Emerging strategies for treatment of systemic sclerosis

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ABSTRACT
Systemic sclerosis is a heterogeneous condition characterized by microvascular damage, dysregulation of the immune system, and progressive fibrosis affecting skin and internal organs. Currently, there are no approved disease-modifying therapies, and management mostly involves treatment of organ-specific complications. In recent years, major advances have greatly improved our understanding of the disease process, especially the molecular mechanisms by which fibrosis becomes self-sustaining. We discuss selected aspects of these mechanisms with a focus on those relevant to ongoing efforts to develop disease-modifying therapies. We also discuss advances in identification of patient subtypes, and selected examples of potential disease-modifying therapies in clinical development.

Keywords: Fibroblast differentiation, IL-6, PPAR-γ, Soluble guanylate cyclase stimulators, TGFβ, Tyrosine kinase inhibitor

Introduction
Systemic sclerosis (SSc) is a heterogeneous disease most commonly associated with fibrosis and thickening of the skin of the hands and arms (1). Pathologic features of SSc include microvascular damage, dysregulation of adaptive and innate immunity, and fibrosis that can involve the skin, heart, lungs, kidneys, gastrointestinal tract and other organs. The rate of progression and extent of organ fibrosis are the primary determinants of clinical outcome (2, 3). For example, the two major lung manifestations of SSc – interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) – together account for about 60% of SSc-related deaths (4, 5).

Currently, there are no treatments that modify the underlying cause(s) of SSc, in part because those causes are incompletely understood. Thus, current therapies generally target disease complications, including organ involvement (1, 6). Early diagnosis of SSc, and assessment and treatment of organ involvement, are critical aspects of patient management because organ involvement is responsible for most of the complications and mortality in SSc. Clinical signs to aid early diagnosis or organ involvement have been identified (7-9), and comprehensive criteria for early diagnosis are being developed (9, 10). Furthermore, efforts to identify and validate circulating biomarkers to assess rate of progression and organ involvement are evolving rapidly (7, 11, 12). When SSc is diagnosed early, potential organ involvement is addressed, and appropriate treatment instituted, the outcomes for many patients can be improved. For example, better management of SSc-related renal crisis is largely responsible for improvements in 10-year survival in recent decades (4). The decline in death due to renal crisis has led to the emergence of lung manifestations as the leading causes of death among SSc patients, highlighting the need for better treatments for these manifestations, or for better treatments to alter the underlying causes of disease. This review will highlight ongoing research into new treatment strategies, especially those targeting the progression of fibrosis in SSc.

Epidemiology and disease classification
Studies to determine the prevalence of SSc have obtained widely varying estimates, in part because of differences in geographic locations, methods used for identifying cases, and the sensitivity of disease classification criteria (13). A case ascertainment study conducted in a major US metropolitan area estimated a prevalence of 276 cases per million adults (14), but a population-based study estimated the prevalence to be 300-500 cases per million (15). Another population-based sample in Canada was consistent with this estimate (443 cases per million). Prevalence rates vary greatly in the EU, from 31-88 cases per million in England to 158, 154, and 277 cases
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per million in France, Greece, and Spain, respectively (16-20). Studies have consistently found prevalence to be substantially higher in women than men (ratios of 4.6 to 5.7:1). There is also evidence for differences in prevalence across racial and ethnic groups, with rates slightly higher among blacks than whites, lower among people of Asian ancestry, and higher in some Native American groups (13, 14, 21).

SSc strongly affects mortality, with more than half of deaths in SSc patients attributable to SSc-related causes (5). Survival duration of patients with SSc has steadily improved in recent decades, in part because of better treatment of renal crisis and other organ manifestations, but probably also in part because of lead-time bias arising from earlier diagnosis (4, 13). Severity of disease and its course can also vary according to gender and ethnic background. For example, black patients are more likely than white patients to have diffuse cutaneous disease, and black patients have a higher risk of mortality (22). Even though the prevalence of SSc is lower in men than women, on average male patients with SSc have a worse prognosis and higher disease-specific mortality than female patients (3).

