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EMERGING TREATMENT MODELS IN RHEUMATOLOGY

Current and Future Outlook on Disease Modification and Defining Low Disease Activity in Systemic Sclerosis

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Systemic sclerosis (SSc) is an autoimmune rheumatic disease with heterogeneous clinical manifestations and a variable course in which the severity of the pathology dictates the disease prognosis and course. Among autoimmune rheumatic diseases, SSc has the highest mortality rate among all rheumatic diseases, though there are exciting new therapeutic targets that appear to halt the progression of SSc manifestations such as skin or lung fibrosis. In selected patients, high-intensity regimens with autologous stem cell transplantation can favorably modify the course. In what was once thought to be an untreatable disease, targeted therapies have now changed the outlook of SSc to a treatable disorder. Herein, we discuss the targeted therapies modifying the outlook on selected organ involvement and creating opportunities for future treatment. We also present a framework for defining low disease activity in SSc.

INTRODUCTION

Systemic sclerosis (SSc) is a rare disease characterized by vasculopathy and fibrosis in the skin and internal organs (1). The proposed pathophysiology is a triad of vascular damage with endothelial dysfunction, dysregulation of innate and adaptive immunity, and widespread fibrosis in multiple organs (2,3). The mortality rate in SSc is higher than in any other rheumatic disease (4,5).

In contrast to rheumatoid arthritis (RA), the concept and use of disease-modifying therapies that attenuate or reverse pathology and clinical impact are not currently applied to SSc. The notion of disease modification in SSc has now advanced to reality based on data from recent clinical trials. Autologous hematopo-

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ietic stem cell transplantation (HSCT) trials in diffuse cutaneous SSc (dcSSc) have demonstrated survival benefit, including meaningful improvements in skin, lung fibrosis, and health-related quality of life (HRQoL) (6–9).

In this report, we discuss specific treatments that have modified the course of organ-specific manifestations in SSc and have started the conversation on defining low disease activity in SSc.

What is disease-modifying therapy?

We borrow the concept of "disease-modifying therapy" from the use of disease-modifying antirheumatic drugs (DMARDs) and biologic response modifiers in RA. In the past 3 decades, RA treatment has evolved from symptom management to the implementation of DMARDs and/or biologic response modifiers. The early institution of DMARDs or biologic response modifiers in RA induces clinical remission, reduces the frequency of relapse, abrogates joint damage, preserves physical function, improves HRQoL, and prevents long-term disability (10). Similarly, we can conceptualize disease-modifying therapy in SSc as therapies or medication regimens that positively impact the disease course by stabilizing and potentially improving organ function. This, in turn, improves HRQoL and reduces morbidity and mortality (11).

Natural history of the disease

Understanding the natural history of the SSc disease process is vital to the concept of disease-modifying therapy in the context of timing and patient selection. Early clinical features include Raynaud's phenomenon (RP) and gastroesophageal reflux disease (12). Skin fibrosis is a pathologic hallmark of the disease and is frequently preceded by puffy and swollen fingers. Patients with puffy fingers, definite RP, typical nailfold capillary changes, and the presence of SSc-specific antibodies can be considered to have very-early-diagnosed SSc (13,14). Thereafter, patients may progress to 1 of 3 clinical disease subsets based on the extent of skin involvement.

Patients with skin involvement restricted to the limbs distal to the elbows or knees, with or without face involvement, are classified as having limited cutaneous SSc (lcSSc). Patients with distal as well as proximal involvement (including the torso) are classified as having dcSSc. A small subset of patients without skin involvement but who have scleroderma-specific antibodies and internal organ involvement are considered to have SSc without scleroderma (15–17). This differentiation is important as dcSSc is associated with higher morbidity and mortality, mainly due to more severe and/or progressive internal organ involvement (18). However, this differentiation of the clinical phenotypes is an oversimplification of the disease process.

