Published in final edited form as:

Expert Opin Pharmacother. 2020 November ; 21(16): 2041–2056. doi:10.1080/14656566.2020.1793960.

An update on the pharmacotherapeutic options and treatment strategies for systemic sclerosis

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Abstract

Introduction: Systemic sclerosis (SSc) is a multi-dimensional connective tissue disease of unknown etiology. Given the immense clinical complexity of SSc, the treatment of this condition is not standardized and considerable heterogeneity exists in SSc management approaches. The purpose of this article is to highlight novel therapeutic strategies and new medications under development for the treatment of systemic sclerosis (SSc).

Areas covered: Herein, the authors focus primarily on recently completed clinical trials and phase 3 and 4 clinical trials of therapeutic agents that show promise in SSc. This review is organized by the clinical complications that occur in SSc, for which novel treatment strategies are under study.

Expert opinion: Combining therapies to address the individual manifestations of SSc is a cornerstone to the comprehensive management of this condition. Therapeutic strategies must take into account the organs involved, the level of disease activity in each area, and the disease stage. Controlling the complex biological network, progressive vasculopathy and fibrosis, as well as manifestations of end-organ dysfunction are all critical considerations when determining the best treatment approach for SSc.

Keywords

Scleroderma; systemic sclerosis; treatment; therapy; update

1. Introduction

Systemic sclerosis (SSc) is a multi-dimensional connective tissue disease of unknown etiology. The pathological hallmarks of this condition (e.g. fibrosis, inflammation, autoimmunity, vasculopathy) uniquely converge to cause varying degrees of organ system dysfunction and damage. The skin is the most common organ system affected in SSc,

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Declaration of interest

ER Volkmann has received grant support from Corbus Pharmaceuticals and Forbius, and consulting fees from Forbius and Boehringer Ingelheim. ZH McMahan has received salary support from Corbus Pharmaceuticals for her work as a subinvestigator on the Lenabasum study. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

followed by the gastro-intestinal (GI) tract and then the lungs. While SSc often presents with the onset of Raynaud phenomenon, the evolution of the disease vastly differs based on a number of defined (i.e. SSc cutaneous subtype, sex, auto-antibody profile) and yet to be defined (i.e. genetics, epigenetics, environmental factors) variables.

1.1. Determining when therapy is indicated

Given the immense clinical complexity of SSc, the treatment of this condition is not standardized and considerable heterogeneity exists in SSc management approaches. General treatment algorithms have been proposed [1]; however, emerging and experimental therapies are changing the land-scape of the treatment paradigm for SSc [2,3]. Selection of therapy is often guided by the extent and severity of organ involvement (Figure 1). For example, if a patient has diffuse cutaneous sclerosis and interstitial lung disease (ILD), preferred interventions would target both organ systems simultaneously.

Beyond the extent and severity of organ involvement, other factors affect treatment decisions, such as the duration of disease and its current activity. For instance, the approach to managing an SSc patient with long-standing ILD and stable lung function may contrast with the approach adopted to treat an SSc patient with new-onset ILD presenting with a decline in lung function. The latter scenario suggests active disease and would likely require a more aggressive treatment strategy, while the former scenario may require a close monitoring approach.

In addition, specific patient characteristics may also contribute to treatment decisions. Factors such as sex and auto-antibody status may confer a heightened or lessened risk for the progression of disease within certain organ systems. As an example, male patients with SSc have an increased risk of progression of ILD compared with female patients [4], while patients who possess the centromere antibody seem to have a decreased risk of ILD progression compared with patients who do not possess these antibodies [5]. Table 1 summarizes some of the key factors that often affect treatment decisions in SSc patients beyond the organ system affected.

The present review describes the current, as well as late-stage, investigational therapies for SSc.

2. Novel strategies for treating complications of SSC

While the review is organized by organ system, we encourage a holistic management approach that targets treating the patient as a whole, considering the factors outlined in Table 1. Where applicable, we will point out certain therapies that may treat multiple dimensions of this disease, as well as therapies that may be combined in potentially synergistic ways. The review will conclude with a review of the areas where more drug discovery and development are needed. This review specifically focuses on late-stage clinical trials, and therefore preclinical and earlier stages of investigations are not in the scope of this review but have been recently summarized else-where [3,6].

2.1. Cutaneous sclerosis

Nearly all patients with SSc have cutaneous involvement. The extent of cutaneous involvement varies immensely with some patients presenting with rapidly evolving diffuse cutaneous sclerosis (dcSSc) and others presenting with stable limited cutaneous sclerosis (lcSSc). In patients with dcSSc, skin thickening occurs in the hands and feet and extends proximally beyond the elbows or knees and often involves the trunk; whereas in patients with lcSSc, skin thickening is confined to the distal extremities, or may only affect the fingers (i.e. scler-odactyly) [7]. The cutaneous manifestations of SSc not only cause functional disability but they substantially contribute to pain, psychological distress, and body image dissatisfaction [8].

2.1.1. Existing therapies for cutaneous sclerosis—While the natural history of cutaneous sclerosis in dcSSc often involves a gradual improvement over time [9], randomized-controlled trials (RCTs) have demonstrated that treatment with immunosuppression can lead to a greater reduction in the extent of cutaneous sclerosis [10]. The mRSS is a measure of skin thickness and is often used as the primary outcome in clinical trials of patients with dcSSc. For instance, in Scleroderma Lung Study (SLS) I (12 months of oral cyclophosphamide [CYC] versus 12 months of placebo for SSc-ILD), patients with dcSSc randomized to CYC had an improvement in their mRSS of −5.3 at 12 months; whereas the dcSSc patients randomized to placebo group had an improvement in mRSS of only −1.7 at 12 months ($P = 0.008$) [10]. The mRSS (score range of 0 [no skin thickening] to 51 [most severe]) is a measure of skin thickness and is often used as the primary outcome in clinical trials of patients with dcSSc. A number of studies have demonstrated that it is sensitive to change in the context of SSc clinical trials; however, it should ideally be performed by the same examiner in a trial who has experience with this assessment to reduce inter-observer variability [11].

In addition to CYC, studies have demonstrated that treatment with mycophenolate mofetil (MMF) leads to improvements in cutaneous sclerosis [12,13]. In SLS II (12 months of CYC, followed by 12 months of placebo versus 24 months of MMF), change in mRSS was a key secondary outcome and improved in a clinically meaningful manner in both treatment groups (CYC: −5.35; MMF: −4.90) [11,12]. In a post-hoc analysis comparing the MMF arm of SLS II, with the placebo arm of SLS I, patients in the MMF arm experienced a greater reduction in the extent of cutaneous sclerosis at 24 months (−4.9 versus −2.4, respectively) in all patients, and in patients with dcSSc (−6.3 versus −3.9, respectively), and this difference was statistically significant [14]. In this post-hoc analysis, mRSS was also a key secondary outcome.