A joint committee of the American College of Rheumatology and the European League Against Rheumatism (ACR-EULAR) recently updated criteria for SSc classification. The new classification criteria are more sensitive and specific than previous versions, including among patients with early disease (23). The ACR-EULAR classification criteria are intended for research purposes but also aid in clinical care.

Patients with SSc are typically sub-classified as having limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc) (24), although these sub-classifications do not adequately capture the variability in disease features and manifestations among different patients (1). Intensive research efforts are focused on identifying biomarkers of disease activity and ways to distinguish subtypes of disease, which could inform clinical trial design and ultimately guide treatment choice (12, 25). A recent study using the EUSTAR database, for example, identified short disease duration, low baseline modified Rodnan skin score (mRSS), and joint synovitis as predictive markers of worsening skin fibrosis in patients with dcSSc (11).

**Emerging treatment strategies**

The identification of several key pathways in the pathogenesis of SSc has opened new avenues for therapies to target this devastating disease (Fig. 1). This quest for specific targeted therapies is complicated by the heterogeneous nature of the disease across patients. Nevertheless, there is great hope that ongoing refinements in clinical and laboratory measures...
Vascular damage and immune activation

The earliest observed pathological changes associated with SSc are activation and apoptosis of endothelial cells in the microvasculature (29). The triggers for these changes are not yet known but could include environmental exposure, infectious agents, autoimmune mechanisms, free radicals, or a combination of these factors (26). Microvascular injury is associated with reductions in the number of capillaries and narrowing of the vessel lumen leading to impaired blood flow and tissue hypoxia.

According to current models of SSc, abnormal vascular repair mechanisms may trigger the initiation of uncontrolled and persistent tissue repair responses that ultimately lead to fibrosis (26, 28). Activation of endothelial cells increases expression of cell adhesion molecules, promoting the recruitment of immune cells. The immune response to microvascular damage in SSc involves dysregulation of both innate and adaptive immune mechanisms, including autoantibodies, alterations in circulating immune cells, and type I interferon activity in immune cells (3).

Although inflammation is more frequently found in earlier disease stages, activation of the immune system persists during later stages, including activation of B cells and production of autoantibodies. Rituximab, which induces B-cell apoptosis by binding cell-surface CD20, is approved for treatment of B-cell lymphomas as well as refractory rheumatoid arthritis. A nested case-control study of patients with severe dcSSc in the EUSTAR cohort found that patients who had been treated with rituximab (n = 63) had significantly greater percentage declines in modified mRSS compared with matched controls (n = 25; -24.0 ± 5.2% vs. -7.7 ± 4.3%; p = 0.03). Patients who received rituximab also had significantly less decline in forced vital capacity (FVC) versus matched controls (30). Ongoing trials are exploring the efficacy and safety of rituximab in SSc-associated polyarthritis (NCT01748084) and SSc-associated PAH (NCT01086540). These trials will also provide information about anti-vasculopathic, anti-fibrotic, and immune modulatory effects of rituximab.

Activated T cells represent another potential immunologic target. Abatacept prevents T-cell activation by binding to CD80 or CD86 on the T-cell surface, and it is approved for treatment of rheumatoid arthritis. A small study in patients (n = 11) with SSc-related refractory polyarthritis or myopathy found that abatacept significantly improved joint parameters, although there was no change in skin or lung fibrosis (31). Another pilot study randomized dcSSc patients to either abatacept (n = 7) or placebo (n = 3) for 24 weeks and followed them by mRSS and skin biopsy (32). Five of seven patients in the abatacept group and one of three in the placebo group had at least 30% improvement in mRSS. There were differences in the disease duration; the placebo group had significantly longer duration of disease and significantly higher mRSS at baseline; however, after adjustment for disease duration, patients in the abatacept group had significantly greater improvements in mRSS during treatment than the placebo group (treatment difference, -9.8; 95% confidence interval -16.7 to -3.0; p = 0.0114). Patients who responded had reductions in the expression of CD28 co-stimulatory genes and other genes involved in immune and inflammatory responses. Interestingly, biopsy specimens from four out of five patients who responded to abatacept had baseline gene expression patterns classified as inflammatory on the basis of previously published criteria (33). Although one cannot exclude the natural course of disease, these results suggest it may be possible to identify a subset of dcSSc patients most likely to respond to abatacept. A phase II multicenter international trial is underway to study abatacept in patients with dcSSc; the trial uses skin fibrosis, as assessed by mRSS, as the primary endpoint (NCT02161406).

