

RECENT ADVANCEMENTS ON THE TREATMENT OF SYSTEMIC SCLEROSIS: A REVIEW

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Abstract

Systemic sclerosis (SSc) is a systemic autoimmune disease in which autoimmune damage, vasculopathy and extensive fibrosis are considered to be the key etiopathogenic factors¹. The choice and evaluation of any treatment regimen for SSc is challenging because the disease is complex, and its pathogenesis is poorly understood. No SSc therapy to date has been proved to be effective in altering the natural history of the disease and this disease carries the highest case fatality among the connective tissue diseases².

Substantial changes have occurred in the last decade, with the appearance of new therapeutic targets and the consequent development of highly selective drugs, some of which, such as endothelin antagonists, are now widely used and others, such as tyrosine kinase inhibitors, which had shown good promise in some studies.

Currently, therapeutic approaches are also changing. Monotherapy is giving way to combined therapy, considering different etiopathogenic mechanisms might play different roles at the various stages of the disease, showing the possibility of sequential use of different drugs at different stage. So, it seems the paradigm is shifting in therapeutic approach of SSc³.

Introduction

Systemic sclerosis (SSc) is a multisystem connective tissue disease of unknown etiology that occurs more commonly in women, follows a chronic course, and is highly heterogeneous in its protean clinical manifestations. The hallmarks of SSc are autoimmunity and inflammation, functional and structural abnormalities in small blood vessels in multiple vascular beds, and progressive interstitial and vascular fibrosis in the skin and internal organs². Despite recent etiopathogenetic advances, it continues to be one of the most complex systemic autoimmune diseases in terms of its therapeutic management.

One of the main problems in reviewing therapies for SSc and offering solid therapeutic recommendations is the limited amount of available evidence. Randomized controlled trials, which are considered to be the 'gold standard' in

clinical investigation for assessing the efficacy and safety of new treatments, are scarce in SSc³. Still we need to consider available evidences for better decision making. This review will discuss targeted therapy according to specific pathophysiology.

1. Immune disturbance

Immunosuppressive agents:

Immunosuppressive agents should not be considered a targeted therapy for SSc as their effects are nonselective and has poor evidence on the efficacy. Nonetheless, immunosuppressive agents are frequently used to treat SSc^{4,5}. For example, cyclophosphamide and azathioprine are most commonly used to treat ILD caused by SSc⁶ and few trials also suggest the possible role of methotrexate in cutaneous SSc^{7,8}.

Combined cyclophosphamide and high-dose corticosteroids enhance the positive results than cyclophosphamide used alone. A meta-analysis⁹ showed that two of the three greatest improvements were achieved in studies that used high-dose corticosteroids^{10,11} and another uncontrolled study on the combined intravenous pulse methylprednisolone and cyclophosphamide has shown stabilization or improvement in pulmonary function in two-thirds of patients¹².

The latest immunosuppressive agent on trial is Mycophenolate mofetil. To date, four uncontrolled studies of mycophenolate mofetil (N = 50), have found a similar benefit to cyclophosphamide, with no marked adverse events

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and follow-up for as long as 24 months makes it a better option over cyclophosphamide¹³⁻¹⁶.

Biologic Agents

Tumor necrosis factor (TNF), though shows promising results in many rheumatological diseases, one study shows no clear benefit¹⁷, rather it has some serious side effects like anti-TNF-induced ILD in more than 100 reported cases¹⁸.

B-cell depletion with rituximab, however, may be a good therapeutic approach. But for limited cases, interpretation has become somewhat difficult. In one study, two fortnightly intravenous rituximab was given in 15 patients without any benefit regarding reduction of the SSc-associated autoantibody level and also any effects on skin disease¹⁹. In contrast, another study with 8 patients found considerable improvements in skin scores and histological skin parameters at 24 weeks²⁰.

The latest immunosuppressive target in SSc is B-cell activating factor (BAFF), a cytokine of the TNF ligand superfamily and an essential growth factor for B cells²¹. Recent experimental studies have suggested that BAFF blockade is a potential therapeutic approach in SSc^{22,23}.

Stem Cell Transplantation:

Although cyclophosphamide was recently observed to have a small beneficial effect, more effective therapies for the severe forms of SSc are required to improve outcome²⁴. Two studies conducted in 2008 in the US and the Netherlands used a protocol based on high-dose cyclophosphamide with autologous grafts and CD34 selection in a total 53 patients with SSc^{25,26}. Patients in the US study also underwent total body irradiation and antithymocyte globulin therapy. After a mean follow-up of 5 years, Kaplan-Meier survival was 85% and event-free survival, defined as survival without SSc relapse or progression, was 57-64%.