In light of the evidence from the aforementioned studies, MMF and CYC are often considered first-line therapies for the treatment of cutaneous sclerosis in patients with dcSSc, with CYC typically reserved for patients with severe cutaneous sclerosis who do not respond to MMF. Although the most recent EULAR treatment guidelines for SSc [15] include methotrexate as a first-line treatment for cutaneous sclerosis in SSc, the evidence for this approach is poor as there have been no RCTs comparing methotrexate with placebo for the treatment of cutaneous sclerosis in SSc. Hematopoietic stem cell transplant (HSCT) is a

potentially viable option for patients with rapidly evolving dcSSc refractory to treatment with immunosuppression. Given the risks (e.g. treatment-related side effects and early treatment-related mortality) associated with this procedure, this option is typically reserved for patients with rapidly progressive cutaneous sclerosis and underlying organ involvement refractory to treatment with immunosuppression. In the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (autologous HSCT versus monthly intravenous CYC for 12 months), the mean improvement in mRSS from baseline to 24 months was greater in the HSCT group (−19.9) than in the control group (−9.8) ($P < .001$) [16]. In the Scleroderma: Cyclophosphamide Or Transplantation (SCOT) trial (autologous HSCT versus monthly intravenous CYC for 12 months) [17], numerically more patients in the HSCT arm experienced a clinically meaningful improvement in mRSS compared with patients in the CYC arm. There was also a long-term survival benefit associated with HSCT in the SCOT trial; however, the results of the survival analysis should be interpreted with caution since the comparator arm only received CYC for 12 months, and typically patients with SSc receive immunosuppression beyond 1 year.

2.1.2. Emerging therapies for cutaneous sclerosis—In clinical practice, a considerable proportion of patients with dcSSc do not respond adequately or are intolerant to treatment with CYC or MMF. New treatment options are needed for patients who possess a progressive, treatment-resistant phenotype of cutaneous sclerosis. Promising therapeutic agents, such as tocilizumab [18] and abatacept [19], have failed to meet the primary endpoint of change in mRSS in RCTs, leaving an unmet clinical need (Table 2).

The novel agonist to the cannabinoid receptor type 2 (CB2), lenabasum, was found to reduce the expression of genes and proteins in key inflammatory and fibrotic pathways implicated in the pathogenesis of SSc [20]. In a phase II study of 43 patients with dcSSc, treatment with lenabasum was associated with an improvement in the American College of Rheumatology (ACR) Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) score (33% achieved a positive response in the lenabasum arm compared with 0% in the placebo arm) and there was a trend for a significant treatment effect on mRSS (P = 0.085) [21]. The CRISS is a composite response index derived from patients with dcSSc and is comprised of the following endpoints with differential weighting: mRSS, forced vital capacity (FVC)%-predicted, Health Assessment Questionnaire Disability Index (HAQ-DI), Patient Global Assessment, and Physician Global Assessment [22]. In the open-label extension to the Phase II study, a clinically meaningful improvement in mRSS was observed under treatment with lenabasum (−8.4 points at 6 months, −9.8 points at 12 months, and −10.7 points at 18 months), although given that there was no placebo arm in the extension study, it is unclear whether this represents a continued treatment effect versus the natural history of the disease [23]. The drug appears to be well-tolerated, and the phase III study (NCT03398837) has completed enrollment (N = 365), and the expected study completion date is in 2020.

The anti-fibrotic, pirfenidone, is currently under investigation in a phase II trial for SSc-ILD (SLS III), in which a key secondary endpoint is a change in mRSS (NCT03221257). An open-label phase II study of pirfenidone in SSc-ILD suggested an acceptable safety and tolerability profile of this agent [24]. In SLS III, pirfenidone is combined with upfront MMF therapy to determine whether combining an anti-fibrotic with MMF leads to an improvement

in skin and lung outcomes compared with MMF alone. Another novel anti-fibrotic, nintedanib was recently approved by the FDA for the treatment of SSc-ILD as described further below; however, this phase III study failed to detect a significant treatment effect for nintedanib on mRSS [25].

The B-cell depleting agent, rituximab, is frequently used in clinical practice to treat patients with dcSSc who fail to respond to conventional immunosuppressive therapies. Large RCTs of rituximab for SSc have not been performed; however, one relatively small RCT demonstrated that rituximab treatment led to a greater improvement in mRSS at 6 months compared with CYC [26]. In addition, small, open-label studies have demonstrated favorable effects on skin thickening [27,28]. A case-control analysis of 63 SSc patients from European Scleroderma Trial and Research (EUSTAR) cohort demonstrated that the patients with dcSSc who received rituximab experienced a greater reduction in MRSS compared with matched controls (N = 25; −24.0 ± 5.2% vs −7.7 ± 4.3%; p = 0.03) [29]. A small observational study of 18 patients with SSc demonstrated that combining rituximab with MMF is safe and leads to significant improvements in mRSS [30]. As discussed further below, there is also evidence that rituximab may possess disease-modifying effects on ILD in SSc, suggesting that this agent may play a role in the management of patients with treatment-resistant skin and lung disease. A phase II study combining rituximab with belimumab and MMF is ongoing (NCT03222492).

2.2. Interstitial lung disease

The majority of patients with SSc have interstitial abnormalities identified on high-resolution computed tomography (HRCT) imaging [31]. Patients with both lcSSc and dcSSc can develop ILD, and when present, the development of ILD in SSc increases the risk of mortality by at least threefold [32]. Furthermore, data from observational studies in both the US [33] and Europe [34] suggest that ILD is likely the leading cause of SSc-related death. While progression rates of ILD in SSc vary [35], patients typically experience progression within the first 4–5 years of their presentation [33]; therefore, treatment should be initiated early in affected patients to prevent ILD progression, especially in patients who possess features that increase their likelihood of ILD progression (e.g. Scl-70 antibody presence, male sex, African American race) [36].

2.2.1. Existing therapies for SSc-ILD—The treatment paradigm for SSc-ILD has historically involved the initiation of immunosuppressive therapy in patients who exhibit signs of or risk factors for the progression of ILD. In SLS I (oral CYC versus placebo), treatment with CYC led to significant improvements in the FVC%-predicted [10], total lung capacity (TLC)%-predicted [10], radiographic fibrosis [37], and quality of life [38] at 12 months. However, a year after cessation of CYC, there was no difference in the FVC%-predicted and TLC%-predicted between patients randomized to CYC versus placebo [39]. Moreover, during a 12-year follow-up period, there was no difference in long-term morbidity and mortality outcomes between patients randomized to CYC versus placebo in SLS I [40], suggesting that 1 year of treatment does not lead to a sustained improvement in health outcomes in SSc-ILD, and maintenance therapy is important. In SLS II [12], treatment with MMF for 24 months led to a significant improvement in FVC%-predicted [12], quantitative

radiographic fibrosis [37], and patient-reported outcomes [41]. There was no significant difference in efficacy outcomes between patients randomized to MMF versus CYC in SLS II, although MMF was better tolerated and had a more favorable safety profile compared with CYC in this study [12]. For instance, there were 15 versus 4 premature study drug withdrawals in the CYC and MMF arms, respectively, and over twice as many deaths in the CYC arm (11 CYC; 5 MMF), with most deaths attributable to progressive of ILD. When the MMF arm of SLS II was compared with the placebo arm of SLS I (with adjustment for baseline disease severity), patients treated with MMF demonstrated a significant improvement in FVC % predicted, DLCO% predicted, and dyspnea compared with the placebo group [14]. The collective findings from SLS I and II suggest that: (1) the duration of treatment for SSc-ILD should be longer than 1 year to yield a sustained benefit; (2) treatment with MMF and CYC both lead to short-term improvements in lung function, radiographic fibrosis, and quality of life; and (3) MMF appears to be safer and better tolerated than CYC.

2.2.2. Emerging therapies for SSc-ILD—Similar to cutaneous sclerosis, a substantial portion of patients with SSc-ILD experience progression of ILD despite treatment with CYC or MMF. HSCT may ameliorate ILD in carefully selected patients with dcSSc [16,17]. In the ASTIS study, in which 86% and 87% of the patients randomized to HSCT and CYC, respectively, had ILD, more patients in the HSCT arm experienced an improvement in the FVC compared with the CYC arm [16]. Similarly, in the SCOT study, in which 100% and 95% of the patients randomized to HSCT and CYC, respectively, had ILD, fewer patients randomized to HSCT experienced respiratory failure in the HSCT arm (N = 5) compared with the CYC arm (N = 13) at 1 year [17].