Fibrosis

Our evolving understanding of the SSc disease process indicates that vascular and immune activation initiate a fibrotic process that then becomes self-sustaining through several mechanisms. Fibrosis may continue long after evidence of immune activity subsides in affected tissues. Thus, many of the current efforts for developing therapies are focused on interfering with the mechanisms responsible for unregulated, self-sustaining fibrosis (28).

The normal wound-healing response involves activation of fibroblasts and production of extracellular matrix. The signals involved in this response are regulated and switched off at appropriate times. In contrast, early studies showed that skin fibroblasts isolated from patients with SSc continued to produce higher amounts of collagen and other extracellular matrix components for several passages in culture compared with fibroblasts from control subjects, highlighting a persistently activated phenotype of SSc fibroblasts even in the absence of exogenous stimuli (34, 35). This phenotype is likely caused by epigenetic alterations and is characterized by sustained activation of several pro-fibrotic pathways.

Transforming growth factor β

Transforming growth factor β (TGFβ) has been recognized as a central mediator of fibrotic signaling in SSc (36). An inactive precursor of TGFβ is secreted by monocytes, lymphocytes, macrophages, and fibroblasts and is stored as a latent complex in the extracellular matrix. Interaction of this inactive complex with cell-surface integrins releases active TGFβ (36). Binding of TGFβ to cell-surface receptors activates the SMAD signaling pathway as well as other signaling pathways, leading to fibroblast activation, increased expression of profibrotic genes, epithelial-mesenchymal transition and other cellular responses (36, 37).

Several factors contribute to activation and persistence of TGFβ signaling in SSc. When activated, endothelial cells secrete endothelin 1 and chemokines, leading to the recruitment and activation of T and B cells and macrophages.
Macrophages and activated type 2 helper T (T\(_h\)\(_2\)) cells secrete TGFβ. TGFβ also promotes the survival of fibroblasts and transformation of mesenchymal cells into apoptosis-resistant myofibroblasts, which are responsible for much of the excess production of extracellular matrix in SSc. SSc fibroblasts have increased expression of TGFβ receptors as well as cell-surface integrins, which can increase the liberation of active TGFβ from the extracellular matrix. These features contribute to an autocrine loop thought to assist in continued fibroblast activation (28, 38, 39). TGFβ and endothelin 1 also induce the secretion of connective tissue growth factor (CTGF) from fibroblasts. CTGF acts in concert with TGFβ to promote production of extracellular matrix, fibroblast adhesion, and proliferation, representing another autocrine loop contributing to sustained fibroblast activation (40). The ability of SMAD7 to negatively regulate the SMAD signaling pathway is dysfunctional in SSc fibroblasts, providing another potential mechanism by which pro-fibrotic TGFβ signaling is maintained (41). Finally, because fibroblasts sense and respond to mechanical stress, the increased tissue stiffness and reduced elasticity of the extracellular matrix in tissues affected by SSc may themselves lead to activation of signaling pathways that further enhance and sustain fibrosis (3).

