Is There a Role for B-cell Depletion as Therapy for Scleroderma? A Case Report and Review of the Literature

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Objectives: Rituximab (RTX) has been successfully used in the treatment of several rheumatic diseases with an acceptable safety profile. We present herein a patient with systemic sclerosis (SSc) who exhibited significant improvement of his lung function and skin fibrosis following RTX administration, and review the literature regarding the role of B-cells in SSc and the potential efficacy of RTX in its treatment.

Methods: We performed an internet search using the keywords systemic sclerosis, scleroderma, rituximab, B-cells, fibrosis, interstitial lung disease (ILD), and therapy.

Results: Our patient, a 40-year old man with severe SSc-associated ILD, received 4 courses of RTX. The patient's lung function improved; forced vital capacity and diffusing capacity of carbon monoxide reached values of 35% and 33%, respectively, compared with 30% and 14% of pretreatment values. Skin thickening assessed clinically and histologically improved as well. Several lines of evidence suggest that B-cells may have a pathogenic role in SSc. B-cells from tight skin mice—an animal model of SSc—exhibit chronic hyperactivity; likewise, B-cells from patients with SSc overexpress CD19 and are chronically activated. Furthermore, studies have revealed that B-cell genes were specifically transcribed in SSc skin and that B-cell infiltration was a prominent feature of SSc-associated ILD. The potential clinical efficacy of RTX in SSc has been explored in a limited number of patients with encouraging results. Preliminary data suggest that RTX may favorably affect skin as well as lung disease in SSc.

Conclusions: Several basic research data underscore the potential pathogenic role of B-cells in SSc and clinical evidence suggests that RTX might be a therapeutic option in SSc. Large-scale multicenter studies are needed to evaluate the potential clinical efficacy of RTX in SSc.

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Keywords: *systemic sclerosis, scleroderma, rituximab, B-cells, fibrosis, ILD, therapy*

Systemic sclerosis (SSc) is a debilitating systemic rheumatic disease characterized by vasculopathy, skin and internal organ fibrosis, and autoimmunity. Rituximab (RTX) is a monoclonal antibody (mAb) against human CD20 that causes B-cell depletion and has been successfully used in the treatment of a variety of systemic autoimmune diseases. Several lines of evidence from basic research studies suggest that B-cells might play a role in the pathogenesis of SSc (1,2). We and others have recently explored the potential clinical efficacy of RTX in SSc with encouraging results (3-5). We report herein improvement of seriously deteriorating lung function and skin thickening in a patient with longstanding diffuse SSc with 4 consecutive courses of RTX every 6 months. We also provide an extensive review of the literature.

METHODS

PubMed, EMBASE, and congress conference proceedings were used for the literature search from 1995 onward. The search was limited to publications in English and the

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Abbreviations	
autoAb	Autoantibodies
BAFF/BAFFR	B-cell activating factor/BAFF receptor
BLM	Bleomycin
CAD	Computer-aided diagnosis
CYC	Cyclophosphamide
DLco	Diffusing capacity of carbon monoxide
FVC	Forced vital capacity
GVHD	Graft versus host disease
HAQ	Health Assessment Questionnaire
HRCT	High-resolution computed tomography
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
mAb	Monoclonal antibody
mRSS	Modified Rodnan skin score
MMP	Metalloproteinase
NYHA	New York Heart Association
PDGF/PDGFR	Platelet-derived growth factor/PDGF receptor
ROS	Reactive oxygen species
RTX	Rituximab
SSc	Systemic sclerosis
TSK	Tight skin mouse
WT	Wild type
6MWD	6-minute walking distance

keywords used were as follows: systemic sclerosis, scleroderma, rituximab, B-cells, fibrosis, interstitial lung disease, and therapy in various combinations. The computerized search was completed with a manual search of reference lists from the articles retrieved.

RESULTS

Case Report

The patient, a 40-year old man, was diagnosed with diffuse SSc in 1993; interstitial lung disease (ILD) was evident with reduced forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLco) values (60% and 70% of predicted, respectively). He gradually developed dyspnea on exertion (New York Heart Association [NYHA] class II) and his lung function tests declined (55% and 41% for FVC and DLco, 3 years after presentation). He received cyclophosphomide (CYC) pulse therapy for 2 years (1996-1998) with improvement of his respiratory symptoms and stabilization of lung function tests. In 2001 his lung function tests declined further (39% and 36% for FVC and DLco) and CYC pulse therapy was administered again (the total cumulative dose of CYC was 30 g). His lung function tests were stable with an FVC of 38% and a DLco of 35% and his modified Rodnan skin score (mRSS) was 20; at that time he had to stop working due to dyspnea. In 2004, he deteriorated further with dyspnea (NYHA class III-IV), an FVC of 32%, and a DLco of 26%. He was then started on mycophenolate mofetil (2 g/d); this treatment resulted in a modest improvement of his dyspnea (NYHA class III) and stabilization of his FVC and DLco.

In October 2006, the patient started complaining of severe dyspnea (NYHA class III-IV) and had an FVC of 32% and a DLco of 18%. At that time he declined further treatment with CYC. In June 2007, his condition had worsened further: FVC was 30%; DLco was 14%; oxygen saturation was 90%; mRSS was 20; Health Assessment Questionnaire (HAQ) score was 2, and the 6-minute walking distance (6MWD) was 400 m. High-resolution computed tomography (HRCT) scan revealed extensive honeycombing with accompanying ground glass lesions.

At that point, the patient agreed to receive RTX infusions. After written informed consent and approval by the local ethics committee, he received 4 weekly infusions of RTX (375 mg/m^2) while his baseline therapy with mycophenolate mofetil remained unchanged. A biopsy of lesional skin of the forearm was obtained before RTX administration.

In January 2008, 6 months after RTX administration, the patient was fully reevaluated. His general status had significantly improved with a HAQ score of 1.5 and no dyspnea at rest (NYHA III). The 6MWD had increased to 450 m, oxygen saturation to 91%, FVC to 33%, and DLco to 22%; mRSS decreased to 14. A second skin biopsy was obtained at that time from lesional skin of the forearm. Based on these encouraging results, we decided to offer the patient a second course of RTX in January 2008.

In July 2008, 1 year after the first RTX course and 6 months after the second, he was generally feeling much better with a HAQ score of 1.250. His dyspnea (class II) had improved significantly and he was able to help in his brother's grocery shop. The 6MWD had increased to 475 m, oxygen saturation to 92%, FVC to 34%, and DLco to 27%; mRSS had declined to 10. The patient received a third course of RTX in July 2008 and was evaluated in January 2009, 18 months after the first RTX course. He was comfortable with moderate exertion (NYHA class II) and the HAQ score was 1.0. The 6MWD had increased to 500 m, oxygen saturation to 93%, FVC to 35%, and DLco to 33%. The mRSS was stable at 9 and a third skin biopsy was obtained. Based on his good clinical response a fourth RTX course was administered. He was last seen in June 2009 in good clinical condition and is being currently fully reevaluated.

The improvement of lung function tests, oxygen saturation, 6MWD, and skin score following RTX administration in our patient is shown in Figure 1. Histologic analysis revealed a significant reduction in collagen deposition in the papillary dermis at 18 months compared with the baseline biopsy; this reduction was already evident but less prominent at 6 months. Computerized image analysis, used to quantify collagen deposition, showed a clear-cut decrease (53.2 ± 9.5, 32.7 ± 7.9, and 19.3 ± 4.1 at baseline, 6 months, and 18 months, respectively). Immunohistochemical analysis showed a gradual decrease in the myofibroblast score in the papillary dermis at 6 and 18 months (49.4 ± 2.1,