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Current Advances in the Treatment of Systemic Sclerosis

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Abstract

Systemic sclerosis (SSc) is a rare, systemic autoimmune disease of unknown etiology. Among the systemic rheumatic diseases, SSc carries the highest mortality, in part due to the historical lack of disease modifying therapies. Recently, landmark randomized controlled trials (RCTs) have been conducted that have illustrated the heterogeneous nature of SSc and furthered our understanding of the key inflammatory and fibrotic pathways involved in SSc pathogenesis. Although SSc affects various organ systems, RCTs have focused on investigating treatments for diffuse cutaneous sclerosis (dcSSc) and interstitial lung disease (ILD). While recent RCTs for dcSSc have failed to demonstrate a treatment benefit, the outcomes of two RCTs led to the approval of two novel therapies for SSc-ILD: nintedanib and tocilizumab. This review summarizes the salient outcome data from recent SSc trials within a practical clinical framework and points out gaps in knowledge that may help inform the design of future SSc studies.

Keywords

systemic sclerosis; interstitial lung disease; cutaneous sclerosis; nintedanib, tocilizumab; therapeutics

Introduction

Systemic sclerosis (SSc; scleroderma) is a rare, chronic connective tissue disease of unknown etiology that portends the highest case-specific mortality among the systemic rheumatic diseases [1]. While pathologic vasculopathy, immune dysregulation and fibrosis uniquely contribute to organ damage in SSc, there is considerable variability in the phenotypic manifestations, rate of disease progression and response to therapy among affected individuals. Historically, scleroderma renal crisis (SRC) carried the highest risk of mortality; however, the implementation of angiotensin converting enzyme inhibitors (ACE-I) in the early 1980s reduced the frequency of deaths in SRC from 42% to 6% over a 3-decade period [2]. Presently, SSc-associated interstitial lung disease (SSc-ILD) and pulmonary hypertension (SSc-PH) are the leading causes of SSc-related death; although, emerging data suggest that improvements in early detection of ILD and PH, along with the discovery of novel therapeutics for these complications has led to better survival [3,4]. Moreover, there are several novel therapeutics under investigation for the treatment of SSc. The purpose of

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this article is to review existing and novel emerging therapies for the treatment of SSc, with an emphasis on recent trials targeting the cutaneous and pulmonary manifestations of this disease.

Pathogenesis

Although the exact etiology of SSc is unclear [1], numerous studies have demonstrated that genetic susceptibility and environmental factors play a large role in the development of disease [5,6]. Vascular injury occurs early in the SSc disease course, promoting endothelial activation, inflammation via innate and adaptive immune responses, vascular remodeling and eventual fibrosis [7,8]. Figure 1 summarizes important immunological participants of SSc pathogenesis with an emphasis on therapeutic targets.

Current Approach to Management

Treatment of SSc can be challenging owning to its rarity and heterogeneous disease manifestations. Prior to initiating therapy, a pretreatment evaluation is warranted to identify active organ involvement and risk stratify patients (Figure 2). Therapy should be implemented to target active organ-specific complications of disease with a preference for therapies that may target more than one active organ system or target overlap connective tissue disease, if present. Table 1 summarizes the current pharmacologic therapies for SSc by organ system.

Current Therapies for Cutaneous Sclerosis

Cutaneous sclerosis is the cardinal symptom of SSc and is present in most patients, either in a diffuse or limited distribution. The modified Rodnan skin score (mRSS) is routinely used to quantify the extent of cutaneous sclerosis in clinical practice and in research. Most clinical trials have focused on early dcSSc, wherein immunomodulatory therapy may serve to reverse and reduce disease burden.

Randomized controlled trials (RCTs) have demonstrated that cyclophosphamide (CYC) [9], mycophenolate (MMF) [10,11] and hematopoietic stem cell transplant (HSCT) [12,13] are associated with a statistically significant improvement in cutaneous sclerosis. In general, MMF, is considered first line therapy given its favorable toxicity and side-effect profile compared with CYC. HSCT is generally reserved for patients with severe dcSSc refractory to immunomodulatory therapy given its high morbidity and mortality, although this approach can lead to the most dramatic improvement in cutaneous sclerosis. Although nintedanib and tocilizumab are approved therapies for SSc-ILD, neither of these medications demonstrated a statistically significant benefit in reducing the extent of cutaneous sclerosis compared with placebo (Table 2).