With its central role in the fibrotic process, including several autocrine loops, TGFβ is a natural target for potential antifibrotic therapies in SSc. An initial attempt at targeting TGFβ involved CAT-192 (metelimumab), a human antibody that neutralizes TGFβ1 (42). When administered at doses of 0.5, 5, or 10 mg/kg to patients with SSc and recent progression of skin disease, there was no evidence of a treatment effect—likely due to low affinity of the antibody. More recently, however, a study of another TGFβ antibody has yielded more promising results. This antibody, fresolimumab, targets all isoforms of TGFβ (1, 2, and 3) and was studied in 15 patients who received either two 1 mg/kg doses 4 weeks apart or one 5 mg/kg dose (43). Although the study was uncontrolled, making interpretation of the results difficult as “spontaneous” regression cannot be excluded, patients in both dosage groups exhibited rapid and statistically significant declines in mRSS scores as soon as three weeks after administration of one or two doses. The patients also exhibited significant declines in the expression of the TGFβ-regulated genes thrombospondin-1 and cartilage oligomeric protein, as well as significant declines in the infiltration of myofibroblasts into the dermis. This study was too small to effectively evaluate adverse events, although several patients had bleeding episodes, and anemia was common.

Another promising approach for targeting the TGFβ pathway is the use of soluble guanylate cyclase inhibitors such as riociguat and BAY41-2272. A recent study revealed that these agents inhibit TGFβ signaling through non-SMAD pathways (44). A study of BAY41-2272 showed inhibition of dermal fibrosis in several animal models (45). A follow-up study of riociguat showed that it ameliorated fibrosis of the skin and intestine in bleomycin-induced fibrosis and experimental chronic graft-versus-host disease (cGVHD) (46). Riociguat has already been shown to be effective and well-tolerated in patients with PAH, including those whose PAH was related to connective-tissue diseases (47). It is now approved for that indication and is being studied in a phase II multicenter international trial of patients with dcSSc (NCT02283762).

**Interleukin-6**

Interleukin-6 (IL-6) is produced by B cells, T cells, and fibroblasts, and it promotes inflammation and fibrosis (3). Serum IL-6 levels are elevated in certain patients with SSc, particularly early dcSSc, and these levels have been suggestively correlated with progression of skin involvement, worsening lung fibrosis, and reduced long-term survival (48). IL-6 signaling has been shown to play important roles in fibrosis in bleomycin-induced fibrosis in mice, and antibodies to the IL-6 receptor prevent fibroblast activation and dermal fibrosis in that model (49, 50). However, in the tight-skin-1 mouse model (Tsk-1) where fibrosis is less inflammation dependent, an anti-IL-6 antibody was ineffective (51). This finding may indicate that strategies targeting IL-6 may be most effective in patients with inflammatory SSc.

Tocilizumab is an antibody to the IL-6 receptor approved for the treatment of rheumatoid arthritis. In a study already described for abatacept, another group of patients (n = 15) with SSc-associated polyarthritis were treated with tocilizumab (31). Treatment with tocilizumab showed significant improvement in joint parameters after five months. Recently, results were published from a phase II, randomized, placebo-controlled, double-blind trial of subcutaneous tocilizumab in patients (n = 87) with early diffuse SSc (52). The participants were selected to have documented worsening skin disease and presence of an elevated acute-phase reactant. After 48 weeks, there were no statistically significant differences between the tocilizumab and placebo arms, but there were several strong trends toward efficacy. Patients in the tocilizumab arm had greater declines from baseline in mRSS score (-6.33 vs. -2.22; p = 0.06). Patients in the tocilizumab arm also fared better on other outcome measures versus placebo, including the percent who had declines in FVC (p<0.05). A phase III trial of tocilizumab in SSc is currently recruiting participants (NCT02453256).

**Tyrosine kinase signaling pathways**

In addition to TGFβ, various other growth factors and cytokines are thought to be involved in promoting fibrosis in SSc, such as connective tissue growth factor (CTGF) and the platelet-derived growth factors (PDGFs). Elevated levels of PDGF have been found in fibrotic lesions, including the skin and lung of SSc patients, and myofibroblasts express elevated levels of PDGF receptor (53). Furthermore, SSc fibroblasts, but not normal fibroblasts, increase expression of PDGF receptors in response to TGFβ (54). There is also evidence of another autocrine loop involving PDGF and PDGF receptors in SSc fibroblasts (53). As before, results should be interpreted with caution as a control group was not included; effects as well as adverse events may result from the natural course of disease.

