.37-9.7) and 4.08% (1.51-6.65) respectively (5). Treatment with RTX compared favourably with other immunosuppressant medication with greater improvement in FVC by 1.03% (95% CI: 0.11-1.94) at 6 months, although this was only based on two studies. Furthermore, patients treated with RTX were less likely to develop infections compared to controls (odds ratio = 0.256, 95% CI: 0.104-0.626) (5).

The study has a number of limitations which the authors highlight in their discussion including the absence of significant RCTs. The number of included studies was small and follow-up duration was limited to one year. The authors could not compare between different RTX treatment regimens and importantly were not able to examine concomitant steroid use. Disease duration varied between the included studies and the authors postulate that drug therapy may be more effective in early disease.

To date, the evidence base for RTX of SSc-ILD is limited; however, controlled clinical trials are ongoing and essential considering that uncontrolled studies in SSc have often overestimated treatment effect both for lung function and skin fibrosis. An initial proof-of-principle study randomised patients with SSc-ILD to receive standard therapy and RTX (375 mg/$m^2$) (n=8) or standard therapy (n=6) alone (6). After one year of treatment, the median improvement in

the RTX treated group was 10.25%, whereas, there was a significant decline (-5.04%) in the patients who received standard treatment (6). A multi-centre, open-label study compared RTX (n=33) and conventional treatment (n=18), the latter of which consisted of azathioprine, methotrexate, and MMF (7). Patients treated with RTX had higher FVC (mean, SD) compared to baseline (80.60 ± 21.21) at 2 years (86.90 ± 20.56) and 7 years (91.60 ± 14.81). Whereas, patients treated with conventional treatment showed no difference in FVC compared to baseline (77.72 ± 18.29) at 2 years (77.72 ± 18.29) and had significantly decreased (61.11 ±15.73) at 7 years (7). Furthermore, in a study from the EUSTAR database, patients (n=9) who received treatment with RTX compared to matched controls prevented worsening lung fibrosis as assessed by decline in FVC (0.4±4.4% vs. -7.7±3.6%, respectively) (8).

The optimal timing for treatment with RTX in SSc-ILD has yet to be fully established (e.g. in early vs. progressive lung disease). Evidence-based consensus statements for the identification and treatment of SSc-ILD have been recently developed through a modified Delphi process by a panel of expert European-based rheumatologists, pulmonologists, and internists (9). Treatment escalation with RTX was recommended as an option when treatment with cyclophosphamide and MMF is not appropriate (10). Narvaez et al (10), reported RTX their experience of RTX as an add-on ('rescue') treatment onto to background therapy with concurrent MMF due to ongoing decline in lung function. The authors included in their analysis 24 patients who were treated with 2 or more cycles of RTX. After one year of treatment with RTX, there was a significant improvement in predicted FVC (+8.8%, 95% CI: -13.7 to -3.9) and predicted DLCO (+4.6%, 95% CI: -8.2 to -0.8) (10). Furthermore, there was a significant reduction in the dose of concurrent prednisolone, and was discontinued in 25% of patients. The optimal role for combination immunosuppressive (including glucocorticoids) and anti-fibrotic therapy is also yet to be defined. However, of note around half (48.4%) of patients enrolled in the randomised controlled (SENSCIS) of nintedanib were receiving treatment with concomitant MMF.

Before we consider incorporating rituximab in our clinical practice, the community needs to consider high-quality double blind randomized controlled trials in SSc-ILD, preferably in both in treatment naïve and those who have failed initial immunomodulatory therapies. With the availability of SLS II, focuSSed, and SENSCIS trials, we have proven trial templates that can be incorporated in design of these trials. In addition, there are ongoing randomised, controlled

trials including the United Kingdom-based RECITAL study (RTX for connective tissue disease-associated ILD including SSc). The optimal time and duration for treatment of RTX for SSc-ILD has yet to be defined including in combination with other immunosuppressive and ant-fibrotic therapies, and for the systemic (disease-modifying) treatment of SSc including skin disease.

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