The tyrosine kinase inhibitor, nintedanib, was recently found to slow the rate of progression of ILD in the largest RCT (SENSCIS) ever conducted in SSc (N = 576) [25]. In this study, patients were randomized to 12 months of nintedanib versus 12 months of placebo, and the entry criteria permitted patients to continue treatment with MMF if they were taking a stable dose of MMF for at least 6 months prior to screening. Approximately half of all patients in each study arm were taking MMF at baseline. The rate of decline of FVC (mL/year) was greatest in the placebo arm not on background MMF at baseline (−119.3), and lowest in the nintedanib arm taking MMF at baseline (−40.2), and similar in the nintedanib alone arm (−63.9) and placebo arm on background MMF at baseline (−66.5). In contrast with MMF and CYC [12,41], treatment with nintedanib did not lead to an improvement in self-reported dyspnea as measured by the St. George's Respiratory Questionnaire (SGRQ), nor mRSS [25]. It is unclear why patients randomized to nintedanib did not experience an improvement in the SGRQ relative to placebo; however, it may be because responses to this questionnaire are influenced by extra-pulmonary manifestations of SSc not targeted by nintedanib (e.g. cutaneous sclerosis, arthritis). In terms of safety, patients on combination therapy (MMF + nintedanib) appeared to have a similar adverse event profile compared with patients on nintedanib alone; however, the majority of patients on nintedanib (76%) reported diarrhea (compared with 32% in the placebo arm), and this should be taken into consideration, particularly when treating patients who have co-morbid SSc-related lower gastrointestinal tract involvement.

Although it is difficult to draw meaningful conclusions about the benefits of upfront combination therapy (MMF + nintedanib) for SSc-ILD since patients were not randomized to MMF in the SENSCIS trial, the results support the hypothesis that using nintedanib as add-on therapy to MMF may be advantageous from a lung function standpoint. To this end, SLS III (NCT03221257) was conceived and designed to test the hypothesis that combining an anti-fibrotic therapy (e.g. pirfenidone) with a cytotoxic, immunosuppressive agent (e.g. mycophenolate) upfront may lead to an improved and faster treatment response compared with using an immunosuppressive agent alone. In SLS III, patients with SSc-ILD who are treatment naïve or early in their course of treatment with MMF (treatment with MMF for ≤6 months prior to enrollment) are randomized to either treatment with MMF alone or treatment with MMF plus pirfenidone for 18 months. In the prior open-label study phase II study on pirfenidone for SSc, MMF was combined with pirfenidone in 63.5% of patients with good tolerability [24].

The monoclonal antibody against the interleukin (IL)-6 receptor, tocilizumab, may play a role in the treatment of ILD in SSc, particularly in patients with early dcSSc with inflammatory features. Two RCTs have investigated the safety and efficacy of tocilizumab in patients with early dSSc with elevated acute phase reactant proteins, and while the primary outcome for these studies was mRSS, the FVC was a key secondary endpoint [18,42]. In the phase II faSScinate trial, fewer patients in the tocilizumab arm experienced a decline in FVC at 48 weeks than in the placebo group ($p = 0.0373$) [42]. Furthermore, the FVC treatment effect appeared to be sustained in the open-label extension period [18]. The phase III trial of tocilizumab for SSc did not meet the primary endpoint of mRSS [43].

As with cutaneous sclerosis treatment, rituximab is frequently used to treat SSc patients with progressive ILD resistant to CYC and MMF. Evidence for using rituximab in SSc-ILD is largely based on observational studies [27–30] and one small RCT of short duration, which demonstrated an improvement in lung function over 6 months in patients randomized to rituximab versus CYC [26]. In addition, a nested case-control analysis of the EUSTAR cohort found that the SSc-ILD patients (N = 9) treated with rituximab experienced stability in the FVC; whereas the matched-control patients experienced a significant decline in FVC over a median of 6 months [29].

To date, only one small RCT has been published on rituximab for SSc-ILD, and this study found that treatment with rituximab was associated with a significant improvement in lung function compared with placebo [44]. In this study, the majority of the rituximab-treated patients also experienced a reduction in ground glass opacities (but not reticulations) on HRCT at 18 months (based on visual assessment) [44]. A larger double-blind, RCT comparing IV CYC (600 mg/m2 body surface area monthly for 6 months) versus rituximab (1 g at baseline and at 2 weeks) for connective tissue disease-related ILD, including SSc-ILD, is currently underway in the UK (NCT01862926). The primary outcome for this study is the change in FVC at 48 weeks [45] (Table 3).

2.3. Raynaud phenomenon

Approximately 90–95% of patients with SSc have Raynaud phenomenon (RP), and it is often the presenting feature of SSc. It is characterized by peripheral vasospasm that leads to

a transient discoloration (erythema, cyanosis, and/or pallor) and/or numbness in the digits immediately following specific triggers, such as exposure to cold temperatures, relative changes in the temperature of the surrounding environment, and/or exposure to stress. The complications of RP are particularly severe in SSc, as the vasospasm compounds the already reduced blood flow in vessels affected by SSc vasculopathy [46]. Up to about 50% of patients with SSc are affected by RP may experience ischemic complications such as digital ulcers, pits, or gangrene [47]. This subset of patients requires more aggressive therapy with medication to prevent the loss of digital tissue. Recent studies have focused on determining whether specific drugs are more effective in preventing or healing digital ulcers, as some medications are known to be more effective for one than the other.

2.3.1. Existing therapies for SSc-Raynaud phenomenon and its ischemic complications—

The current standard of care for the management of patients experiencing RP-related digital ischemia involves minimizing environmental triggers and initiating medications that maximize peripheral blood flow (e.g. calcium channel blockers, phosphodiesterase inhibitors, endothelial receptor antagonists). On-demand therapy with phosphodiesterase inhibitors (i.e. sildenafil) for the treatment of primary or secondary RP was recently shown not to have clinically relevant efficacy, given the significant heterogeneity in patient responses [48]. Few studies have focused on the prevention of RP-associated ulcers. In the past decade, these areas of study have become areas of increasing interest (Table 4).

2.3.2. Emerging therapies and new applications of existing therapies for SSc-associated Raynaud's

2.3.2.1. Phosphodiesterase inhibitors.: The specific roles of phosphodiesterase inhibitors in healing RP-associated digital ulcers in SSc continues to be an active area of investigation, as this class of medications improves digital blood flow, and has been shown to have significant efficacy in secondary Raynaud's [49,50]. The SEDUCE study group recently evaluated the effects of sildenafil on ischemic digital ulcer healing in SSc in a randomized placebo-controlled trial [51]. Eighty-three patients with a total of 192 digital ulcers were included in the intention-to-treat analysis (89 in the sildenafil group, 103 in the placebo group), however the primary endpoint was not reached.

In order to expand therapeutic options for the treatment of SSc-related RP attacks, tadalafil was studied in a prospective double-blind placebo-controlled crossover study. Patients were randomized to receive a fixed dose of tadalafil at 20 mg daily or placebo for a 4 week period, and the RP condition score, frequency of RP episodes, and duration of RP episodes between treatment groups was compared. While tadalafil was well-tolerated, there was no significant difference in treatment response between the tadalafil arm and the placebo arm [52].

