



# Systemic sclerosis (scleroderma): remaining challenges

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**Abstract:** Despite progress in treating internal organ involvement in systemic sclerosis (scleroderma) (SSc), such as pulmonary disease, effective treatments for the hallmark of the disease, cutaneous fibrosis, remain elusive. None of the disease-modifying antirheumatic drugs (DMARDs) have shown proven efficacy for SSc skin fibrosis, and there remain no FDA-approved medications, all of which are off-label, for cutaneous fibrosis in SSc. This review article will briefly summarize conventional therapies, biologics and hematopoietic stem cell transplants and select ongoing clinical trials in SSc. The gold standard for measuring skin fibrosis in SSc is the modified Rodnan skin score (MRSSS). This is a validated test that measures skin thickness (0 to 3) at 17 locations for a total score of 51. Improvements in skin score over time are used in clinical trials to quantitate skin fibrosis. Although recording the Rodnan skin score is technically straightforward, requiring no special equipment, and noninvasive, the fluctuating natural history of the disease includes improvement over time without interventions, rendering meaningful trials difficult to assess. Understanding of the basic molecular mechanisms driving pathologic fibrosis in SSc remains lacking, and underpins the often empiric nature and likely the lack of efficacy of many therapeutics that have been tried. Although repeated skin biopsies might be a more precise way to follow disease progression and regression, this is necessarily invasive and requires special tools. Here, this review will look at conventional therapies, biologics, autologous hematopoietic stem cell transplantation, and catalog some of the ongoing clinical trials in SSc with a focus on cutaneous fibrosis.

**Keywords:** Systemic sclerosis; therapy; biologics; clinical trials

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## Introduction/conventional therapies in SSc (Table 1)

Therapies in SSc are divided into three broad categories: (I) anti-immunologic and anti-inflammatory medications that target dysregulated immune and inflammatory pathways; (II) anti-fibrotic medications that target extracellular matrix and collagen production pathways; and (III) vascular medications to improve blood flow in Raynaud's phenomenon and treat pulmonary artery hypertension. We will organize this review according to these general categories (1-3).

Despite the widespread use of corticosteroids and immunosuppressive drugs in clinical practice, conclusive trial data that support the use of these medications remain lacking (4). It is challenging to do clinical trials

in SSc because of its low prevalence, its diverse clinical manifestations, and its variable and fluctuating course. Aside from low-dose prednisone for arthralgias, moderate to high doses of prednisone are contraindicated in SSc because of their association with scleroderma renal crisis (1). Although prednisone has been very effective in treating systemic lupus erythematosus or polymyositis/dermatomyositis, particularly in combinations with other DMARDs, efficacy in SSc has not been shown and significant side effects continue to limit its use.

Conventional therapies for SSc include the immunosuppressive agents methotrexate, azathioprine, mycophenolate mofetil (MMF) and cyclophosphamide (CYC) (Table 1) (1,5). These drugs work by broadly suppressing the immune system thought to play a critical

**Table 1** Current treatment options for internal organs in SSc

Internal organs	Medications
Gastrointestinal: upper (GERD)	Proton pump inhibitors
Lower: constipation	Promotility agents
Diarrhea	Antibiotics
Pulmonary	Immunosuppression:
Interstitial lung disease (ILD)	Cyclophosphamide
	Mycophenolate mofetil
	Azathioprine
Pulmonary artery hypertension (PAH)	Endothelial receptor antagonist
	Phosphodiesterase inhibitors
	Prostacyclin analogs
	Prostacyclin receptor agonist
Kidney: Scleroderma renal crisis	ACE inhibitors
Musculoskeletal system joints	Methotrexate

SSc, systemic sclerosis; GERD, gastrointestinal reflux disease; ACE inhibitors, angiotensin-converting enzyme inhibitors; ILD, interstitial lung disease; PAH, pulmonary artery hypertension.