The biology of SSc is complex, heterogeneous, and dynamic, with sequentially overlapping features of inflammation, autoimmunity, tissue injury, and fibrosis. Skin thickness is generally progressive within the first 3 years after the start of RP in dcSSc, but there is individual variability (15,16). The extent and severity of skin involvement in dcSSc generally level off by years 4 and 5, and then clinically appear to improve both via de-remodeling and atrophy (19). Only a minority of patients have a new emergence of progressive cutaneous involvement beyond 5 years after disease onset. There is an increased risk for the development of internal organ involvement during the progressive skin phase. For example, in dcSSc, most internal organ involvement (lung, renal, cardiac, and gastrointestinal) occurs in the first 3–5 years after disease onset (Figure 1) (16). In the early phase of dcSSc, internal organ involvement—although clinically silent—may evolve at the same time as progressive skin disease. There are, however, exceptions. For example, pulmonary arterial hypertension (PAH) is generally a late complication that is more common in lcSSc (20). Lung fibrosis can also develop separately from or in conjunction with pulmonary hypertension. Fibrosis can advance in a self-perpetuating manner and may not be driven solely by an immune-mediated process (21).

We believe SSc can be conceptualized as a family of similar diseases—an idea supported by the identification of molecular subsets by whole-genome gene expression profiling, with distinct clinical and serologic features and recognized phases within some subtypes (22). The delayed emergence of new organ involvement and gradual progression of the disease provide clinicians with a realistic opportunity to impede disease progression and change disease course.

Why is disease-modifying therapy a challenge in SSc?

Many challenges exist in demonstrating disease-modifying effects in SSc patients. First, the disease is heterogeneous with different patterns of evolution among the clinical subsets, as previously outlined (5,23–25). Patients usually present with predominantly vasculopathic complications (such as RP, digital

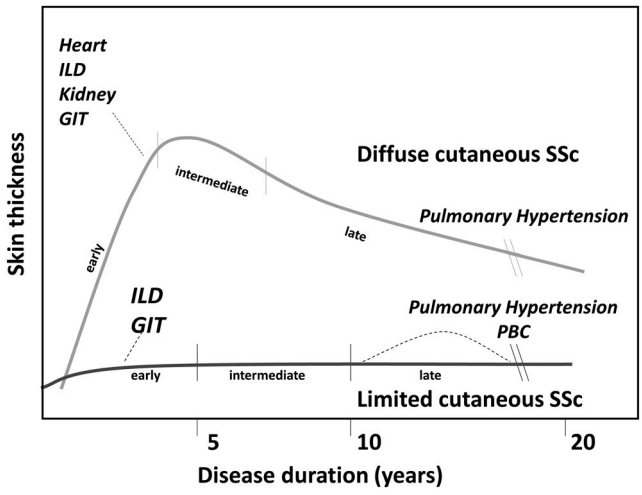

Figure 1. The usual timing of organ-specific manifestations in systemic sclerosis (SSc). ILD = interstitial lung disease; GIT = gastrointestinal tract; PBC = primary biliary cirrhosis. Adapted, with permission, from Steen V, Medsger TA. Systemic sclerosis. Lippincott Williams & Wilkins; 1996.

ulcers, PAH, scleroderma renal crisis [SRC], and gastrointestinal involvement), predominately fibrotic complications (such as skin fibrosis, joint involvement, lung fibrosis, and cardiac fibrosis), or a combination of these features. Within each cutaneous subgroup, there is heterogeneity in internal organ involvement (18). Second, there are molecular differences in the skin gene expression data in patients with a similar phenotype. One such formulation identified 4 subsets based on skin gene expression data: normal-like, inflammatory, fibroproliferative, and limited (22,26). These subsets help identify patients at risk for internal organ involvement, such as interstitial lung disease (ILD), as well as their response to current therapies (26,27). Measuring gene expression subsets in clinical trials, and possibly even in routine clinical care, may clearly distinguish and clarify patient heterogeneity in the near future and provide a window through which to understand and predict patient response to therapy. Third, the predictors of disease status at a specific time point (incidence or severity of organ-based complications, which is largely influenced by autoantibodies) may differ from predictors of disease progression (28,29).