However, a subsequent study examined the benefits of tadalafil as an add-on therapy for the healing and prevention of digital ulcers. This double-blind, randomized, cross-over trial evaluated the efficacy of tadalafil as add-on therapy in patients with treatment-resistant RP. Patients with SSc and MCTD who were on vasodilators, but still having 4 or more episodes

of RP attacks per week were included and randomized to receive either tadalafil 20 mg per day or placebo. Significant improvements from baseline were observed in several outcome measures during tadalafil therapy compared to placebo, including mean daily frequency of RP episodes, mean daily duration of RP, and mean daily RP condition score. In the tadalafil group, all 24 digital lesions healed compared to only 3 of 13 in the placebo group, and only one new ulcer was reported during tadalafil therapy compared to 13 in patients on placebo therapy [53]. Collectively, these data suggest that phosphodiesterase-inhibitors play an important role in the healing and prevention of digital ulcers in SSc-related RP.

2.3.2.2. Prostacyclins and prostaglandins.: Prostacyclins and prostaglandins continue to serve as key therapies used to treat challenging cases of RP in the context of SSc. Iloprost, for example, serves as a standard treatment of existing digital ulcers [54–56]. It is currently indicated for patients with severe disabling Raynaud's unresponsive to other therapies for the prevention of ischemic pain, peripheral ulcers, and necrosis of the digits to prevent amputation. It may be administered by one of three schedules: (a) 3-day schedule as an inpatient for RP/SSc; (b) 5-day schedule as an outpatient for RP/SSc; or (c) continuous infusion for the treatment of patient with active or extensive digital ulcers, severe digital ischemia, or for patients who cannot tolerate higher rates of the infusion. Details of the complex infusion protocols can be found here [57].

Treprostanil, a synthetic analog of prostacyclin (PGI_2), has also been studied as a therapy for patients with SSc-associated Raynaud's and/or digital ulcers, in both oral and topical formulations. Oral treprostanil initially showed promise in patients with SSc and digital ischemia in a phase 1 study, where effective absorption and temporal associations with improved cutaneous perfusion and temperature were noted [58]. The recurrence of digital ulcers in patients with SSc after discontinuation of oral treprostanil was also noted in a multicentered retrospective study, also suggesting some benefit [59]. However, the association between vascular biomarkers and digital ulcerations in SSc was recently evaluated using the DISTOL-1 randomized controlled trial cohort, and a lack of strong response to any vascular, angiogenic, or inflammatory markers suggested that these patways are not primary drivers in the development of digital ulcer clinical outcomes in an SSc population [60].

The effects of topical treprostanil have also been a focus of recent work. Treprostanil iontophoresis in patients with SSc was also studied to determine its ability to improve digital blood flow during local (hand) cooling [61]. It showed promised as digital treprostanil iontophoresis shifted skin blood flow upward during local cooling on the hand and during the initial rewarming phase in patients with SSc. The safety profile of treprostinil hydrogel iontophoresis was also recently examined in a 2-stage randomized, placebo-controlled single ascending-dose study among healthy volunteers and patients with SSc-related digital ulcers and was found to be fairly well-tolerated, with 2 minimal local adverse effects reported among 5 SSc patients with digital ulcers [62].

A phase 2 multi-center, double-blind, RCT is currently examining the effects of intravenous iloprost on RP in patients with SSc. Forty-one patients were enrolled and randomized to receive either intravenous iloprost or placebo infusion, and the primary endpoint is the

change in weekly frequency of symptomatic RP attacks at 21 days. Results of this study are pending (NCT03867097), and the phase 3 trial is enrolling (NCT04040322).

2.3.2.3. Endothelin receptor antagonists.: Endothelin-1 is a well-recognized promoter of vasculopathy in SSc. Prior studies have demonstrated that bosentan, a dual endothelin receptor antagonist, successfully prevents RP-related digital ulcers in SSc. In an earlier clinical trial, RAPIDS-1, which enrolled SSc patients with or without digital ulcers at baseline, bosentan significantly reduced the number of new digital ulcers compared to placebo. The purpose of subsequent RAPIDS-2 trial is to evaluate the effects of bosentan compared to placebo on ulcer prevention and healing over a 24-week treatment period. Patients received bosentan 62.5 mg twice daily for 4 weeks and then 125 mg twice daily for 20 weeks or the equivalent placebo, and time to complete healing of the cardinal ulcer and the total number of new digital ulcers per patient over 24 weeks was assessed [63]. The investigators found that bosentan treatment was associated with a 30% reduction in the number of new ulcers compared with placebo (mean ± standard error: 1.9 ± 0.2 vs 2.7 ± 0.3 new ulcers; $p = 0.04$), and that the effect was greater in patients who entered the trial with more ulcers. There was no significant difference between treatments in healing rate of the cardinal ulcer [63]. This data suggests that bosentan may play an important role in digital ulcer prevention in SSc, but its role in digital ulcer healing is unclear.

As bosentan demonstrated success in its positive effects on digital ulcer preventions, an international group of investigators evaluated the efficacy of a newer dual endothelin receptor antagonist, macitentan, in reducing the number of new digital ulcers in SSc patients. Two double-blind placebo-controlled trials were conducted and enrolled patients with SSc and active digital ulcers, and patients were randomized to receive oral doses of 3 mg macitentan, 10 mg of macitentan, or placebo once daily and stratified according to the number of digital ulcers at baseline. In both trials, patients on placebo had a lower mean number of new digital ulcers and had fewer adverse events than patients in both treatment groups. As a result, the investigators recommended against using macitentan for the prevention of digital ulcers in this patient population [64] (NCT01474109; NCT01474122).

2.3.2.4. Topical agents.: The data supporting the efficacy of a variety of topical agents in the management of RP have been variable. A systematic review and meta-analysis recently examined the effects of local topical nitrates in primary and secondary RP with respect to parameters of digital blood flow, and clinical severity was recently completed [65]. Seven placebo-controlled trials were included (346 patients) in the meta-analysis, with 4 trials involving nitroglycerin ointments, 2 involving the nitroglycerin gel vehicle MQX-503, and 1 involving a compounded nitrite. The results of the meta-analysis demonstrated a moderate-to-large treatment effect in RP (standardized mean difference [SMD] = 0.70; 95% CI, 0.35–1.05; $P < .0001$). Subgroup analyses showed a large treatment effect in secondary RP (SMD = 0.95; 95% CI, 0.25–1.65; $P = .008$) and moderate effect in primary RP (SMD = 0.45; 95% CI, 0.05–0.85; $P = .03$) [65].

2.3.2.5. Other therapies under study.: A relatively novel therapy that shows promise in RP involves the local injection of botulinum toxin type A (Btx-A) in the hands of patients with SSc. Btx-A is a neurotoxin that acts as a neuromuscular blocking agent by blocking the

release of acetylcholine from presynaptic nerve terminals, thereby interfering with vascular smooth muscle contraction and enhancing local circulation [66]. In a recent double-blind, RCT, Btx-A was administered (50 units in 2.5 ml sterile saline) in one randomly selected hand and sterile saline (2.5 ml) in the opposite hand [67]. Follow-up at 1 and 4 months post-injection included laser Doppler imaging of hands, patient-reported outcomes, and physical examination. At 1-month follow-up, a significantly greater reduction in average blood flow was observed in Btx-A-treated hands compared to placebo-treated hands ($p = 0.024$). Change in blood flow at a 4-month follow-up was not significantly different between groups. Ultimately, the investigators concluded that there may be a role of Btx-A in treating a subset of patients with RP, and that further studies defining the patients who are most likely to benefit from this intervention are warranted. A phase 3 study is currently recruiting in France to assess whether or not a single injection schedule of BTX-A in both hands improves RP secondary to SSc better than a placebo at 4, 12, and 24 weeks after the treatment. (NCT03717961).