role in the pathogenesis of SSc. Methotrexate is used for musculoskeletal involvement, which is common, and includes both arthritis/arthralgias and myositis/myalgias (1), and efficacy has been demonstrated among adults with SSc (6). Methotrexate has also shown success in treating children with juvenile localized scleroderma (7,8). For these reasons, MTX is considered somewhat effective and safe. One drawback of MTX is minimal activity in interstitial lung disease (ILD), which occurs frequently in SSc and remains the most common cause of death. Further, MTX can itself cause pneumonitis that is hard to differentiate from ILD. For this reason, alternative agents, including azathioprine, MMF and CYC, are preferred because they have been shown to have some benefit in SSc-ILD (9-11). CYC can be given as an oral daily dose or a monthly IV infusion (1). After an induction phase, patients are switched to either AZA or MMF for a maintenance phase due to their lower toxicity as compared to continuation of CYC. Between the two, MMF is preferred over AZA because of its demonstrable efficacy and its increased tolerance with fewer side effects. In general, these immunosuppressive medications are associated with improved lung function and skin scores. Both have potential serious side effects and

require laboratory monitoring.

### Biological therapies and hematopoietic stem cell transplantation (HSCT) in SSc

The original biologic was intravenous immunoglobulin (IVIg) created from pools of thousands of plasma donors was one of the first biologic products. First used in the 1980s, IVIg was initially used to restore antibody levels in patients with primary immunoglobulin deficiency, where it proved life-saving. The precise mechanism whereby IVIG works is not completely understood, one mechanism is by saturating the neonatal Fc receptor, FcRn, which normally serves to recycle adsorbed antibodies and return them to serum, IVIg reduces endogenous antibody levels, including autoantibodies, by promoting accelerated clearance, and has shown efficacy in a number of antibody-mediated autoimmune diseases. Among patients with early acute severe diffuse SSc, there are only small trials and case reports indicating some efficacy (12,13), and further study is needed.

Biologicals refer to a class of medications made by recombinant DNA technology and include cytokines and monoclonal antibodies targeting a variety of cells, cytokines and receptors (5). A theoretical advantage of biologicals is the specificity of the target, in contrast to the broad effects on the immune system that are associated with conventional immunosuppressive medications like corticosteroids. Tumor necrosis factor alpha (TNF-alpha) antibodies targeting the cytokine or its receptor were among the first biologicals with success in human autoinflammatory diseases, where they have been used with success in treating rheumatoid arthritis, psoriasis and psoriatic arthritis, spondyloarthritis and inflammatory bowel disease (1). Unfortunately, these drugs have shown little efficacy in SSc (14,15). Recombinant interferon-alpha, despite some efficacy in multiple sclerosis, was not effective for SSc (16), nor were efforts to block the type 1 interferon (IFN) receptor using MEDI-456 (17).

Transforming growth factor beta (TGF beta) is an ubiquitous growth factor associated with fibrosis and associated with the pathogenesis of SSc, and efforts to block its effects in a variety of fibrosing syndromes of humans are ongoing. A small phase I/II trial with a human recombinant neutralizing TGF-beta 1 antibody (CAT-192) was unable to show benefit as compared to placebo (18). A current trial is using Fresolimumab, a human IgG4 kappa recombinant

monoclonal antibody capable of neutralizing all forms of TGF-beta, perhaps increasing the likelihood to attacking the multiple different isoforms of the growth factor (19).

Rituximab (RTX) is a chimeric monoclonal antibody against CD20, which is expressed on pre-B cells and B-cells, which can target and remove potentially pathogenic auto-antibody-producing B cells. There are several open label trials with small numbers of patients that suggest some benefit in skin and lung disease (5), but larger randomized control trials are needed; these are underway (20-30). Although there is an increased risk of infections with RTX, but most were mild and could be managed in the outpatient setting with replacement antibody therapy as necessary.