Unlike the Disease Activity Score in 28 joints (30), Clinical Disease Activity Index (31), or other disease activity measures in RA, we lack reliable tools with which we can define the achievement of remission in SSc. In dcSSc, the modified Rodnan skin score (MRSS) (32), and recently, a combined responder index in dcSSc (American College of Rheumatology Combined Response Index in diffuse cutaneous Systemic Sclerosis [ACR CRISS] [33]—a composite end point that captures cardiopulmonary-renal involvement and change in MRSS, Health Assessment Questionnaire disability index [HAQ DI] [34], patient global assessment of disease activity, physician global assessment of disease activity, and forced vital capacity percent predicted [FVC%]) are used as outcome measures to assess the efficacy of drugs. These measures have not been validated in lcSSc, and some of these may not perform well (35). Further, clinical heterogeneity of the disease does not allow for precise definition of global disease activity. Composite scores such as the revised European Scleroderma Research Group Activity Index (28) have been proposed but not widely accepted in the evaluation of disease activity. Novel approaches for assessing disease activity in SSc are currently under development (36).

Are there currently disease-modifying therapies for SSc?

Despite the limitations in disease activity measurement in SSc, treatment approaches directed toward specific biologic targets appear to be positively influencing outcomes in SSc (Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41246/abstract). This concept can be approached by categorizing SSc manifestations into vasculopathic, immunologic, or inflammatory involvement as well as tissue fibrosis.

Vasculopathy

The predominant vascular complications in SSc are RP, PAH, SRC, and digital ulcers. Morbidity and mortality are high in patients with PAH and SRC. RP and digital ulcers are chronic complications that can limit hand function, increase morbidity and disability (37), and impact HRQoL. Pathophysiologic mechanisms in SSc vasculopathy are characterized by initial vascular endothelial injury and dysfunction followed by vessel wall remodeling with intimal and medial thickening, leading to luminal narrowing, vascular stiffness, and tissue hypoxia (38).

Pulmonary arterial hypertension. One of the relevant vasculopathic manifestations, which is associated with significant mortality and morbidity in SSc patients, is PAH. The prevalence of PAH measured by right-sided heart catheterization in large cohorts of SSc patients ranges from 5% to 12% (39,40). SSc-PAH is associated with a worse outcome compared to idiopathic PAH because there are non–PAH-related factors in SSc like coexistent ILD-associated pulmonary hypertension, pulmonary venoocclusive disease, SSc-related myocardial disease, and later age at disease onset (41,42). Greater emphasis has been put on early screening and detection of SSc-PAH with the use of composite algorithms, allowing for the earlier institution of PAH-specific therapy (43–45). There is a growing body of evidence that this approach may improve morbidity outcomes, although the effect on long-term mortality is unclear (46). The lower incidence of SSc-PAH in patients treated with dihydropyridine calcium antagonists offers a tantalizing glimpse into the potential disease-modifying actions of fairly modest vasodilator therapy on long-term outcomes in SSc (47).

There are multiple approved therapies for PAH management that target 1 of the 3 pathogenic pathways: 1) endothelin antagonists, 2) nitric oxide (NO)/soluble guanylate cyclase (GC) agonists/stimulators, and 3) prostacyclin analogs (48). High-quality randomized controlled trials (RCTs) have shown that upfront or sequential combination therapies delay time to clinical worsening in PAH patients. Similar approaches with combination therapies have suggested efficacy in treating SSc-PAH. In a recent meta-analysis, combination therapy targeting PAH was demonstrated to have greater therapeutic efficacy than monotherapy in patients with SSc-PAH. There was a 27% reduction in clinical worsening (pooled relative risk 0.73 [95% confidence interval 0.60–0.89]) (P = 0.002) and probable improvement of exercise capacity in these patients (49). A recent trial of rituximab (RTX) in SSc-PAH showed trends of benefit on functional status (6-munute walk test) and pulmonary vascular resistance versus placebo (ClinicalTrials.gov identifier: NCT01086540), and there is also an ongoing trial of tocilizumab in the background of currently approved therapies (ClinicalTrials.gov identifier: NCT02676947) (50,51).