Mortality associated with autologous HSCT has fallen over time, from 17% in the first cohort of 41 patients with SSc from the European registry to 9% in a subsequent analysis extended to 65 patients²⁶.

2. Vasculopathy

Prostacyclin analogs:

The main indication for prostacyclin analog therapy in SSc is a severe vascular complication, with epoprostenol being used predominantly in PAH and iloprost in complicated Raynaud phenomenon. Intravenous epoprostenol was approved for the treatment of severe PAH following successful trials in patients with idiopathic PAH^{27,28}. In SSc, one randomized controlled trial found that continuous epoprostenol infusions improved exercise capacity, functional class and hemodynamic measures²⁹. The high number of adverse events, however, together with the problems inherent in continuous intravenous administration, mean that epoprostenol should be limited to patients with SSc and PAH who are refractory to other treatments³⁰.

The AIR (Asthma Intervention Research) trial studied the

effects of inhaled iloprost in 203 patients with PAH (35 with systemic autoimmune disease), and found significant improvements in the treatment group compared with placebo controls³¹. To date, there have been no specific controlled studies on the efficacy of inhaled iloprost in SSc³¹. In one trial of SSc-related Raynaud phenomenon, intravenous iloprost therapy resulted in a marked reduction of digital ulcers and considerable improvements in digital ulcer healing in comparison with placebo⁴⁴. In two other randomized controlled trials, however, improvements in Raynaud phenomenon were only slightly better with iloprost compared with nifedipine^{32,33}.

Endothelin Antagonists:

Bosentan, an oral antagonist of endothelin receptor subtypes A and B³⁴, the drug for which the most clinical experience is available.

RAPIDS-1 and RAPIDS-2 (RANdomized Placebo-controlled Investigation of Digital ulcers in Scleroderma) trials have shown positive results for the treatment of digital ulcers. RAPIDS-1 demonstrated that bosentan could reduce the number of new digital ulcers (DUs)³⁵. Another trial, RAPIDS-2, built upon the findings of RAPIDS-1 and examined the effects of bosentan treatment on a designated cardinal ulcer. The results were similar to the RAPIDS-1 study³⁶, but bosentan was not associated with improved healing of existing active ulcers.

The BUILD-2 (Bosentan in Interstitial Lung Disease in Systemic Sclerosis 2) trial compared the effects of bosentan with those of placebo on clinical outcomes of patients with SSc with ILD. It was designed to select patients with progressive disease. The study found no differences in effect on 6-minute

walk distance (6MWD) and no effect on key secondary outcomes, including forced vital capacity (FVC) and carbon dioxide diffusing capacity of lungs (DLco), and time to desaturation³⁷.

Sitaxsentan is an endothelin antagonist with high selectivity for the endothelin-A receptor. The agent was shown to have similar benefits to bosentan in two randomized controlled trials of patients with pulmonary arterial hypertension (PAH)^{38,39}.

Phosphodiesterase type-5 inhibitor:

Sildenafil is a selective phosphodiesterase type-5 inhibitor which acts in the nitric-oxide-mediated vasodilation pathway. Two randomized controlled trials have shown that sildenafil improved exercise capacity, functional class, mean pulmonary artery pressure and pulmonary vascular reserve in patients with PAH^{40,41}.

3. Fibrosis

The development of selective therapies blocking fibrotic pathways is currently considered to be one of the most promising novel therapeutic approaches in SSc.

Tyrosine Kinase Inhibitors:

Imatinib is a tyrosine kinase inhibitor. It exerts its antifibrotic effect by blocking activation of SMAD1 and early growth response protein 1, and also by blocking TGF- β -dependent upregulation of type I collagen gene protein 142-44. Experimental studies on animals have shown that it can prevent the development of fibrosis^{45,46}. It is also effective in fibrosing conditions, such as chronic graft-versus-host disease, nephrogenic systemic fibrosis and localized scleroderma⁴⁷⁻⁵².

The first reports of the use of imatinib mesylate, with or without cyclophosphamide, in patients with diffuse SSc, are waiting⁵³⁻⁵⁶. In addition, six trials of imatinib and one of dasatinib for the treatment of fibrosis in patients with SSc are ongoing³.

Anti-TGF- β therapies:

As fibrosis is associated with fibroblast activation mediated by transforming growth factor β ; therefore, blocking TGF- β signaling pathways is a rational approach to antifibrotic therapy. Some non-biological agents have antifibrotic effects by inhibiting TGF- β ¹ production are currently being evaluated as a possible therapeutic option, these are: losartan, statins, rosiglitazone, pioglitazone, imatinib mesylate and related kinase inhibitors (dasatinib, nilotinib), tranilast (approved in Japan), and paclitaxel. A Randomized controlled trial on the use of atorvastatin in SSc has shown that mean number of new digital ulcers per patient in the statin group was considerably lower than in the placebo group. It also shows the considerable improvement of severity and pain of digital ulcers and overall disability⁵⁷. But small sample size and cross-sectional design of this study has made its authenticity limited.