Interleukin 6 (IL-6) is a cytokine that has also been associated with fibrosis and inflammation. Tocilizumab is a humanized antibody against the IL-6 receptor that was initially used in rheumatoid arthritis with some success. It was tried on 2 patients with diffuse SSc and based on success then expanded to a phase 2/3 trial (31-35), which showed a trend toward skin and lung improvement in 87 patients (5). A larger, multicenter trial (N=210) in SSc has been completed and did not meet their primary endpoints (36).

IL-1 is another cytokine associated with inflammation and fibrosis. Blockers of IL-1 have been used in CAPS (cryopyrin-associated periodic syndromes), DIRA (deficiency of IL-1 receptor antagonist and JIA (juvenile idiopathic arthritis) (5). A well-design trial using biomarkers from skin biopsies as well as the standard MRSS, however, was unable to show efficacy of the drug on biomarkers of disease or the MRSS (37).

Abatacept (CTLA-4Ig) is a fusion protein that blocks T cell activity and has shown efficacy among patients with rheumatoid arthritis. It has also shown some benefit in joint and muscle involvement with SSc (38,39).

Because of their therapeutic successes in a variety of inflammatory diseases, including rheumatoid arthritis and psoriasis, various Janus kinase inhibitors will undoubtedly be used in patients with SSc, particularly given some success in preclinical models.

Hematopoietic stem cell transplantation (HSCT) was originally used to treat blood cancers of the blood or bone marrow such as leukemia and multiple myeloma in the 1950s. Radiation or chemotherapy was used to wipe out the patient's own bone marrow cells as a conditioning regimen is myeloablative. There are newer gentler regimens that are non-ablative that are better tolerated. It was recognized to be helpful in some autoimmune disorders such multiple sclerosis and SSc. These procedures do come with serious

side effects and an increase mortality.

HSCT is the most extreme form of immunosuppression with both myeloablative and nonmyeloablative conditioning regimens and was first used in SSc in the 2000s. There have been quite a number of studies looking this intervention. Although there can be rapid improvement in skin and lung disease, it comes with a significant morbidity and mortality and an increase incidence of relapse. Therefore, it is only recommended for a select group of very severe early patients at select centers (40-64). The three largest studies 46, 49 and 60 include just over 300 patients and demonstrate that HSCT is superior to CYC with regard to event-free survival and survival. Because of the early expected morbidity and mortality with HSCT within the first year, it takes 2-years to start to see the benefit of HSCT, but that advantage remains for the follow up periods of 4 to 5 years follow up.

### Anti-fibrotics in SSc

SSc is a disease characterized by an abundance of connective tissue production and increased extracellular matrix, particularly collagen in the skin and internal organs (65). Drugs that inhibit collagen production are considered antifibrotics and have a long history of use in SSc. Older drugs like D-Penicillamine, a chelating agent that blocks collagen production by inhibiting cross-linking, were used for many years but have fallen out of favor due to side-effects and uncertain efficacy (1). Tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib) are small molecules that block ABL-kinases and platelet derived growth factors that have been implicated in fibrotic pathways. The early trials in SSc were encouraging but no significant benefits have been reliably shown despite the occurrence of significant toxicities such as fluid retention and elevated creatinine kinases (66-69).

Pirfenidone has shown some success in the treatment of idiopathic pulmonary fibrosis in trials which also included some patients with SSc-ILD (70). Sirolimus (rapamycin) is an immunosuppressive drug used to prevent kidney transplant rejection that also has some efficacy in SSc (71).

There are a number of animal models of SSc that have been used to screen various drugs before human use (72). Halofuginone, a plant-derived alkaloid with antifibrotic properties has been used with some success in animal models.