Raynaud's phenomenon and digital ulcers. In SSc, common and burdensome vascular manifestations include RP and digital ulcers. RP can be an early sign preceding the diagnosis of SSc, usually emerging prior to tissue fibrosis (52). RP is a manifestation of abnormal cutaneous vessel function involved in thermal regulation of blood flow (53). The presence of RP and the loss of normal regulation of cutaneous vascular tone are often predictors of SSc development—although they are not specific to SSc, cannot be used alone as predictors, and may be long-delayed symptoms (52,54).

Digital ulcers are a significant cause of morbidity, with ~50% of SSc patients developing digital ulcers during their disease course (18). Digital ulcers can be a sporadic phenomenon, but for some patients, they are recurrent, continuous, and/or refractory (55). Digital ulcers can lead to significant disability in the form of impaired hand function and increased pain, loss of employment, and medical complications like gangrene, cellulitis, osteomyelitis, and digital amputation. Progress has been made in secondary prevention, although with mixed results. Phosphodiesterase 5 (PDE5) inhibitors, especially sildenafil, can reduce the frequency of RP episodes in SSc (56). A recent RCT comparing the use of oral sildenafil (20 mg/3 times a day) to placebo favored sildenafil in significantly decreasing the number of digital ulcers at week 12, but did not meet the primary end point of time to healing (57). In SSc patients with refractory and recurrent digital ulcers, it has been shown that 62.5 mg of bosentan (an endothelin 1 receptor antagonist) 2 times a day over a 4-week-period, followed by 125 mg of bosentan 2 times a day can reduce the number of new digital ulcers in those with >4 previous digital ulcers, without any effect on healing digital ulcers that already present (58,59). Intravenous (IV) prostanoid therapy improves digital ulcer healing and reduces the number of new digital ulcers. In 2 multicenter, double-blind, randomized trials, IV prostanoid therapy (iloprost 0.5–2.0 ng/kg/minute over 6 hours for 5 consecutive days) was associated with significant improvement in the frequency of RP episodes and greater improvement in digital ulcer healing (60,61).

Scleroderma renal crisis. A major, life-threatening vasculopathic manifestation of SSc is SRC (62). SRC is a rare complication that affects 2–15% of patients with SSc (11% of dcSSc patients and 4% of lcSSc patients) (40). SRC typically presents in patients with early, rapidly progressive dcSSc, often with the presence of anti-RNA polymerase III antibodies (63). The prognosis of SRC substantially improved in the 1980s with the introduction of angiotensin-converting enzyme (ACE) inhibitors for rapid blood pressure control and with additional antihypertensive agents as required (62). In a prospective analysis of 108 patients with SRC in a single center, patients who received ACE inhibitors (captopril [n = 47] and enalapril [n = 8]) had a significantly better survival rate at 1 year (76%) and 5 years (66%) compared to patients who did not receive ACE inhibitors (1 year [15%] and 5 years [10%]) (62). In another prospective trial, 145 patients with SRC treated with ACE inhibitors demonstrated survival rates of 90% and 85% at 5 and 8 years, respectively, after onset of SRC (64). Furthermore, treatment with ACE inhibitors decreased the need for permanent dialysis (16). Overall, current patient survival is 70–82% at 1 year, but decreases to 50–60% at 5 years despite dialysis support.

In summary, there are therapies available for vasculopathy that have disease-modifying effects, including improved HRQoL, morbidity, and survival. These effects are well-demonstrated for SRC and PAH with unequivocal benefits in clinical trials.

Immunoinflammatory involvement

The concept of ablating an autoreactive immune system followed by its replacement with a self-tolerant one (also called HSCT) has been successfully explored in SSc (7,8). Oral or pulse IV cyclophosphamide (CYC) therapy in individuals with symptomatic, established SSc-ILD has a significant, though modest, beneficial effect on lung function, thickening of the skin, dyspnea, and HRQoL (65,66) and has no impact on long-term survival (67,68).