Current Therapies for SSc-ILD

Scleroderma Lung Studies

SSc-ILD is recognized as the major cause of disease-related mortality; however, review of contemporary literature suggests improved survival among patients with SSc-ILD due to

more aggressive monitoring and treatment [4,14]. In clinical trials of SSc-ILD, change in forced vital capacity (FVC) is commonly used as a primary outcome measure, as low FVC predicts morbidity and mortality [15]. Two landmark clinical trials, SLS-I [9] and SLS-II [10], established CYC and MMF as disease modifying therapies for SSc patients with active ILD. In SLS-I, treatment with CYC resulted in a clinically significant improvement in FVC%-predicted, total lung capacity (TLC)%-predicted and radiographic fibrosis compared with placebo at 12 months [10]. In SLS-II, treatment with MMF for 24 months or CYC for 12 months led to significant improvement in the course of the FVC%-predicted over 24 months [11]. Treatment with MMF and CYC was also associated with improvements in radiographic fibrosis [16] and self-reported dyspnea [17]. Given its favorable tolerability and side effect profile, MMF is currently considered first-line therapy for patients with SSc-ILD. For patients with progressive dcSSc with ILD, refractory to immunosuppressive therapy, autologous HSCT may be considered, as studies have demonstrated improvement in FVC [12] and decreased progression to respiratory failure [13] in patients randomized to HSCT compared with CYC.

Nintedanib

Nintedanib inhibits intracellular tyrosine kinase and fibroblast growth receptor (FGFR) [18]. In a RCT of 576 patients with SSc-ILD, treatment with nintedanib slowed the rate of decline of FVC over 52 weeks compared with placebo; the adjusted annual rate of change in FVC was −52.4 ml per year in the nintedanib group and −93.3 ml per year in the placebo group (P=0.04) [19]. Background immunosuppressive therapy was permitted, and nearly half (48.4%) of patients were receiving MMF for at least 6 months prior to enrollment. Patients who were taking MMF at baseline and randomized to nintedanib had the slowest decline in lung function; however, because patients were not randomized to MMF, confounding factors may account for these outcome disparities. Currently, more data is needed to determine when anti-fibrotic therapy should be initiated in SSc-ILD. Results of the ongoing SLS III study (MMF vs. MMF plus the anti-fibrotic, pirfenidone) may help us understand whether early upfront combination therapy is advantageous in SSc-ILD.

Tocilizumab

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that is frequently overexpressed in systemic sclerosis, promoting inflammation and profibrotic effects via the Janus kinase (JAK) 2/signal transducer and activator of transcription protein (STAT) 3 pathway [20]. Tocilizumab is a humanized monoclonal antibody that functions as an antagonist of the IL-6 receptor, thereby blocking its downstream effects. Tocilizumab in systemic sclerosis (focuSSced) was a phase III trial that enrolled 210 adult patients with relatively early dcSSc with evidence of worsening cutaneous sclerosis and systemic inflammation. Patients were randomized to receive either tocilizumab 162 mg subcutaneous weekly or placebo. While a treatment benefit of tocilizumab on the primary endpoint (change in mRSS) was not observed, the investigators found that treatment with tocilizumab was associated with stabilization of the FVC%-predicted from baseline to 48 weeks [21,22]. While the data from the focuSSced trial resulted in FDA approval of tocilizumab for SSc-ILD, it is unclear whether SSc-ILD patients with lcSSc or SSc-ILD patients without elevated inflammatory markers would also benefit from tocilizumab. Furthermore, in patients with dcSSc-ILD, it

is unknown whether tocilizumab can be safely combined with existing immunosuppressive treatments for dcSSc (e.g., MMF).

Emerging Therapies for SSc

A number of novel therapeutic agents have been recently studied for the treatment of dcSSc and SSc-ILD. While some of these therapies, including lenabasum [23], abatacept [24], and riociguat [25], have failed to demonstrated treatment benefit (Table 2), several new agents are currently under investigation as described below.