Riociguat, a stimulator of soluble guanylate cyclase which has downstream effects stimulating vasodilation, was recently studied to determine its efficacy and safety in SSc-associated digital ulcers [68]. In this multi-center randomized, double-blind, placebo-controlled pilot study, SSc patients with at least one visible active or painful digital ulcer were enrolled and randomized (1:1 placebo or riociguat maximum of 2.5 mg three times daily) for an 8-week titration period, followed by an 8-week stable dosing period. An optional 16-week open-label extension phase for patients with active DU/reoccur-rence of DUs within 1 month of the end of the main treatment phase followed. Ultimately, treatment with riociguat did not reduce the number of digital ulcer burden compared to placebo at 16 weeks.

The effects of statins on endothelial dysfunction and RP in SSc are currently under study by a group in Pittsburgh [69]. In this double-blind, randomized, placebo-controlled trial of atorvastatin 40 mg once daily vs placebo, 24 patients with early diffuse SSc (<3 years of SSc symptoms and RP) were enrolled if they had been on stable RP medications for at least 4 weeks. Improvement in microvascular endothelial function measured by reactive hyperemia index (RHI) was the primary outcome, and secondary outcomes included change in macrovascular endothelial function by brachial flow-mediated (FMD) dilation, and RP severity using the RP condition score (RCS) and visual analog scale (RP-VAS). In the atorvastatin treatment group, 60% (6/10) of patients improved their RHI, compared to 29% (4/14) in the placebo group ($p = 0.12$). No difference in change in peak FMD% was noted between groups. The RCS decreased 2 points in the statin group compared to no change in the placebo ($p = 0.12$; Table 2). While the results demonstrated a non-significant improvement in microvascular endothelial function and RCS scores with the treatment of atorvastatin, the number of patients enrolled into the trial was small and thus it may have been underpowered to capture a significant difference between groups.

Although acetylsalicylic acid (ASA) has been available for over 100 years, it has not been systematically studied in SSc, and it may potentially play a role in preventing SSc-related vascular injury. An ongoing study in Brazil aims to evaluate the effectiveness of ASA on microcirculation alterations in SSc patients. In this phase 4 placebo-controlled clinical trial,

70 patients will be randomized to take either 100 mg daily ASA or placebo for 4 weeks. Outcome measures will include periungual panoramic capillary microscopy, videocapillaroscopy and laser Doppler imaging, as well as a panel of vascular biomarkers. This study is still recruiting and results are not yet available.

2.4. Pulmonary hypertension

Pulmonary arterial hypertension (PAH) affects approximately 7–12% of patients with SSc, and it is recognized as a leading cause of SSc-related death [70,71]. Right ventricular failure has been associated with poor survival in SSc-PAH, and modest responses to existing therapies leave SSc patients with PAH with a higher relative mortality compared to PAH from other causes [72,73]. Monotherapy with prostacyclins, phosphodiesterase inhibitors, and endothelin receptor antagonists were the standard of care for many years. However, given the significant morbidity and mortality still associated with SSc-PAH, ongoing studies are now exploring alternative strategies, including the novel approach of combining these therapies (Table 5). [74] In addition, because approximately 50–70% of the pulmonary vasculature needs to be affected or obstructed before resting mPAP is elevated, investigators are also now exploring the treatment of exercise pulmonary hypertension (abnormal hemodynamic response to exercise), which is likely a marker of early pulmonary vascular disease. Determining whether the initiation of therapy at this earlier stage of PAH is beneficial for patients is another key focus of ongoing investigation [74].

2.4.1. Novel combinations of existing therapies for SSc-pulmonary arterial hypertension—

Data from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry suggest that patients with SSc-related PAH have a significantly shorter time to clinical worsening when treated with phosphodiesterase-5 inhibitor (PDE5i) monotherapy compared to patients treated with endothelin receptor antagonists (ERA) and PDE5i combination therapy [75]. Such data have fueled interest in the study of combination therapy for PAH in SSc. Upfront combination therapy with phosphodiesterase inhibitors and endothelial receptor antagonists was recently studied in the a treatment-naïve group of patients with SSc-PAH. In this multi-center, open-label, clinical trial, patients were treated for 36 weeks with tadalafil 20 mg daily and ambrisentan 5 mg daily, with medication up-titration occurring at week 4 as tolerated. Investigators then compared the change in RV mass on cardiac MRI (standard volumetric cine images) from baseline to 36-week follow-up within subjects. They found that measures of right and left ventricular systolic and diastolic function were improved after treatment. In addition, combination therapy was associated with significant improvements in RV and LV function as measured by cardiac MRI [76], suggesting that combining these medications is a promising therapeutic strategy.

Although trials comparing the efficacy of combination therapy vs. monotherapy for pulmonary hypertension in SSc are limited, one study compared the efficacy and safety of monotherapy with phosphodiesterase inhibitors (sildenafil) versus initial combination therapy with phosphodiesterase inhibitors and endothelial receptor antagonists (sildenafil and bosentan) for treatment of SSc-PAH. In this single-center, double-blind, RCT, 34 patients with SSc-PAH (Pulmonary Artery Systolic Pressures >35 mmHg by echocar-

diography), with a forced vital capacity >60% were randomized to receive either sildenafil plus placebo or to combination therapy with sildenafil plus bosentan for 24 weeks. Ultimately, there were no significant changes between groups in pulmonary artery pressures at 24 weeks from baseline, or in secondary end points including change in 6 Minute Walk Distance or Time To Clinical Worsening (TTCW is defined as the first occurrence of all-cause deaths, PAH related hospitalization, worsening of symptoms defined as a decrease of >15% in 6 min walk distance and worsening of NYHA functional class); however, the investigators recommended larger, better powered studies, as combination therapy was well-tolerated in these patients [77] (NCT03053739).

Because of the interest in treating early PAH, investigators have also explored the role of treating exercise-induced pulmonary hypertension (PH) in SSc. In cardiology, stress tests are increasingly utilized to better characterize hemodynamic changes, and a strong rationale now exists to suggest that a reduction in pulmonary vascular reserve may be an early signal of subclinical pulmonary hypertension [78]. Some studies now suggest that among SSc patients with normal resting mPAP, an excessive increase in mPAP during exercise coupled with an impairment in vascular dispensability may be indicative of an early stage of pulmonary vasculopathy, associated with reduced survival similar to patients with PH measured at rest [79,80].

A pilot study recently evaluated whether treatment of exercise-induced PH open-label daily ambrisentan positively affects changes in a 24-week interval in hemodynamics and exercise capacity in patients with SSc. Exercise-induced PH was defined as a mean pulmonary artery pressure of >30 mm Hg with maximum exercise and a transpulmonary gradient (TPG) of >15 mm Hg. Patients had normal hemodynamics at rest and were treated with 5–10 mg of ambrisentan daily. From baseline to 24 weeks, significant changes were identified in mean exercise pulmonary vascular resistance, mean 6 minute walk distance, mean exercise cardiac output, mean pulmonary artery pressure, and total pulmonary resistance. Placebo-controlled studies are now needed to confirm that these findings are attributable to a drug effect and to define the optimal therapeutic regimen for these patients [81].

The application of statin therapy is novel in the management of PAH. Statins have a vasoprotective effect, and may therefore add value to the management of PAH, a condition in which vascular dysfunction is prominent. The effects of rosuvastatin on ameliorating vascular dysfunction in SSc-related pulmonary hypertension were recently examined in a study of 40 patients with SSc randomized to receive either rosuvastatin or placebo. All participants completed transthoracic echocardiography, 6 minute walk tests, were categorized by WHO functional class, and had tolerability and safety monitored. The results of this phase-3 trial are not yet reported (NCT00984932).