### Vascular medications that are used in SSc

Raynaud's phenomenon (RP) is extremely common in SSc

**Table 2** Select ongoing clinical trials in SSc (ClinicalTrials.gov)

Medication	Trials (references)
Rituximab (RTX)	12 listed trials:
Anti-CD20 B cells	+belimumab, US +methylprednisolone, Belgium -For PAH, multicenter, US -Efficacy & safety, Japan -For Localized scleroderma, EF, Belgium -For Graft versus host disease, multicenter, US -RTX versus CYC, UK -Cardiac safety, US -RTX + HSCT for ILD, PAH, US -ILD, PAH, Canada
Tocilizumab	3 listed trials:
Anti-IL6 receptor	RCT, US (completed) RCT, multicenter, US (completed) RCT, Canada
TGF-beta	1 study, phase 1, N=18
Fresolimumab	Multicenter, US for dSSc
Tyrosine kinase	References: (65-68)
Inhibitors: Imatinib (Gleevec)	RCT terminated, Canada 2008
Nilotinib	RCT for SSc-ILD, phase 3, N=580, 150 mg bid for 1 year, completed 2018
Dasatinib	1 phase I/II, N=47, 2011, multicenter, US discontinued because of side effects
Alemtuzumab/lemturda	B-CLL (B-chronic lymphocytic leukemia)
Campath-1H (anti-CD52)	Multiple sclerosis, relapsing Graft-versus-host disease Children; Pilot I/II Withdrawn; 2018
Rilonacept	1 Trial SSc, US
IL-1 receptor	
Abatacept	1 Trial completed, US single center (37,38)
CTLA-4	
Hematopoietic stem cell transplantation (HSCT) (39-63)	23 studies listed, looking at different conditioning regimens, cardiac safety, ILD, +RTX Children, other autoimmune diseases SLE, DM Multicenter, US, Germany, China, France ASSIST I conditioning regimen

SSc, systemic sclerosis; RTX, Rituximab; PAH, pulmonary artery hypertension; EF, eosinophilic fasciitis; US, United States; UK, United Kingdom; HSCT, hematopoietic stem cell transplant; ILD, interstitial lung disease; RCT, randomized controlled trial; dSSc, diffuse systemic sclerosis; SLE, systemic lupus erythematosus; DM, dermatomyositis; ASSIST, Autologous Stem Cell Systemic Sclerosis Immune Suppression Trial.

patients and reflects recurrent vasospasm of the small and medium peripheral blood vessels, particularly of the hands (73). Medical management with vasodilators, calcium channel blockers, and phosphodiesterase-5 inhibitors (PDE5), has been effective for RP and helps to reduce end-organ damage in other tissues. Botulinum toxin has been used successfully to treat RP (74).

In addition to the common small and medium-size vessel involvement of RP, there is also less common larger vessel involvement which can manifest as scleroderma renal crisis (SRC) and pulmonary arterial hypertension (PAH). ACE inhibitors have been shown to be very effective in treating SRC. There is also new therapies for PAH including PDE5 inhibitors, endothelin antagonist, prostacyclin and combination therapy (1).

### Select clinical trials in SSc (Table 2)

There are 431 studies related to SSc (136 clinical trials) and 64 studies related to Raynaud's phenomenon on ClinicalTrials.gov.

The Scleroderma Clinical Trials Consortium (SCTC) is an active international organization that follows, organizes and participates in SSc trials. Their meetings and website can provide a wealth of information and help to physicians and patients interested in SSc.

### Conclusions

Although there is some progress in treating this complex disease, there remain significant barriers and challenges. There are dedicated investigators who are designing and participating in quality clinical trials like the Scleroderma Clinical Trials Consortium. There are successful efforts to form collaborating coalitions that can work together. Nonetheless, despite many trials, aside from using immunosuppression for SSc-lung disease there are no effective skin fibrosis treatments available (1). Although a number of the biologicals have been tried, none have been shown to work in SSc (5). Despite these challenges, there are many dedicated investigators who continue to work hard with patients, academicians and industry to continue the rigorous clinical trials required to demonstrate the successes so sought after by all.

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