Rituximab

Dysregulation of adaptive immunity is implicated in the pathogenesis of SSc [8]. Rituximab is a humanized chimeric anti-CD20 monoclonal antibody that depletes peripheral B cells through antibody-dependent cell-mediated cytotoxicity. Although large RCTs studying the efficacy of rituximab in SSc are lacking, a meta-analysis of 24 articles concluded that rituximab improves mRSS, quality of life and may effectively stabilize internal organ involvement in SSc [26]. A small RCT (DESIRES) in Japan randomized patients with both dcSSc and lcSSc to rituximab (375mg/m^2) (N=28) or placebo (N=28) once per week for 4 weeks [27]. At 24 weeks, the absolute change in mRSS from baseline in the rituximab arm was −6.30 compared with +2.14 in the placebo arm (P=0.0001). Rituximab was well-tolerated during the study, and the frequency of adverse events were similar between the rituximab and placebo arms. In this study, rituximab demonstrated a treatment benefit regardless of SSc disease duration or subtype. However, a recent post-hoc analysis of the same study found that high CD-19 positive cell count and high mRSS predicted treatment response to rituximab [28].

In the DESIRES trial, the absolute change in FVC%-predicted from baseline to 24 weeks was analyzed as a key secondary endpoint [27]. Among patients randomized to rituximab, 25 patients (89%) and 23 patients (88%) had ILD in the rituximab and placebo arms, respectively. Patients randomized to rituximab experienced an increase in FVC%-predicted of (mean change 0.09), while patients in the placebo arm experienced a decrease (mean change −2.87) (P=0.044). Patients randomized to rituximab also experienced significant radiographic improvement in the percent of lung fields occupied by interstitial changes. An open-label, 24-week RCT in India compared the safety and efficacy of rituximab 1000mg × 2 doses at 0 and 15 days to intravenous CYC 500mg/m2 monthly in patients with dcSSc and SSc-ILD. In this study, patients receiving rituximab (N=30) experienced an improvement in FVC%-predicted at 6 months (+6.22) whereas those in the CYC arm (N=30) experienced decline in FVC%-predicted (−1.19) (P=0.003) [29]. A RCT (RECITAL) assessing the efficacy of rituximab versus CYC for patients with CTD-ILD, including SSc-ILD [30] was recently completed. Although the results are not yet published, this study will undoubtedly provide more insight into rituximab’s efficacy in treating SSc-ILD. Based on current clinical data, rituximab offers a promising role in treating both cutaneous sclerosis and ILD.

Romilkimab

In SSc, endothelial injury prompts activation of T cells, which differentiate into T-helper type 2 (Th2) response with subsequent release of interleukin-4 (IL-4) and interleukin-13 (IL-13). Romilkimab is a humanized IgG4 antibody that binds and neutralizes IL-4/IL-13, halting the promotion of fibrosis. In a recent study, 97 patients with dcSSc, with or without background immunosuppressive therapy, were randomized to receive romilkimab or placebo for 24 weeks. Change in mRSS from baseline was the primary endpoint. At 24 weeks, patients randomized to romilkimab had a greater decline in mRSS (−4.76) compared with placebo (−2.45) (P=0.029) [31]. Among study participants, 18 patients (38%) in the romilkimab group and 18 patients (37%) in the placebo group had a history of SSc-ILD, with a mean baseline FVC%-predicted of 92.8 in both groups. There was a trend towards improvement in FVC in the romilkimab arm compared with placebo. While the aforementioned findings are encouraging, a phase III trial is needed as prior candidate treatments for dcSSc that showed promising phase II trial data ultimately failed to demonstrate a treatment benefit in the phase III trial (e.g., lenabasum, tocilizumab).

Allogenic bone marrow-derived multipotent mesenchymal stromal cells

Mesenchymal stromal cells (MSC) contain immunomodulatory, proangiogenic, and antifibrotic therapeutic benefits and represent a novel intervention for patients with SSc [32]. In a recent open-label phase 1/2 study, 20 patients with severe dcSSc received a single infusion of allogenic bone marrow-derived MSC [33]. All 20 patients enrolled had evidence of SSc-ILD. Single infusions of both 1×10^6 bone marrow-derived MSC per kg body weight and 3×10^6 bone marrow-derived MSC per kg body weight were safe and well tolerated during short and long-term follow-up. Following the first infusion of MSC, an improvement in mRSS was appreciated and sustained at 12 months, while FVC remained stable at 12 months. Unlike HSCT, which is associated with high risk of complications and mortality, MSC may represent a safer option for treating severe dcSSc. Future studies are needed to understand which patients may benefit from this therapeutic strategy over conventional immunosuppression for dcSSc.