2.4.2. Emerging therapies for SSc-pulmonary hypertension secondary to ILD

—A new study is now seeking to understand patients with interstitial lung disease (ILD) and scleroderma who develop pulmonary hypertension (PH) and how they fit into the treatment schema in SSc. Investigators from National Jewish and the University of Pittsburgh are using pressure-volume loops to derive right ventriculo-vascular coupling, pulmonary impedance, and invasive cardiopulmonary exercise testing to compare the efficacy of chronic macitentan

therapy in improving right ventricular hemodynamics, exercise capacity, and symptoms in scleroderma ILD-PH patients with and without PVL. The trial is currently ongoing (NCT03726398).

2.4.3. Emerging therapies for PAH secondary to connective tissue disease—

As connective tissue disease-associated PAH has a relatively poor prognosis relative to PAH from other causes, recent trials have focused on identifying novel therapies to improve outcomes for such patients. The safety and efficacy of riociguat were recently evaluated in an exploratory analysis using the 12-week, phase III Pulmonary Arterial hypertension sGC-stimulator Trial (PATENT)-1, and the long-term extension PATENT-2 data. Investigators specifically examined the results of the study in the subset of patients enrolled who had PAH-associated with SSc or another defined connective tissue disease. In the prospectively planned analysis, it was determined that riociguat was well-tolerated and associated with positive trends in several endpoints, including 6-minute walk distance, and that these findings were sustained at 2 years in this patient subgroup, though further studies need to be done [82].

A similar approach was taken to examine the effects of selexipag using the GRIPHON study population, specifically looking at the subset of patients with PAH-associated connective tissue disease. Of the 334 patients with PAH from connective tissue disease in this population, 170 patients had SSc. Selexipag was associated with delayed progression of PAH, as measured by a reduction in PAH related morbidity/mortality events, and was well-tolerated among the PAH-connective tissue disease population, including patients with SSc [83].

2.5. Gastrointestinal disease

The majority of patients with SSc experience gastrointestinal tract involvement. The gastrointestinal (GI) complications of SSc are variable, and include dysmotility, sphincter dysfunction, vascular malformations, and dysbiosis, each of which is managed differently. As there are no measures of immune-mediated disease activity in the GI tract, differentiating disease activity from damage is a major challenge. Furthermore, since no proven disease-modifying therapies exist for SSc-related GI involvement, the management of SSc-GI complications is currently focused on addressing and ameliorating patient symptoms. Patient symptoms may result from a variety of factors including underlying GI dysmotility and microbiota dysbiosis [84,85]. Recent studies have therefore focused on evaluating the role of probiotics in SSc, as well as identifying novel medications that can be used to enhance GI transit in this population.

2.5.1. Emerging therapies for SSc-GI disease

2.5.1.1. Probiotics.: The role of probiotics in patients with GI complications and SSc is unclear. The effects of probiotics on GI symptoms and on the immune system in patients with SSc with moderate-to-severe total scores on the UCLA GIT 2.0 were recently reported [86]. Patients were randomly assigned to receive a daily dose of probiotics (several strains of Lactobacillus) or placebo for 8 weeks. Seventy-three patients were randomized to receive probiotics or placebo. While there was no difference in UCLA GIT 2.0 scores, the probiotic

group showed a significant decrease in the proportion of Th17 cells compared to placebo, suggesting a possible immunomodulatory effect in SSc.

In another probiotic RCT, 37 patients with SSc with a moderate to severe total score on the UCLA GIT 2.0 were randomized to receive probiotics (containing *Lactobacillus* and *Bifidobacterium)* and 36 patients were randomized to placebo. Both groups were followed for 8 weeks, completed UCLA GIT 2.0 questionnaires and HAQ-DI surveys. Because probiotics are thought to act by modulating the microbiome and the immune response, the authors also collected serum samples to explore changes in the circulating levels of Th1, Th2, Th17, and regulatory T cells. At week 8, there was no significant difference in total or subdomain UCLA GIT 2.0 scores between the two groups, in the HAQ-DI score, or in the proportion of Th1, Th2, and regulatory T cells; however, the probiotic group did have a significantly decreased proportion of Th17 cells compared to placebo ($p = 0.003$). Overall, the authors concluded that probiotics did not improve GI symptoms in SSc patients [86], however the use of the UCLA GIT total score as an outcome measure may not have been a sensitive enough tool to detect improvement in symptoms of distention, bloating, and diarrhea.

Another study, which focused on a more homogenous SSc population, recently determined that the addition of probiotics may enhance existing therapeutic GI strategies [87]. In this open-label pilot trial, investigators sought to evaluate how treatment with probiotics, antibiotics, or a combination of both compare in the management of GI symptoms in 40 SSc patients with small intestinal bacterial overgrowth (SIBO) assessed by hydrogen breath test. Patients were assigned to one of the three treatment groups (Saccharomyces boulardii, metronidazole, or combination therapy) for 24 weeks, and patient-reported outcomes were collected (NIH-GI PROMIS). Interestingly, at the end of the 2 month period, SIBO was eradicated in 55% of the combination therapy group, 33% of the probiotic group, and 25% of the antibiotic treatment group. In addition, the probiotic group and combination therapy groups had decreased diarrhea, abdominal pain, and gas, bloating, and flatulence. These symptomatic improvements were not identified in the antibiotic group. Reductions in expired hydrogen at 45 to 60 min were 48% and 44% in the combination group, 18% and 20% in the antibiotic group, and 53% and 60% in the probiotic groups in the first and second months, respectively ($p < 0.01$). These data support a role for probiotics to alleviate clinical symptoms in a subset of patients with SSc.

2.5.1.2. Promotility agents.: The safety and efficacy of prucalopride, a $5HT_4$ receptor agonist was recently demonstrated in a cross-over 2 × 2 study [67]. Patients with mild to moderately severe SSc-GI symptoms were enrolled (n = 40) and randomized 1:1 to prucalopride 2 mg/day or no treatment for 1 month and vice versa after a 2-week washout period. Prucalopride was significantly associated with more intestinal evacuations and improved orocecal transit times, as well as significant improvements in the UCLA GIT 2.0 constipation, reflux, and bloating scores, suggesting that it may be effective in treating dysmotility symptoms in SSc patients.

Interestingly, buspirone, an oral 5-HT1A receptor agonist, may improve the dysfunction of the lower esophageal sphincter in patients with SSc. In an open-label trial, the effects of

buspirone on esophageal motor function and symptoms in SSc patients with esophageal involvement were evaluated. All 30 patients enrolled had symptomatic esophageal involvement, despite PPI use, and underwent high-resolution manometry and CT chest for assessment of motor function and esophageal dilatation, respectively. Visual analog scales were used to score GI symptom severity. In the 22 patients who completed the trial, lower esophageal sphincter resting pressure significantly increased after buspirone administration. Scores for heartburn and regurgitation significantly decreased at 4 weeks compared to baseline. These findings suggest that buspirone could improve symptoms in patients with SSc who report reflux symptoms despite under-going standard treatment [88].

While several other agents have been proposed in case series to target dysmotility in SSc GI disease (e.g. IVIG, pyr-idostigmine), large prospective placebo-controlled trials are lacking and should be a focus of future research.

2.5.1.3. Other considerations.: Among patients with severe GI disease, it is important to ensure nutritional goals are met, as the prevalence of malnutrition in SSc is estimated to be between 15% and 58% [89]. A validated screening tool to assess for malnutrition is the Malnutrition Universal Screening Tool (a.k.a. 'MUST'), and it has been recommended by some experts that all SSc patients should be screened [90,91]. This tool includes body mass index (BMI), uninten-tional weight loss in the preceding 3–6 month period, and an acute disease effect score to estimate the risk of malnutrition. In patients who screen positive, referrals to a nutritionist and gastroenterologist should be considered. Supplemental enteral or parenteral nutrition may be necessary to sustain nutrition and weight in patients with severe disease [89].

