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Editorial

Rituximab for the treatment of systemic sclerosis-interstitial lung disease

This editorial refers to 'Rituximab in the treatment of systemic sclerosis–related interstitial lung disease: a systematic review and meta-analysis', by Rudra Goswami *et al.*, on pages 557–567.

Interstitial lung disease (ILD) is a leading cause of disease-related morbidity and mortality in patients with 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 for Rheumatology (BSR) 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 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. For example, B-cell infiltration has been described in SSc-ILD lung tissue and generation of SSc-associated autoantibodies e.g. anti-Scl-70 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 that sought to assess the effect of RTX on lung function perimeters in SSc-ILD. The authors identified 20 studies, which included 575 patients with SSc, and only two of these were randomized controlled trials. RTX was associated with a significant improvement (95% CI) from baseline in Forced vital capacity (FVC) and Diffusing capacity for carbon monoxide (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 with controls (odds ratio = 0.256, 95% CI: 0.104, 0.626) [5].

The study has a number of limitations including the absence of significant randomised controlled trials (RCTs) and inclusion of case series/reports and publication bias where positive reports are noted. The two trials were not double blinded. Although FVC is a semi-objective test, known and unknown variables can confound the results, both with safety and efficacy. 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. The history of SSc trials (e.g. d-penicillamine) teaches us that lack of high quality RCTs can lead to false-positive data that may influence practice but are later found to lack efficacy.

An initial proof-of-principle study randomized patients with SSc-ILD to receive standard therapy and RTX (four weekly 375 mg/m^2 infusions) ($n = 8$) at baseline and 24 weeks 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 multicentre, 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 (S.D.)] compared with 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 with baseline [77.72 (18.29)] at 2 years [77.59 (19.45)] and had significantly decreased [61.11 (15.73)] at 7 years [7]. Limitations of this RCT were the small number ($n = 14$) and heterogeneity of the studied patients. Furthermore, in a study from the EUSTAR database, patients ($n = 9$) who received treatment with RTX compared with 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]. Narváez *et al.* [10] reported their experience of RTX as an add-on ('rescue') treatment onto background therapy with concurrent MMF due to ongoing decline in lung function. The authors included in their analysis 24 patients who were treated with two 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, −3.9) and predicted DLCO (+4.6%, 95% CI: −8.2, −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 randomized, controlled trial (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 randomised controlled trials in SSc-ILD, preferably in both 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 the design of these trials [9]. In addition, there are ongoing randomized, 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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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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