B cell block: is rituximab a new possible treatment for systemic sclerosis?

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Abstract There is no treatment for fibrotic diseases, including the autoimmune disease systemic sclerosis (scleroderma, SSc). Although broad spectrum immune suppressants have little to no effect on the fibrosis in SSc, agents targeting specific proinflammatory agents are currently being considered as possible therapeutic approaches to combating SSc. B cells are lymphocytes that proliferate and secrete antibody molecules which drive the autoimmune response. CD20 is a B cell marker; the agent rituximab is an antibody against CD20. In a recent report by Bosello and colleagues (*Arthritis Res. Ther.* 12(2): R54, 2010), rituximab was tolerated in SSc patients and appeared to result in an improvement of the skin score and of clinical symptoms of SSc. This report is one of a series of recent studies suggesting that rituximab may be a possible treatment for SSc. This commentary summarizes these observations.

Keywords B cell · Scleroderma · Rituximab · Autoantibody

The disease systemic sclerosis (SSc, scleroderma) is characterized by organ fibrosis, vascular damage and the presence of autoantibodies; in particular the presence of antinuclear antibodies (ANA) (Bunn and Black 1999; Gabrielli et al. 2009). Absolute survival is poor: 78% at 5 years and 55% at 10 years (Mayes et al. 2003). In SSc, antibodies to centromere (ACA) and DNA topoisomerase I (ATA) are especially common; whereas anti-fibrillarin (AFA) and anti-Th ribonucleoprotein (RNP) antibodies are rare. In SSc/polymyositis overlap syndrome, specific anti-

bodies to the exosome are the most common, whereas antibodies against aminoacyl-tRNA synthetases occur infrequently. Taken together at least one of the above mentioned antibodies is found in approximately 75% of SSc patients (Bunn and Black 1999). Moreover, SSc patients often possess antibodies against RNA polymerase (ARA); ARA is associated with diffuse disease with severe skin involvement and with high incidence of renal disease (Kuwana et al. 1993, 1999; Bunn et al. 1998).

Although their presence correlates with disease severity and the risk of specific organ complications, whether autoantibodies have pathogenetic relevance is unclear. In this regard, it is interesting to note that autoantibodies which stimulate the cell-surface platelet derived growth factor receptor have been reported; although the presence, specificity and role of these antibodies remain controversial (Baroni et al. 2006; Classen et al. 2009; Loizos et al. 2009). Broad spectrum immunosuppressants that are effective in other autoimmune disease have not been successful in the treatment of SSc, making the clinical management of this disease very difficult (Del Galdo and Artlett 2006). These results occur possibly because cytokines involved with the immune system can be both profibrotic and antifibrotic, depending on the situation; for example $\text{TNF}\alpha$ and prostacyclins can promote or suppress the fibrotic activity (Abraham et al. 2000; Verrecchia and Mauviel 2004; Leask and Abraham 2004; Stratton and Newton 2010; Stratton and Shiwen 2010).

Only recently has the potential involvement of B cells in the pathogenesis of SSc been fully appreciated (Del Galdo and Artlett 2006; Sato et al. 2004). B-cells produce antibodies that mediate humoral immune response, function as antigen-presenting cells and activate T-cells. Activated B-cells may also produce pro-inflammatory cytokines that aggravate local inflammation. In SSc, B cells show features

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of hyperactivation including overproduction of IgG (Sato et al. 2004). Moreover, a highly up-regulated immunoglobulin and B-cell gene expression signature exists in SSc skin (Whitfield et al. 2003). Thus therapies targeting B cell activation in SSc have a scientific basis.

A series of recent studies used rituximab, an antibody against CD20, to induce effective B-cell depletion in patients, significantly reduce skin score, and improve dermal hyalinised collagen content and dermal myofibroblast numbers (Smith et al. 2010; Bosello et al. 2010). In another study, lung function was improved (Daoussis et al. 2010). That said, another study could find no benefit to rituximab treatment (Lafyatis et al. 2009). Rituximab was considered to be well-tolerated (Lafyatis et al. 2009; Daoussis et al. 2010; Smith et al. 2010; Bosello et al. 2010).

Although these open-label studies are all limited by small numbers of patients where the subjects nor the investigators are blinded (Lafyatis et al. 2009; Daoussis et al. 2010; Smith et al. 2010; Bosello et al. 2010), these reports support the notions that B-cell depletion in SSc has a potential therapeutic benefit, and that B cells, possibly through production of autoantibodies, have an important role in the pathogenesis of scleroderma. Clearly, however, prior to recommending that patients with SSc receive rituximab, these findings will have to be confirmed by a larger multicenter, randomized controlled trials. Nonetheless, they do suggest that B-cell depletion in SSc may have therapeutic potential.

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