3. Conclusion

An expanding pipeline of investigational therapeutic agents now exists for treating the unique clinical manifestations of SSc. This review highlighted products in development in phase 3 and phase 4 clinical trials. However, our growing understanding of the pathogenesis of SSc supports the clinical application of several novel therapies, including anti-fibrotic therapies and biologic agents. While these interventions have the potential to change the clinical course of the disease, determining the optimal drug and/or combination of drugs will remain an ongoing focus of future work. In addition, the early identification of organ involvement and application of targeted therapy, prior to the development of severe organ damage, will remain an important priority. We remain optimistic that current drug development and clinical trials will continue to yield promising therapeutic strategies for improving health outcomes for all patients with SSc.

4. Expert opinion

In the last decade, the number of therapeutic options available to treat the unique clinical dimensions of SSc has dramatically increased. As highlighted in this review, these agents target different aspects of the immune system and elicit differential effects on various organ systems within and between individual patients. Data from all of the clinical trials conducted to date suggest that SSc is a heterogeneous disease both in terms of manifestations and

response to therapies. This heterogeneity is perhaps the most challenging component of drug discovery and development in this field.

It is our opinion that future therapeutic studies should consider combining therapies that target different aspects of the immune system (e.g. Anti-inflammatory plus anti-fibrotic). Similar to other complex connective tissue diseases that employ combination therapy (e.g. systemic lupus erythematosus and rheumatoid arthritis), patients with SSc may also benefit from this approach. Research studies are therefore needed to understand the optimal timing to add on certain therapies and to determine whether this should be done upfront or whether treatments should be added sequentially over specified time frames.

In addition, improved clinical and biological phenotyping may help homogenize study cohorts to increase the likelihood of detecting significant treatment effects. Our clinical experience has shown us that certain patients derive benefit from IL-6 inhibition, even though the phase III RCT of the IL-6 inhibitor, tocilizumab, did not meet its primary endpoint. To us, this suggests that we need to do a better job of enriching study cohorts to include the patients who may derive the most benefit from the therapeutic intervention under study. While this may constrain local enrollment into studies, improved global recruitment efforts, as demonstrated in the SENSCIS trial [25], may overcome this limitation.

Another hurdle in SSc therapeutics is identifying and defining objective treatment-responsive endpoints. While we have several valid endpoints to study ILD in SSc, endpoints for the other clinical manifestations of SSc are lacking. The GI tract is the perfect example of this. How can we determine whether biologics or anti-fibrotics modify the course of GI disease in SSc if no valid, objective SSc-GI endpoints exist? To this end, we are currently conducting studies to investigate whether the GI microbiome may be a marker of GI disease activity in SSc. However, additional dedicated research efforts primarily aimed at developing and validating endpoints in SSc are greatly needed.

Finally, a significant unmet therapeutic need in SSc is prevention. The collective efforts to halt inflammation, fibrosis, and vascular changes in SSc are typically initiated after there is already evidence of end-organ damage (i.e. loss of lung function, renal insufficiency, etc.). Furthering our knowledge of the pathobiology of SSc may help uncover treatment targets that could curtail the progression of early SSc. The goal here would be to intervene early with an agent that could selectively target key mediators of profibrotic and proinflammatory pathways to reduce the likelihood of a patient developing specific clinical manifestations of SSc, such as ILD.

In summary, despite the fact that the number of clinical trials in SSc has increased in recent years, there is still a great deal more work to do in SSc research to: (a) understand the optimal timing to initiate therapy in SSc; (b) discover how to combine therapies; (c) improve our ability to phenotype patients; (d) define new disease-specific endpoints; and (e) determine the best preventative treatment strategies. We anticipate that research conducted in the next decade will help address these unanswered questions and propel this field forward in new and exciting ways.

Funding

Z McMahan is supported by the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases via grant K23 AR071473, the Scleroderma Research Foundation and the Jerome L Greene Foundation. ER Volkmann is supported by National Institutes of Health/The National Heart, Lung, and Blood Institute via grant K23 HL150237-01 and the Rheumatology Research Foundation.

Reviewer disclosures

One referee has received speaker's fees, travel grants, research funding, or compensation for consultancies or board memberships from Abbvie, Actelion, Baxalta/Shire, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Chugai, Genzyme, Gilead Biosciences, Hexal/Sandoz, Janssen-Cilag, Merck Sharp and Dohme, Novartis, Pfizer, Roche, Sanofi Pasteur and UCB Pharma. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

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Article highlights

- A variety of novel therapeutic strategies for the management of SSc now exist and are grounded in solid scientific research.
- These therapeutic strategies primarily target individual organ manifestations of SSc.
- Immunosuppressants with potential disease-modifying effects continue to be important components of the therapeutic armamentarium for SSc.
- Patients with refractory disease may require combination therapy with anti-fibrotics and/or other agents.
- Defining mechanistically based SSc subgroups based on biological and clinical profiles will reduce heterogeneity in clinical trial cohorts and may enhance our ability to detect treatment effects.
- Preventing both the onset and progression of individual organ manifestation remains an important unmet clinical need in SSc.

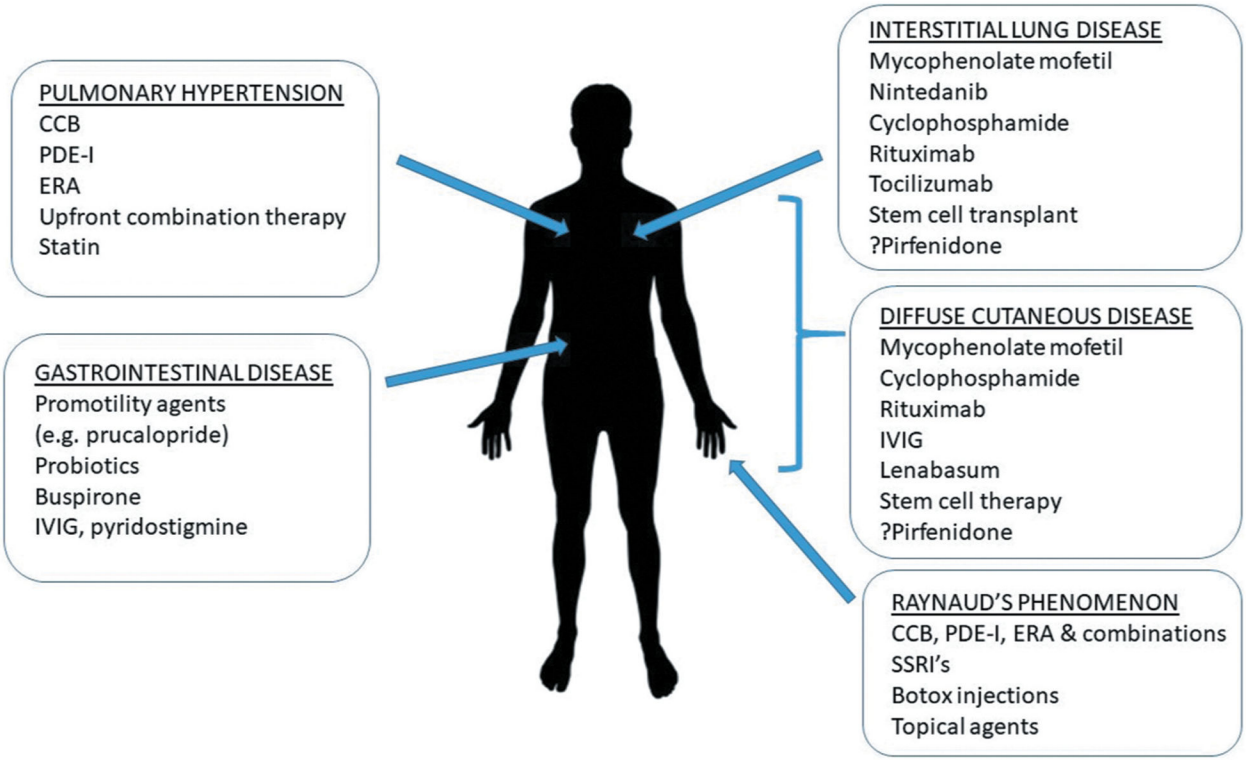

Figure 1.

