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Treating skin and lung fibrosis in systemic sclerosis: a future filled with promise?

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Systemic sclerosis (SSc) is a rare autoimmune disorder characterized by immune activation, vascular damage and an excessive accumulation of extracellular matrix proteins in the skin and internal organs. Despite its high morbidity and increased mortality, currently available treatment options for fibrotic manifestations of SSc remain limited and their clinical antifibrotic effects are borderline. In this review, novel insights from recently published clinical trials in SSc on treatment concepts such as mycophenolate mofetil, oral type I collagen, recombinant human relaxin and autologous hematopoietic stem cell transplantation are discussed. In the past decade the most significant progress in this field has been made by the identification of a large number of cellular and molecular key players in the pathogenesis of fibrotic disease manifestations. This has led to the identification of novel candidates as molecular targets for treatment of fibrotic diseases. On the basis of their level of evidence from preclinical studies and based on the availability of first clinical results, the most promising targets are presented including inhibitors of B-cells, tyrosine kinases, 5-hydroxytryptamin receptors, interleukin-6 and Wnt signalling.

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Introduction

Systemic sclerosis (SSc) is an autoimmune disorder of unknown etiology in which microangiopathy and subsequently fibrosis affects the skin and eventually multiple internal organs. Two major subsets exist: limited and diffuse systemic sclerosis. In the limited form, skin fibrosis is restricted distal to the elbows and knees, and the face. Raynaud's phenomenon is often present several years before fibrosis appears, pulmonary hypertension is frequent and anti-centromere antibodies are characteristic. The diffuse form is characterized by antibodies against topoisomerase I and RNA polymerase III, is more rapidly progressing, affects larger areas of the skin, especially proximal limbs or trunk, and compromises internal organs in an earlier phase of the disease [1].

The pathogenesis of SSc is complex and not entirely understood. Vascular damage leading to obliterative vasculopathy and capillary rarefication, perivascular inflammatory infiltrates and autoimmune activation with production of autoantibodies may be the basis for an uncontrolled, chronic overexpression of profibrotic cytokines and chemokines. Beyond immune activation and vascular damage, an excessive production and accumulation of collagen by activated fibroblasts (myofibroblasts) in the skin and internal organs is among the hallmarks for systemic sclerosis [1].

This review will focus on two of the most severe fibrotic complications of the disease: skin fibrosis and interstitial lung disease (ILD). Pulmonary manifestations including ILD account for more than 60% of SSc-related mortality [2]. Skin fibrosis is a major contributor to disease related morbidity, and rapid, progressive skin involvement predicts later mortality [3]. Despite its morbidity and mortality, currently available treatment options for fibrotic manifestations of SSc remain limited and clinical effects are of questionable significance (Table 1; see also [4•] for details). However, on the basis of the identification of cellular and molecular profibrotic key players, significant progress has been achieved in the past decade unraveling new potential targets for treatment [5]. Herein, we will discuss (a) novel insights from randomized controlled clinical trials (RCTs) on existing treatment concepts, and (b) the most promising molecular targets for therapy based on their level of evidence from preclinical studies.

Novel insights in existing treatment concepts for skin and lung fibrosis

Mycophenolate Mofetil (MMF)

MMF is a pro-drug of mycophenolacid, an inhibitor of inosine monophosphate dehydrogenase, thereby inhibiting de novo synthesis of purine and suppressing T-lymphocyte and B-lymphocyte proliferation [10]. At present, MMF is licensed in combination with cyclosporine and corticosteroids in prophylaxis of renal, cardiac and hepatic transplant rejection. It is also widely used off label in systemic lupus erythematosus particularly in treatment of lupus nephritis.

Table 1

EULAR/EUSTAR treatment recommendations for skin and lung fibrosis in SSc [4•].