Three major prospective trials were initiated to examine the role of HSCT in SSc treatment—the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (7), the American Scleroderma Stem Cell versus Immune Suppression trial (ASSIST) (8), and the Scleroderma: Cyclophosphamide Or Transplantation (SCOT) trial (6). These studies compared autologous HSCT (with and without radiation) to various IV CYC treatment regimens. All studies included patients with early dcSSc who had moderate-to-severe skin thickness and internal organ involvement (lung involvement largely accounted for the vast majority of patients). Study patients were those who were predicted to have disease activity that would rapidly progress. Although there were substantial differences in the study design among these trials, the results of the 3 studies allowed for valid conclusions to be drawn with regard to the effect of HSCT in patients with early SSc who have progressive skin and/or lung involvement. The notable observations of outcomes among patients who underwent HSCT were as follows: 1) clinically meaningful improvement in skin thickness, 2) overall stabilization of lung function, 3) clinically meaningful improvement in HRQoL, 4) overall survival benefit (although higher short-term serious adverse events in the ASTIS and SCOT trials and a higher mortality rate during the first year after transplantation in patients who underwent HSCT in the ASTIS trial were recorded), and 5) the observation that SSc heart disease (myocardial involvement and PAH) appears to be the main driver of transplantation-related death (6–8,69).

In summary, HSCT trials provide clear evidence of immune-mediated pathogenesis in SSc and document long-term, clinically important disease modification in early aggressive disease.

Tissue fibrosis

Three important manifestations of tissue fibrosis include skin fibrosis, ILD, and myocardial fibrosis.

Skin involvement. Skin fibrosis is a cardinal manifestation and is observed in most SSc patients, although a small minority have no skin involvement (SSc without scleroderma) (17,70). Skin fibrosis is associated with significant morbidity due to pruritis, digital ulcers, skin tightness, and skin ulcers at other sites as well as markedly decreased function. A rapidly progressive phenotype of skin fibrosis is associated with a higher mortality rate due to progressive internal organ involvement (71). Recently, immunosuppressive therapies such as CYC, mycophenolate mofetil (MMF), and biologic response modifiers (such as abatacept and tocilizumab) have been evaluated for their effects on skin thickening in dcSSc. Based on the data from Scleroderma Lung Studies I and II (SLS I and II), treatment of patients with dcSSc with CYC or MMF resulted in clinically meaningful improvement in the MRSS as compared to those receiving placebo (72). In a recent RCT, abatacept treatment (versus placebo) resulted in clinically meaningful change in ACR CRISS scores despite no significant change in MRSS. Decline in MRSS over 12 months was clinically and significantly higher in the abatacept group versus the placebo group for the inflammatory and normal-like skin gene expression subsets (73). In another RCT, subcutaneous tocilizumab trended to improve MRSS but also highlighted a marked heterogeneity in individual response (74).

Interstitial lung disease in SSc. ILD is present in 70–80% of patients with SSc, with ~20–25% developing symptomatic ILD (75,76). ILD is the leading cause of death in SSc and accounts for over one-third of SSc-related deaths (25). Immunosuppressive therapies have been consistently explored for the treatment of SSc-ILD, with differing results.

In SLS I, patients with SSc-ILD received oral CYC or matching placebo for 12 months and were followed up in a double-blind trial for an additional 12 months (65). After 12 months, significant (though modest) treatment effects of CYC versus placebo were observed on FVC and total lung capacity (TLC), but not on diffusing capacity for carbon monoxide (DL_{CO}). The effect on FVC persisted at 18 months in the CYC group (although CYC was no longer being given), but was no longer present at 24 months. Additionally, CYC improved dyspnea, HRQoL, and functional ability. CYC treatment did not change long-term survival, a finding that was not unexpected, given that the treatment was administered for only 1 year (68). In SLS II, patients with SSc-ILD were randomized to receive either 3 grams of oral MMF each day for 24 months or oral CYC each day for 12 months (followed by placebo for 12 months) (77). No significant differences were observed in the long-term survival or organ failure for patients who randomly received CYC versus MMF.