PDGF, CCN2 and HDAC blockade:

Studies conducted in the mid-2000s have investigated the blockade of other molecules involved in the progression of fibrosis in SSc. The enhanced expression of PDGF and its receptors in the skin and lung tissue of patients with SSc suggests that PDGF blockade could be a potential therapeutic target⁵⁸, although the results of experimental studies on the effect of PDGF receptor-stimulating autoantibodies on fibrosis have been inconsistent^{59,60}.

CCN2 is also overexpressed in SSc and has recently been shown to have a profibrotic effect in lung fibrosis⁶¹. Silencing CCN2 gene expression or antagonism of CCN2 activity might, therefore, be potential approaches for preventing the progression of fibrosis in SSc⁶².

HDAC-7 inhibition is another potential antifibrotic therapy in SSc. A recent study found that HDAC-7 gene silencing using small-interfering RNA was associated with a significant reduction in cytokine-induced transcription of type I collagen and fibronectin in skin fibroblasts from patients with SSc⁶³.

4. The antioxidant pathway

An oxidant-antioxidant imbalance has been suggested as another etiopathogenic mechanism in SSc, especially in the development of pulmonary fibrosis⁶⁴, and drugs with antioxidant effects have been tested in SSc.

More interest has been shown in N-acetylcysteine, a precursor of the antioxidant glutathione, which has been shown to restore depleted pulmonary glutathione levels in patients with fibrosing alveolitis⁶⁵. There are no controlled trials of N-acetylcysteine in patients with SSc, the almost complete lack of toxicity of the agent makes it an attractive adjuvant treatment for ILD. Furthermore, an observational study of the use of intravenous N-acetylcysteine in patients with SSc and Raynaud phenomenon or digital vasculopathy has shown promising results⁶⁶.

Relaxin

Relaxin is a pregnancy-related hormone that has tissue remodeling and antifibrotic effects owing to its ability to increase degradation of the extracellular matrix⁶⁷. Experimental studies have shown a progression of dermal fibrosis and thickening in a relaxin-gene knockout mouse⁶⁸, and relaxin levels are higher in patients with SSc than controls⁶⁹. In 2000, a phase I/II trial in 68 patients with SSc found that the administration of recombinant human relaxin was associated with reduced skin thickening and improved function⁷⁰. In a more-recent phase III randomized controlled trial in 239 patients with SSc, however, the agent was ineffective and resulted in severe side effects (renal failure, severe hypertension) when it was discontinued⁷¹. These results clearly restrict the rationale for future trials based on this molecule.

The changing paradigm in therapeutic approach

Currently, monotherapy is giving way to combined therapy, as many consider that the simultaneous blockade of a number of pathways might produce better and longer-lasting results. Recent examples of this shifting paradigm are studies combining prostacyclin analogs with endothelin antagonists or phosphodiesterase inhibitors⁷²⁻⁷⁴, endothelin antagonists with phosphodiesterase inhibitors⁷⁵, imatinib and cyclophosphamide, and even triple therapy with bosentan, iloprost and sildenafil⁷⁶. Another possible approach focuses on the potential synergy of combining non-disease-specific drugs with a good safety profile, such as N-acetylcysteine and statins, and highly-specific agents such as prostanoids, endothelin antagonists or phosphodiesterase inhibitors.

Different etiopathogenic mechanisms might play different roles at the various stages of SSc⁷⁷, which could open the way to sequential use of different drugs. Autoimmune mechanisms involved in the inflammatory response predominate in the early stages of SSc, suggesting that immunosuppressive therapy might be more helpful during this period. By contrast, the immune system probably plays a lesser role in more-advanced stages SSc, with fibrogenesis and vasculopathy being the main etiopathogenic scenarios. This hypothesis is an argument for a better prognostic

classification, and the development of markers that would help to quantify the specific impact of each of the main pathways in a given patient at a given time during the course of their disease³.

Conclusion

The long-term outcome of SSc is a major concern at the time of diagnosis. There was substantial improvement in the mortality in last 25 years, and more recent analysis indicates greater than 80% 5-year survival². Still, it is a grievous disease with life threatening complications. We should attempt to follow the advances that have been made in other rheumatic autoimmune diseases which have led to increasingly disease-specific therapies targeting distinctive biological pathways.

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