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EDITORIAL

B cell depletion in scleroderma lung disease: A promising new treatment?

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Abstract

Evidence suggests that B cells may participate in the fibrotic process Based on this experimental evidence, treatment with rituximab (RTX) has been tried in systemic sclerosis (SSc) with promising results. In a randomized controlled study from our research group it was shown that treatment with 2 courses of RTX leads to a significant improvement of lung function at 1 year compared to baseline. All relevant studies have so far reported clinical and/or histologic improvement of skin fibrosis something that adds further evidence in favor of a disease modifying role of RTX in SSc. It is more than obvious that novel therapies for SSc-associated lung disease are needed. A large scale, randomized, controlled study assessing the efficacy of RTX in SSc associated interstitial lung disease is warranted. If RTX turns out to be effective it would be a major therapeutic advance in SSc since it can be administered on a long term basis due to its acceptable safety profile.

Key words: Rituximab; Scleroderma; Systemic sclerosis; Interstitial lung disease; Treatment

Core tip: Rituximab (RTX) may be an effective treatment for systemic sclerosis (SSc)-associated interstitial lung disease (ILD). A large scale study assessing the efficacy of RTX in SSc associated ILD is warranted. If RTX turns out to be effective, it would be a major therapeutic advance in SSc since it can be administered on a long term basis due to its acceptable safety profile.

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INTRODUCTION

Lung involvement, especially in the form of interstitial lung disease (ILD), is nowadays the leading cause of mortality in patients with systemic sclerosis (SSc). So far, treatment of this fearful complication has been disappointing. Therapy has been relied on intense immunosuppression in the form of cyclophoshamide (CYC). Administration of CYC leads to a modest reduction in the rate of pulmonary function decline but this effect wanes following drug discontinuation. Therefore, continuous treatment is needed; however long term treatment with CYC is not feasible due to its toxicity. It is more than obvious that we need to develop effective, less toxic therapies that can be safely administered over a long time.

A PROMISING NEW TREATMENT

Evidence suggests that B cells may be actively involved in the fibrotic process[1]. B cells are overactivated in both experimental models of fibrosis[2] as well as in humans with SSc[3]. Moreover, treatment with rituximab (RTX), a monoclonal antibody that depletes B cells was effective in

Table 1 All relevant studies have so far reported clinical and/or histologic improvement of skin fibrosis

Study	Participants (*n*)	Evaluation time point (mo)	Clinical assessment skin	Histologic improvement-skin	Lung function tests
Smith *et al*[9]	8	6	Improved	Yes	Stable
Lafyatis *et al*[8]	15	6/12	Stable	Yes	Stable
Bosello *et al*[10]	9	6-36	Improved	Not reported	Stable
Daoussis *et al*[11]	8	12	Improved	Yes	Improved

an animal model of fibrosis[4]. Based on this experimental evidence, RTX has been tried in SSc with promising results. In a randomized controlled study from our research group it was shown that treatment with 2 courses of RTX leads to a significant improvement of lung function at 1 year compared to baseline[5]. Based on this clinical improvement, patients remained on this treatment and received 2 additional courses of RTX. The beneficial effect on lung function was still evident with patients exhibiting an almost linear improvement of lung function parameters throughout the 2 years of treatment[6]. A favorable effect on lung function has also been recently reported by another research group[7]. Of note, patients with SSc associated ILD tend to worsen over time; improvement in lung function tests is something not usually seen within the natural course of the disease.

All relevant studies have so far reported clinical and/or histologic improvement of skin fibrosis, something that adds further evidence in favor of a disease modifying role of RTX in SSc[8-11]. Additional information is provided in Table 1.

So far, we do not know exactly how RTX mediates its beneficial effects in SSc (if indeed this treatment turns out to be effective). Our research group has recently shown that treatment with RTX associates with a significant decrease in platelet derived growth factor (PDGF) receptor expression and activation in the skin[12]. This is an important finding, taking into account the pivotal role of PDGF in fibrosis. Of note, agonistic auto-Abs against PDGF receptor have been found in patients with SSc[13]; one may hypothesize that RTX acts by eliminating these auto-Abs. However, RTX seems to have a broad effect on the immune system, beyond B cell depletion, and therefore other mechanisms may apply.

CONCLUSION

We believe that all efforts should focus on a large scale, randomized, controlled study assessing the efficacy of RTX in SSc associated ILD. Recently, the Rituximab group of EUSTAR reported encouraging results in 72 patients with SSc treated with RTX[14]. Taking into consideration that the beneficial effect of RTX on lung function in our study was evident at 12 mo, following two consecutive treatment courses, we propose that this scheme is the most appropriate if a randomized controlled study is to be performed (*i.e.*, at least 1 year duration, administration of two consecutive RTX courses). Based on the calculations made in the Scleroderma Lung Study[15], at least 160 patients (80 in the RTX group and 80 in the control group) will need to be recruited so that the study can have sufficient statistical power to detect significant differences between groups. If RTX turns out to be effective, it would be a major therapeutic advance in SSc since it can be administered on a long term basis due to its acceptable safety profile.

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