Conclusions

With improved understanding of the important pathways that drive the pathogenesis of SSc, a number of new therapies are currently available to treat cutaneous and pulmonary manifestations of SSc. Future studies are needed to determine the optimal time to introduce these therapies, to understand whether combing therapies leads to improved outcomes and to develop improved strategies for personalizing treatment for patients based on molecular profiling.

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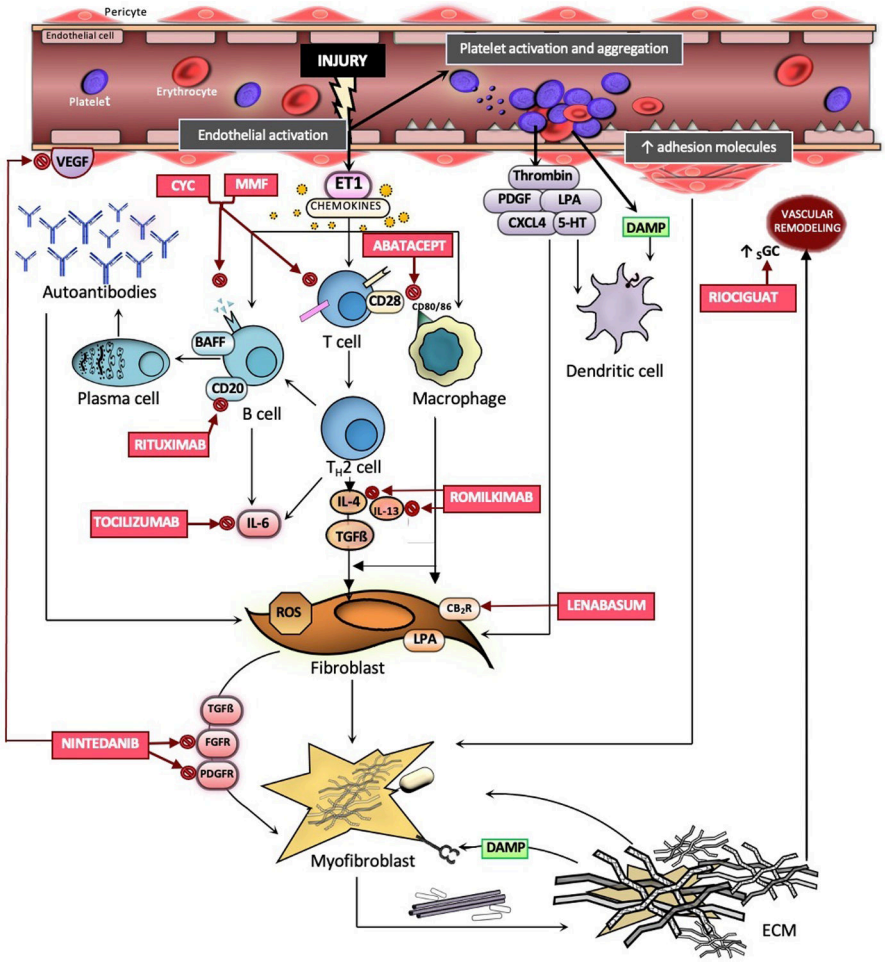
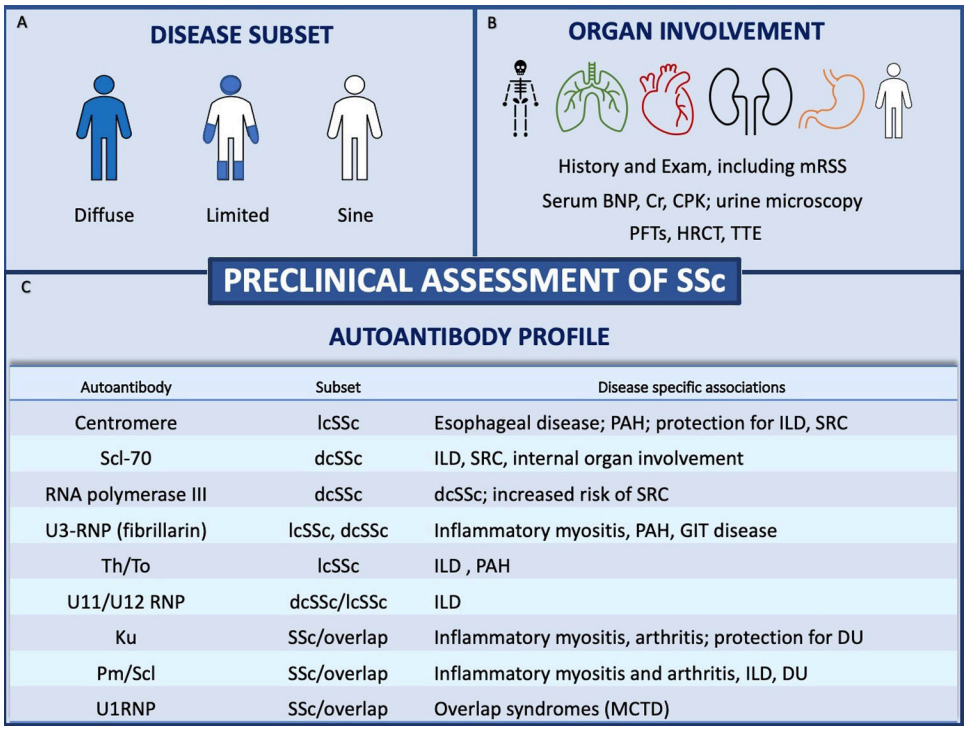