In a recent long-term follow-up of patients in SLS I and II, the majority of patients died of complications related to SSc, with respiratory failure from end-stage lung disease as one of the leading causes of death (68). Data from a phase III clinical trial suggested that interleukin-6 inhibition in early SSc with elevated C-reactive protein levels led to stabilization of FVC% in the tocilizumab group versus a clinically meaningful decline in the placebo group over 48 weeks (treatment difference of 4.2%; $P = 0.0002$) (74). The mean ± SD FVC% was 82.1 ± 14.8 at baseline, which highlights the benefit of treating patients with subclinical ILD who have high-risk features (early dcSSc and elevated C-reactive protein levels). RTX therapy in SSc has shown promising effects on both ILD and skin thickening. In a recent open-label, randomized, controlled trial of RTX treatment (administered in 2 doses of 1,000 mg each) versus monthly pulse CYC therapy, a population of 60 treatment-naive, anti–Scl-70 positive patients with early dcSSc and ILD were analyzed (78). FVC% was improved in the RTX group at the end of 6 months (+5.8% in the RTX group versus –1.2% in the CYC group). The data, overall, suggest that targeted biologic therapies may have disease-modifying effect in ILD with regard to preservation of lung function (74,79).

A recent 52-week, placebo-controlled RCT, treatment with nintedanib, a tyrosine kinase inhibitor, slowed the progression of FVC decline in SSc-ILD, which led to approval by the Food and Drug Administration (80). The adjusted annual rate of decline in FVC was lower in the nintedanib-treated group than in the placebo-treated group (difference 41.0 ml per year; $P = 0.04$), although no clinical benefits for other manifestations of SSc, dyspnea, or function were observed. Overall, ~50% of the patients were receiving MMF at baseline. Among these patients who had received prior MMF treatment, those who were given placebo experienced a smaller decline in the FVC, and in the nintedanib group, the magnitude of the nintedanib treatment effect on the FVC was lower. The rate of gastrointestinal adverse events was higher in the nintedanib group versus the placebo group. Currently, there is an ongoing double-blind RCT (SLS III) comparing the combination of MMF with pirfenidone (an antifibrotic agent approved for treating idiopathic pulmonary fibrosis) versus MMF alone in the treatment of SSc-ILD (ClinicalTrials.gov identifier: NCT03221257) (80).

Cardiac involvement. Cardiac involvement is marked by myocardial fibrosis and has been reported in >50% of autopsies (81). It is frequently encountered in SSc patients, is often asymptomatic, and is associated with higher mortality rate (23,40,63). Alteration in heart rhythm with hemodynamically significant arrhythmias, including ventricular tachycardia, is associated with high mortality. Apart from medical therapy for systolic heart failure, other supportive measures such as implantable cardioverter defibrillators, dual-chamber pacing, or cardiac transplantation may be necessary.

In summary, with regard to fibrosis, data suggest that improvement in skin involvement may not be an achievable end

point in trials at present due to measurement tools that lack sensitivity, difficulty in defining sufficiently uniform entry criteria for trials, and individual heterogeneity in clinical manifestations. However, fibrosis in other organs, particularly in the lungs, may be amenable to treatment with biologic agents, and recently, a tyrosine kinase inhibitor.

Other unmet needs

There are other disabling manifestations in SSc wherein the pathogenesis is poorly understood and/or does not have validated outcome measures. The gastrointestinal tract is involved in up to 95% of patients with SSc and is a presenting feature in ~10% of patients (82). Gastrointestinal involvement causes substantial morbidity and is responsible for 6–12% of deaths in SSc patients. Calcinosis, characterized by the deposition of insoluble calcium salts in the skin and subcutaneous tissue, is observed in ~25% of patients with SSc (83). In SSc, arthritis and joint contractures of the small and large joints are commonly seen in about one-third of patients, with the presence of large joint contractures being predictive of mortality (84,85). Telangiectasias, while themselves harmless in the skin, can be a major source of body image dissatisfaction in addition to a predecessor of pulmonary vascular disease, which would make them valuable markers of disease progression. They may also be a source of gastrointestinal bleeding, leading to potential increased morbidity (86). These manifestations are often unaccounted for as a disease outcome in pharmacologic trials and need to be included in future trials with consistent ways to measure the treatment outcome.