**Imatinib**

Imatinib is a tyrosine kinase inhibitor (TKI) targeting PDGF, c-abl, and c-kit, and has been shown to prevent fibrogenesis...
in bleomycin-induced fibrosis (55). To date, a handful of studies have investigated the efficacy of imatinib in the treatment of dcSSc and SSc-associated ILD with mixed results; these studies are again limited by their uncontrolled design. Enrollment in an initial proof-of-concept study of imatinib 200 mg bid in patients with dcSSc was discontinued after high rates of adverse events (AEs) and poor tolerability were noted in patients; no significant difference in mRSS was seen in patients receiving imatinib (56). A phase IIa open-label, single-arm trial assessed the safety and effectiveness of imatinib 400 mg daily in patients with dcSSc. After 12 months of treatment, notable improvements in skin thickness and FVC were observed; AEs were common although most were mild to moderate. Of note, FVC improvement was significantly greater in patients without ILD (57). Another phase II, randomized, double-blind trial of imatinib 400 mg daily in patients with dcSSc found no significant difference in mRSS, dermal thickness, diffusing capacity of the lung for carbon monoxide (DLco), and quality-of-life measures after 6 months of treatment compared with placebo (58). Two studies in SSc-ILD yielded varied results. A 1-year open-label pilot study of imatinib 600 mg/day in SSc patients with ILD saw large numbers of AEs; a trend toward increased FVC and improved mRSS were noted and the authors concluded that lower dosages of imatinib may be of benefit in the SSc-ILD population (59). A phase II pilot study of imatinib 200 mg daily for 6 months in SSc-ILD patients unresponsive to cyclophosphamide saw stabilization of lung function in a large proportion of patients (73.1% stabilized or improved) (60). An additional randomized, double-blind controlled trial compared imatinib 600 mg QD with placebo in patients with idiopathic pulmonary fibrosis (IPF) (61). Imatinib showed no benefit compared with placebo regarding the primary endpoint and time to disease progression (a composite score of >10% reduction in FVC or death). Analysis of secondary endpoints was similar, with no benefit seen for imatinib in FVC, DLco, or six-minute walk distance (6MWD). Imatinib was also associated with a higher incidence of study withdrawals due to AEs than was placebo.

Nilotinib is a TKI active against the PDGF receptor as well as c-Abl and other tyrosine kinases (62). It is approved for treatment of chronic myelogenous leukemia, and was shown to inhibit bleomycin-induced skin and lung fibrosis in mice (63, 64). Recently, nilotinib was studied as a treatment for dcSSc in a small group of patients (n = 10) who had early and active disease (median duration of disease was 0.7 months) (65). Among the 7 patients who completed 12 months of treatment, mRSS scores improved by an average of 6.3 points (23%). This study also found evidence for predictive markers of response. Higher baseline levels of expression of genes related to TGFβ or PDGF signaling were associated with response and expression of these genes declined during treatment. Nilotinib was associated with abnormalities in liver function tests and QTc prolongation, the latter of which required discontinuation of treatment in two patients.

Dasatinib is another multi-target TKI approved to treat chronic myelogenous leukemia. It inhibits c-Abl, PDGF, and other kinases, and was shown to inhibit bleomycin-induced pulmonary fibrosis in mice (66) as well as myofibroblast differentiation in vitro (67). The safety of dasatinib has been studied in patients with scleroderma-associated pulmonary fibrosis, and 7 of 31 patients had serious AEs. Subsequent trials have not been announced.