Figure 1. Key pathways involved in SSc pathogenesis and therapeutic targets of current and emerging therapies.

Vascular injury occurs early in the SSc disease course, resulting in endothelial cell activation, expression of adhesion molecules, chemokine production, release of ET1, and platelet activation with subsequent coagulation. Chemokines recruit macrophages from the circulation into the tissue. DAMPs activate dendritic cells via toll-like receptor 4. Activated T cells undergo differentiation to T_h2 cells, releasing IL-6, IL-4, and IL-13. B cells are subsequently activated via IL-4 and undergo transformation into plasma cells with subsequent production of autoantibodies. Resident fibroblasts are activated by TGF-B, IL-13, and IL-6, generating ROS and differentiating into myofibroblasts. Myofibroblasts secrete profibrotic growth factors and produce extracellular matrix molecules, forming a fibrotic matrix. Abbreviations: CYC: cyclophosphamide; MMF: mycophenolate mofetil; IL-6: interleukin-6; IL-4 ; interleukin-4; IL-13: interleukin-13; ET1: Endothelin-1; PDGF: Platelet-derived growth factor; LPA: lysophosphatidic acid; CXCL4: chemokine ligand 4; 5-HT: serotonin receptor; BAFF: B-cell activating factor; TGFß: Transforming growth factor beta; FGFR: fibroblast growth factor receptor; PDGFR: Platelet-derived growth factor receptor; VEGF: Vascular endothelial growth factor; CB2: cannabinoid receptor type 2; ROS: reactive oxygen species; sGC: soluble guanylate cyclase; DAMP: Damage-associated molecular patterns; ECM: extracellular matrix.



Autoantibody	Subset	Disease specific associations
Centromere	lcSSc	Esophageal disease; PAH; protection for ILD, SRC
Scl-70	dcSSc	ILD, SRC, internal organ involvement
RNA polymerase III	dcSSc	dcSSc; increased risk of SRC
U3-RNP (fibrillarin)	lcSSc, dcSSc	Inflammatory myositis, PAH, GIT disease
Th/To	lcSSc	ILD , PAH
U11/U12 RNP	dcSSc/lcSSc	ILD
Ku	SSc/overlap	Inflammatory myositis, arthritis; protection for DU
Pm/Scl	SSc/overlap	Inflammatory myositis and arthritis, ILD, DU
U1RNP	SSc/overlap	Overlap syndromes (MCTD)

Figure 2. Approach to pre-treatment evaluation in patients with SSc.

