

Letter

Upfront Combination Therapy With Rituximab and Mycophenolate Mofetil for Progressive Systemic Sclerosis

To the Editor:

Systemic sclerosis (SSc) is a complex disease involving multiple pathophysiological pathways: autoimmunity, vasculopathy, and fibrosis, all of which are interrelated. Most of the damage consists of skin and lung fibrosis, and is accumulated within the first 2 years of disease in rapidly progressive patients with a serology of anti-SCL-70 or anti-RNA polymerase III (RNAP3)¹. Indeed, this group of patients carry a great risk of morbidity and excess mortality. A combination “induction” therapy at an early stage—a window of opportunity—in which it is still possible to change the course of disease in this group of patients, is logical. We report herein our recent experience with early upfront combination therapy for progressive SSc, directed at different aspects of disease: iloprost for treating vasculopathy, rituximab (RTX) for blocking B cells, and mycophenolate mofetil (MMF) for inhibiting T cells.

Until recently, the gold standard therapy for diffuse SSc with lung involvement was cyclophosphamide (CYC), which was evaluated in the Scleroderma Lung Study (SLS) I². Unfortunately, this treatment resulted only in a modest initial beneficial effect on lung function, dyspnea, thickening of the skin, and a health-related quality of life that was not evident after 24 months. After 11 years, there was no difference in mortality between therapy and placebo (> 70% mortality)³. MMF soon replaced CYC as a safer and more tolerable drug; alas, in the SLS II study the hypothesis that it would have greater efficacy at 24 months than CYC was not confirmed⁴. Thus, current gold standard therapies have a marginal effect on skin and lung disease and do not improve mortality. In the past decade, combination therapies have been reported as a promising treatment option for SSc. Autologous stem cell transplantation is the most powerful “combination therapy” and has been found efficacious in 3 controlled clinical trials^{5,6,7}, but in many cases, the patient’s preferences, along with cardiac disease, cost, and availability may preclude this treatment option.

In our present study, we concluded a 1-year follow-up of 10 SSc patients (6 women and 4 men) with either a modified Rodnan skin score (mRSS) > 15 progressing within 6 months from diagnosis and/or lung involvement with diffusing lung capacity for carbon monoxide (DLCO) or forced vital capacity (FVC) < 70% predicted. The mean age was 44 ± 12 years. Five patients had SCL-70 antibodies and 5 had RNAP3 antibodies. All patients received upfront combination therapy of RTX 2000 mg every 6 months, MMF 2000 mg daily, and iloprost 50 µg weekly. One patient received additional intravenous (IV) Ig. Seven of the 10 patients had lung fibrosis, 5 patients had nonspecific interstitial pneumonia pattern, 1 patient had a usual interstitial pneumonia pattern, and 1 had organizing pneumonia. The other 3 patients had ground glass opacities. All patients had an mRSS assessment by 1 experienced assessor, a computed tomography (CT) scan, and pulmonary function tests at base line and at 1 year. The extent of fibrosing alveolitis was quantified as described previously⁸. The mRSS reduced from 23.6 ± 14.5 to 9 ± 7.9 ($P = 0.01$) over 12 months (Figure 1). Lung fibrosis as evaluated on CT scans reduced from 20.8% ± 23.4% to 10.5% ± 16.4% ($P = 0.01$; Figure 2). FVC improved from 66.4% ± 17.3% predicted to 72.8% ± 17.01% predicted ($P = 0.14$). DLCO improved from 58.1% ± 19% predicted to 63.2% ± 19.2% predicted ($P = 0.43$). There were no severe infections requiring IV antibiotics. One patient developed breast carcinoma. There were no deaths. These results are in line with 1 former report of upfront combination therapy with MMF and RTX⁹. Several studies are currently evaluating other combination therapies such as MMF and pirfenidone (SLS III; ClinicalTrials.gov NCT03221257), or RTX and belimumab¹⁰.

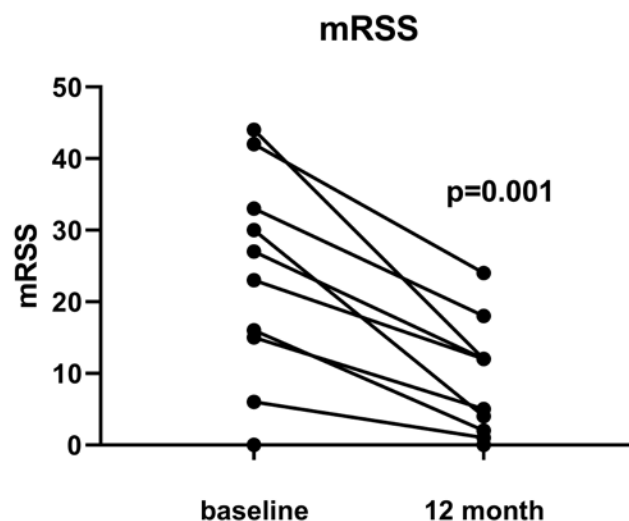


Figure 1. The modified Rodnan Skin Score (mRSS) over 12 months.

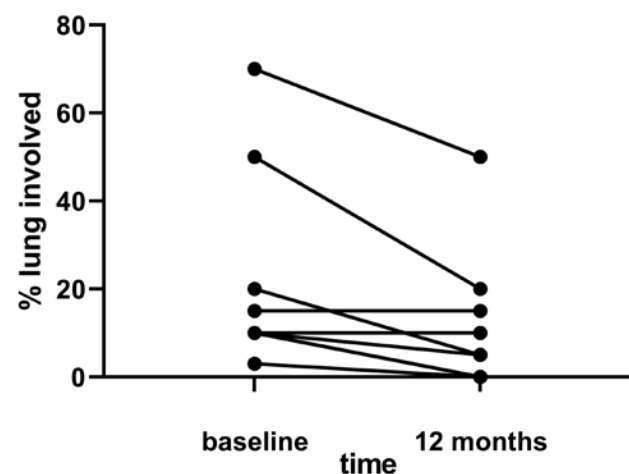


Figure 2. Lung fibrosis as evaluated on computed tomography scans over 12 months.

These preliminary results suggest that early upfront combination therapy in rapidly progressive SSc patients is safe and efficacious treatment option. Further randomized controlled studies are needed to validate these results, possibly with an addition of an antifibrotic agent to the regimen.

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This study has been approved by the Bnai-Zion ethics committee (ethics board approval number BZ-20-0073). Informed consent was obtained from all recruited patients.

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