Nintedanib is a TKI-targeting fibroblast growth factor (FGF) receptor, PDGF receptor, and vascular endothelial growth factor (VEGF) receptor, as well as Src-family tyrosine kinases (68). It is approved for the treatment of IPF (69, 70). Nintedanib has been shown to inhibit bleomycin-induced skin and lung fibrosis, to ameliorate skin fibrosis in Tsk-1 mice and in experimental cGvHD and to reduce fibrosis in multiple organs in Fra2 transgenic mice (71, 72). It was also shown to inhibit proliferation and transformation of human lung fibroblasts (71), as well as collagen synthesis in skin fibroblasts from patients with SSc (72). A phase III trial of nintedanib began enrolling patients with SSc and ILD in December, 2015 (NCT02597933). Although the primary outcome is FVC, skin thickness will also be evaluated as a secondary endpoint.

Pirfenidone

Pirfenidone is an anti-fibrotic agent with anti-inflammatory properties including inhibition of pro-inflammatory cytokines and inhibition of inflammatory cell proliferation. Pirfenidone is approved for the treatment of patients with IPF. A study was designed to evaluate the safety and tolerability of pirfenidone in SSc-ILD (73). Thirty-six patients were randomized 1:1 to receive pirfenidone titrated over 2 or 4 weeks from a starting dose of 801 mg/day to a maintenance dose of 2403 mg/day. Patients received pirfenidone for 16 weeks in total. Assessments included treatment-emergent AEs (TEAEs) and exploratory disease outcomes; 96.8% experienced a TEAE and more patients reported TEAEs during the titration versus maintenance period. The most commonly reported TEAEs were consistent with those observed for pirfenidone in IPF (nausea, headache, fatigue) and the frequency and type of TEAEs were similar regardless of titration schedule. More patients discontinued treatment due to TEAEs in the 2- versus 4-week titration group (5 vs. 1, respectively). Exploratory disease outcomes remained largely unchanged and tolerability was affected by titration length. A controlled clinical trial in patients with SSc-ILD is planned.

PPAR-γ

In the last decade, several lines of evidence have shown that the peroxisome proliferator-activated receptor-γ (PPAR-γ) is a key endogenous suppressor of fibrosis (28). Activation of PPAR-γ inhibits TGFβ-induced fibrosis in fibroblasts (74) and reduces bleomycin-induced fibrosis in mice (75). Furthermore, a genome-wide association study provided evidence for a role of PPAR-γ in susceptibility to SSc (76) and PPAR-γ is downregulated in patients with SSc (77). Because of these findings, PPAR-γ agonists are also being studied as potential treatments for SSc. The use of selective PPAR-γ agonists, however, is limited due to its increased risk of cardiovascular events. The pan-PPAR agonist IVA337 has not been associated with this AE and is the subject of an ongoing proof-of-concept phase II trial in patients with dcSSc (NCT02503644).
Lysosphosphatidic acid-related ligands

Lysosphosphatidic acid (LPA) is a lipid with numerous important signaling functions mediated through G-protein-linked LPA receptors, of which six are known (78). Antagonism of the LPA_1 receptor has been shown to reduce bleomycin-induced fibrosis in a mouse model (79). Furthermore, the LPA antagonist SAR 100842 reduces expression of fibrosis-related genes in SSc skin fibroblasts (79). SAR100842 was studied in a phase II trial in patients with dcSSc of recent (<36 months) onset (80). Patients treated with SAR100842 exhibited declines in mRSS scores. Other LPA antagonists in clinical development include BMS-986202 (formerly AMS152).

Conclusion

Management of SSC still rests on the treatment of organ-specific complications, and no disease-modifying therapies are yet available. However, recent years have seen major advances in our understanding of the pathophysiologic processes responsible for the immunologic and fibrotic mechanisms of disease. This is complemented by development of better outcome measures and data-driven approaches to assess for cohort enrichment. These advances have supported the development of several potential treatment strategies that may finally hold the promise of interfering with the self-sustaining fibrotic process in SSc. Concurrently, studies in large patient cohorts have yielded valuable insights into clinical and laboratory markers of disease activity and prognostic markers of progression, which should serve to identify clinically relevant disease subtypes to refine enrollment criteria for clinical trials. Considered together, these advances hold great promise for the development of disease-modifying therapies that will improve the well-being of patients with SSc, reduce or prevent complications of the disease, and ultimately prolong survival.

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