Drugs targeting specific complications of systemic sclerosis in the skin, lungs, peripheral vasculature, pulmonary arteries, and gastrointestinal tract.

Table 1.

Examples of some factors that often drive treatment decisions in SSc beyond the organ system involved.

Factor	Example
Sex	Male patients with SSc-ILD have an increased risk of progression of ILD and may warrant more aggressive upfront therapy for ILD.
Disease duration	Patients with SSc of <5 years disease duration may require a more aggressive approach for the management of ILD and/or cutaneous sclerosis since these dimensions of the disease are more likely to progress within this time frame.
Scl-70 antibody positivity	Patients with newly diagnosed SSc-ILD who have normal lung function may benefit from treatment for ILD because their ILD is more likely to progress rapidly.
Centromere antibody positivity	Patient with newly diagnosed SSc-ILD who have normal lung function may *not* benefit from treatment for ILD because their ILD is less likely to progress rapidly.
Overlap syndromes	Patients with overlap syndromes, such as rheumatoid arthritis, may benefit from therapy which targets both inflammatory arthritis and SSc
Age	Older patients with co-morbidities may have an increased risk of infectious complications when multiple immunosuppressant therapies are used in combination

Table 2.

Existing and phase 2, 3 investigational therapies for dcSSc.

Agent	Trial Phase (NCT)	Skin endpoint	Efficacy outcomes
Cyclophosphamide	3 (NCT00004563)	Secondary endpoint: mRSS	Significant improvement at 12 months compared with placebo arm
Mycophenolate mofetil (MMF)	2 (NCT00883129)	Secondary endpoint: mRSS	Clinically meaningful improvement at 24 months with no difference between cyclophosphamide arm
Abatacept	2 (NCT02161406)	Primary endpoint: mRSS	No significant skin treatment effect compared with placebo arm
Tociluzimab	3 (NCT02453256)	Primary endpoint: mRSS	No significant skin treatment effect compared with placebo arm
Belimumab + Rituximab + MMF	2 (NCT03844061)	Primary endpoint: CRISS	Trial ongoing
Brentuximab Vedotin	1/2 (NCT03222492)	Exploratory endpoints: mRSS, CRISS	Trial ongoing
Pirfenidone	2 (NCT03221257)	Secondary endpoint: mRSS	Trial ongoing
Nintedanib	3 (NCT02597933)	Secondary endpoint: mRSS	No significant skin treatment effect compared with placebo arm
Intravenous immunoglobulin (IVIG)	2 (NCT04138485)	Primary endpoint: CRISS; Secondary endpoint: mRSS	Trial ongoing

Table 3.

Existing and phase 2, 3 investigational therapies for SSc-ILD.

Agent	Trial Phase (NCT)	Skin endpoint	Efficacy outcomes
Cyclophosphamide (CYC)	3 (NCT00004563)	Primary endpoint: FVC%-predicted	Significant improvement at 12 months
Mycophenolate mofetil (MMF)	2 (NCT00883129)	Primary endpoint: FVC%-predicted	Significant improvement at 24 months
Tociluzimab	3 (NCT02453256)	Secondary endpoint: FVC%-predicted	Trial ongoing
Pirfenidone	2 (NCT03221257)	Primary endpoint: FVC%-predicted	Trial ongoing
Nintedanib	3 (NCT02597933)	Primary endpoint: Rate of decline of FVC	Significant treatment effect at 12 months
Rituximab + MMF	3 (NCT02990286)	Primary endpoint: FVC%-predicted	Trial ongoing
Rituximab vs. CYC	2/3 (NCT01862926)	Primary endpoint: Absolute change in FVC	Trial ongoing
Bortezomib + MMF	2 (NCT02370693)	Secondary endpoint: Change in FVC	Trial ongoing

Table 4.

Existing and phase 3 and 4 investigational therapies for SSc Raynaud phenomenon.

		Raynaud's phenomenon	
Agent	**Trial Phase (NCT)**	**Vascular endpoint**	**Efficacy outcomes**
Sildenafil vs. Placebo	3 (NCT01295736)	Primary endpoints: time to healing of ischemic digital ulcers	No significant differences in primary endpoint at 90 days
Tadalafil vs. Placebo	3 (reference 47)	Primary endpoints: Raynaud's Phenomenon (RP) condition score, frequency of RP episodes, duration of RP episodes	No significant differences in primary endpoint
Add-on tadalafil vs. add-on placebo	3 (NCT00626665)	Primary endpoints: frequency and duration of RP attacks, evolution of trophic digital lesions	Significant improvement relative to baseline and placebo
Bosentan vs. placebo	3 (NCT00077584)	Primary endpoints: time to complete healing of the cardinal ulcer and the total number of new digital ulcers	Significant improvement in the reduction of number of new ulcers compared to placebo
Macitentan vs. placebo	3 (NCT01474109)	Primary endpoints: Incidence rate of new digital ulcers	No significant differences in primary endpoint at 16 weeks
Macitentan vs. placebo	3 (NCT01474122)	Primary endpoints: Incidence Rate of New Digital Ulcers	No significant differences in primary endpoint primary endpoints at 16 weeks
Intravenous Iloprost vs. Placebo	3 (NCT04040322)	Primary endpoint: Frequency of symptomatic RP attacks	Trial ongoing
Botox-A vs. Placebo	3 (NCT03717961)	Primary endpoint: Absolute change from baseline in the number of RP attacks per week at 4 weeks	Trial ongoing
Aspirin vs. placebo	4 (NCT03558854)	Primary endpoints: Serum level of thromboxane A	Trial ongoing

Expert Opin Pharmacother. Author manuscript; available in PMC 2021 February 27.

Table 5.

Existing and phase 3 and 4 investigational therapies for SSc pulmonary hypertension.

Pulmonary hypertension			
Agent	**Trial Phase (NCT)**	**Endpoint (s)**	**Efficacy outcomes**
Upfront tadalafil and ambrisentan	4 (NCT01042158)	Primary endpoint: Assessment of change in right ventricular mass via standard volumetric cine images of the right heart	Significant therapeutic effect at 36 weeks
Sildenafil vs. Sildenafil plus bosentan	4 (NCT03053739)	Primary endpoint: Change in Pulmonary artery pressures measured by echocardiography	No significant change in primary endpoints at 24 weeks
Ambrisentan (open label)	4 (NCT01051960)	Primary endpoint: Change in multipoint exercise total pulmonary resistance (TPR)from baseline	Significant treatment effect at 24 weeks
Macitentan (open label)	3 (NCT03726398)	Primary endpoint: Change in exercise pulmonary vascular resistance (PVR)	Trial ongoing
Rosuvastatin vs. placebo	3 (NCT00984932)	Primary endpoints: exercise capacity measured by the SMWT, mPAP and WHO functional class change	Recruitment completed, Results pending

Expert Opin Pharmacother. Author manuscript; available in PMC 2021 February 27.