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EDITORIAL

B-cell depletion with rituximab: a promising treatment for diffuse cutaneous systemic sclerosis

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See related research by Bosello *et al.*, http://arthritis-research.com/content/12/2/R54

Abstract

Recent preclinical and clinical studies lend support to the notion that B-cell depletion is a promising therapeutic target in patients with diffuse cutaneous systemic sclerosis. A recent open-label trial provides further evidence showing marked effects of rituximab treatment on skin thickening, functional ability, and disease activity in conjunction with effects on lesional and circulating B cells and on interleukin-6 and BAFF (B-cell activating factor of tumor necrosis factor family). The excellent safety profile of rituximab in this and other trials warrants further well-designed clinical trials in larger patient groups combined with comprehensive biomarker studies.

'No drug should be discarded until it has been tried in systemic sclerosis'. A phrase of this sort can still be found in many textbooks and reviews on systemic sclerosis (SSC), but the time has come to raise our expectations. The study by Bosello and colleagues [1] in this issue of *Arthritis Research & Therapy* provides tantalizing data on the effects of rituximab in nine patients with diffuse cutaneous systemic sclerosis (dcSSc) nonresponsive to cyclophosphamide. A single treatment course induced a consistent and sustained improvement of skin thickening, disease activity, and functional ability, notably in the seven patients with early disease. In those with organ involvement, function remained stable. Retreatment was given in one patient with clinical relapse and pre-emptively in two patients who had rapid reconstitution of B cells. The clinical effects were paralleled by biological effects, including depletion of circulating B cells, and changes in serum levels of interleukin-6 (IL-6) and BAFF (B-cell activating factor of tumor necrosis factor family). IL-6 has a role in fibrogenesis, and the reduction in IL-6 following rituximab treatment may be one of the explanations for the effect on skin fibrosis as found in this and other recent studies. Several cell types produce IL-6, including B cells, macrophages, and stromal cells, and so the effect of rituximab on IL-6 in dcSSc could be due to direct depletion of IL-6-producing B cells or, more likely, indirect effects of B-cell depletion on IL-6 production by stromal cells or macrophages or both.

The study extends the results of other recently published papers reporting clinical benefit of rituximab therapy [2-4]. Together, they confirm earlier predictions that B cells might be an attractive target in SSc [5,6]. What is most striking in these studies is the prospect that this drug has a more favorable risk-to-benefit ratio of treatment when compared with other therapies such as imatinib, cyclophosphamide, or immunoablative therapy and autologous stem cell transplantation. No serious adverse events attributable to rituximab were reported in any of the rituximab studies, and toxicity seemed mild at worst. In contrast, remarkable effects on skin thickening were found in three of the four studies, including a small placebo-controlled, randomized trial [1,3,4]. All three, in contrast to the first published study, in which a single treatment course failed to induce a marked effect on skin thickening [2], involved either optional or preplanned repeat treatment. In one case, repeat treatment was successfully continued at 6-month intervals for 2 years [7]. The one randomized trial and a number of case reports also showed a beneficial effect of rituximab treatment on SSc lung disease [3,8,9].

So what's the price? First, rituximab (and any other biological for that matter) does not come cheap, especially when repeat treatment is necessary. As a result of this and in the absence of consensus or guidelines on the use of biologicals in connective tissue diseases such as SSc, access is problematic in many health care systems. Second, although rituximab is generally well tolerated (as exemplified in the SSc patients treated so far), studies in

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other conditions have suggested an increased, albeit low, risk of progressive multifocal leukoencephalopathy in patients on concomitant or previous immunosuppressive therapy. Of note, numbers of circulating B cells and serum concentrations of IgM dropped significantly in the study by Bosello and colleagues [1], consistent with data in rheumatoid arthritis, but long-term safety data on repeat treatment in SSc are lacking. In the context of the poor prognosis of dcSSc, the risk of infection may be one worth taking in patients with few effective treatment options. Third, rituximab is not effective in all patients and, in one case, reportedly had divergent effects on different disease manifestations [10]. In this patient, rituximab had an effect on myositis, but not on skin thickening. At present, it is not possible to predict which SSc patient will respond to rituximab, as illustrated by the observation that rituximab was also effective in SSc patients whose skin biopsies did not contain detectable B-cell numbers. Whether this points to sampling error or a pathogenetic role of B cells at other sites (for example, lymph nodes) remains to be determined. Clearly, improved prediction models are needed.

The combined results of recent rituximab studies warrant adequately powered clinical trials in larger patient groups to compare safety and efficacy of rituximab versus placebo or rituximab versus conventional therapy (for example, cyclophosphamide, at the moment still the considered the gold standard for severe SSc). Long-term outcome analyses are essential to evaluate feasibility, safety, and efficacy of (repeat) treatment. Criteria for retreatment should be developed once efficacy of a single treatment course has been proven. To understand whether and how rituximab affects the different pathogenetic pathways implicated in SSc, comprehensive biomarker studies should be part of the clinical trial protocol. Such trials require a multicenter, maybe even a multinational, approach and concerted action from specialists, patients, and funding agencies. Any such trial will be costly and complex and demand stamina and creativity to deal with study methodology issues resulting from its low incidence, heterogeneity in clinical presentations, and natural disease course. With a potentially effective and relatively safe drug in hand, however, the time has come to try to break the deadlock in SSc treatment.

Abbreviations

dcSSC, diffuse cutaneous systemic sclerosis; IL-6, interleukin-6; SSc, systemic sclerosis.

Competing interests

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