(A) Disease subsets are defined by the extent of skin thickening and include diffuse cutaneous SSc (dcSSc), limited cutaneous SSc (lcSSc) and systemic sclerosis sine scleroderma. (B) Recommended baseline evaluation in SSc. (C) Autoantibodies and their associated subsets and disease-specific associations. Abbreviations: Scl-70: topoisomerase 1; RNA: ribonucleic acid; RNP: ribonuclear protein; DU: digital ulceration; PAH: pulmonary arterial hypertension; SRC: scleroderma renal crisis; GIT: gastrointestinal tract disease; MCTD: mixed connective tissue disease.

Table 1.

Current pharmacological therapies for organ-specific manifestations of SSc

Therapeutic agent	Benefit in SSc
Diffuse cutaneous sclerosis	
MMF	Improvement in mRSS
CYC	Improvement in mRSS
HSCT	Improvement in mRSS
Raynaud phenomenon/digital ulcers	
Calcium channel blocker	Reduction in frequency and severity of Raynaud phenomenon attacks
Fluoxetine	Reduction in frequency and severity of Raynaud phenomenon attacks
Sildenafil, tadalafil	Reduction in frequency and severity of Raynaud phenomenon attacks
Iloprost	Reduction in frequency and severity of Raynaud phenomenon attacks and digital ulcers
Bosentan, ambrisentan	Reduction in development of new digital ulcers
Interstitial lung disease	
CYC	Improvement in FVC, radiographic fibrosis and dyspnea
MMF	Improvement in FVC, radiographic fibrosis and dyspnea
Tocilizumab	Stabilization of FVC in early dcSSc with and without ILD
Nintedanib	Reduction in annual rate of decline of FVC
Pulmonary hypertension	
Sildenafil, tadalfil	Improvement in exercise capacity, hemodynamics, functional class
Riociguat	Improvement in exercise capacity, hemodynamics, functional class
Bosentan	Improvement in 6-minute walk distance; delayed progression to clinical worsening
Ambrisentan plus tadalafil	Reduction in risk of clinical failure compared with single agent; Improvement in 6-minute walk distance
Selexipag	Reduction in hospitalizations and disease progression
Prostanoids (Treprostinil, Epoprostenol, Iloprost, Beraprost)	Improvement in 6-minute walk distance and time to clinical worsening
Gastrointestinal disease	
Proton-pump inhibitors	Improvement in acid reflux symptoms; decreased risk of upper GI ulcers
H2 blockers	Improvement in acid reflux symptoms
Pro-kinetic agents	Improvement in symptoms related to GI tract dysmotility
Renal disease	
ACE inhibitors	Improvement in morbidity and mortality due to scleroderma renal crisis
Cardiac disease	
Calcium channel blockers	Prevention and treatment of left ventricular systolic dysfunction
ACE inhibitors, Calcium channel blockers	Improvement in myocardial perfusion
Anti-arrhythmic agents	Improvement in arrhythmias due to SSc-myocardial involvement
Immunosuppressive therapy	Improvement in mortality in myocarditis

Table 2.

Recent Phase II/III RCTs for dcSSc

Therapeutic	Sample Size	Skin Outcome Measure	Result of skin outcome measure
Tocilizumab [21]	N=212	Primary outcome: ΔmRSS at week 48	Least squares mean ΔmRSS −6.1 in tocilizumab arm and −4.4 in placebo arm; P=0.10
Nintedanib [19]	N=576	Secondary outcome: ΔmRSS at week 52	Adjusted mean ΔmRSS −2.17 in the nintedanib arm and −1.96 in the placebo arm; P=0.58
Lenabasum [23]	N=363	Secondary outcome: ΔmRSS at week 52	Mean ΔmRSS −8.1 in the placebo arm and −6.7 in the lenabasum arm
Abatacept [24]	N=88	Primary outcome: ΔmRSS at week 52	Adjusted mean ΔmRSS from baseline −6.24 in abatacept arm and −4.49 in placebo arm; P=0.28
Riociguat [25]	N=109	Primary outcome: ΔmRSS at week 52	Mean ΔmRSS −2.09 for riociguat arm and −0.77 for placebo arm; P=0.08