Treatment indication	Recommended immunosuppressant	RCT trial references
Skin fibrosis in early diffuse SSc	Methotrexate 'may be considered'	[6,7]
SSc-ILD	Cyclophosphamide 'should be considered'	[8,9••]

Regarding diffuse systemic sclerosis, a large retrospective cohort study showed a lower frequency of clinically significant pulmonary fibrosis in the MMF-treated group than in the control group ($p = 0.037$) and a significantly better 5 year survival from disease onset and from beginning of treatment ($p = 0.027$ and $p = 0.012$ respectively) [11]. Notably, the control group included patients with other immunosuppressive and potentially anti-fibrotic treatments such as azathioprine, intravenous or oral cyclophosphamide, methotrexate, D-penicillamine, anti-thymocyte globulin and α-interferon. The skin improved similarly in both cohorts over five years. MMF was overall well tolerated in this retrospective observational cohort.

There is further evidence for a potential efficacy of MMF from a recently published large retrospective cohort study using a historical control group design [12•]. In SSc patients with diffuse and active skin fibrosis, statistically significant benefit on the modified Rodnan skin score (mRSS) as a measure of skin fibrosis was seen at 12-months follow-up compared to a pooled historical control group from previous RCTs. Furthermore, another smaller, but prospective, observational study without a control group suggested an improvement of skin fibrosis under MMF treatment over time when compared to baseline [12•].

It is, however, difficult to draw definite conclusions on the antifibrotic efficacy from these trials, especially in the light of the natural course of the disease often showing spontaneous improvement of the mRSS [13]. Therefore, these promising results need to be proven by prospective, randomized controlled trials. There is currently a prospective, randomized, double-blind phase 2 study for SSc-ILD recruiting (scleroderma lung study II, SLS II), which compares the safety and efficacy of a 2-year treatment with MMF in one arm versus 1-year treatment with cyclophosphamide followed by placebo in the other arm (www.clinicaltrial.gov).

Oral type I collagen

The potential mechanisms of oral type I collagen CI is based on inducing immune tolerance, as a variety of autoantigens have been identified in patients with SSc, including type I collagen, which is the most abundant protein in the body.

A prospective, randomized, double-blind placebo-controlled trial was performed with 168 diffuse SSc patients using the mRSS as the primary endpoint. The study was exceptional from other RCTs in SSc in that also patients with longer disease duration of up to 10 years could be included. There was no difference in the mRSS after 12 months between treated and placebo patients, thus the primary endpoint was not met. However, a sub-analysis showed a statistical significant improvement of the mRSS in patients with late-phase diffuse systemic sclerosis [14], which warrants further investigation.

Recombinant human relaxin

Relaxin is a naturally occurring protein produced primarily by the ovary and/or placenta in pregnancy and by the prostate of mammals. It has an antifibrotic effect in down-regulating collagen production and increasing collagen degradation.

After promising phase I and II trials, a two-dose, phase III RCT was recently published, which failed to show significant benefits of relaxin over placebo on mRSS or functional disability [15,16]. Additionally, withdrawal of relaxin led to abrupt appearance of severe hypertension and renal impairment including acute renal crisis in a disproportionate number of the patients [15].

Bosentan

Preclinical *in vitro* and to a lesser extent also *in vivo* data convincingly support a pro-fibrotic role of endothelin 1 in SSc. Bosentan is a nonselective, dual endothelin receptor antagonist, which is established in treating PAH and in preventing digital ulcers in SSc patients.

On the basis of the preclinical antifibrotic data, RCTs for both idiopathic pulmonary fibrosis and SSc-related ILD were conducted [17,18]. Both trials failed to meet their primary endpoints. The SSc-ILD study was designed as prospective, double-blind, randomized, placebo-controlled, parallel group study with inclusion criteria aiming at enriching for active and progressive lung disease. Over 12 months, no differences were observed between placebo and bosentan, both in the primary endpoint (change in 6-minute walk distance), and the secondary endpoints (time do death and worsening of pulmonary function tests) [18]. Despite the enrichment strategy, pulmonary function tests were stable in 74–77% of the patients, underlining the relatively slow rate of progression of SSc-ILD.