What should modification of disease course look like today, and how should it be measured?

Ideal disease-modifying therapy should halt the progression of the disease and hopefully induce remission, and preferably also reverse some major organ complications, as seen in the recent HSCT trials on fibrotic complications (Figure 2). It is reasonable to expect disease-modifying therapy to stabilize organ function without any further worsening of other domains.

Reliable, valid, and responsive outcome measures are needed to assess the effect of disease-modifying therapy. Based on the RCTs conducted for key clinical manifestations in SSc (shown in Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41246/abstract), lessons have been learned about outcome measures. MRSS (a measure of skin thickness) has shown natural regression, despite enrichment for early disease and/or elevated acute reactants at baseline (73,74,87). Combined measures of response, analogous to such measures used in RA, may be a way forward.

In the RCTs of abatacept and tocilizumab in dcSSc, MRSS was not able to distinguish the efficacy of active therapies compared to placebo, but there were statistically significant and clinically meaningful improvements in the ACR CRISS, a combined measure designed to capture the global or holistic evaluation in early SSc. In the tocilizumab trial, the ACR CRISS was driven by improvement in and stabilization of FVC%, whereas results from the HAQ DI and physician global assessments of disease activity were statistically significant in the abatacept trial. ACR CRISS core set of outcome measures should be included in forthcoming clinical trials.

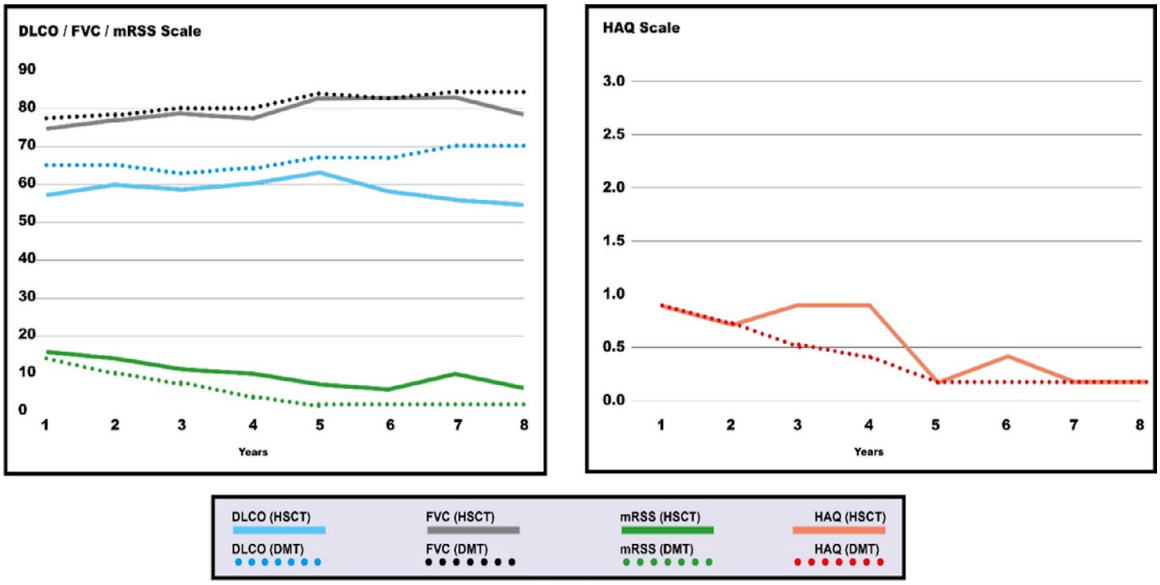

Figure 2. The long-term impact of ideal disease-modifying therapy (DMT), in comparison to hematopoietic stem cell therapy (HSCT), on outcomes in systemic sclerosis (SSc) with a predominantly fibrotic phenotype. DLco = diffusing capacity for carbon monoxide; FVC = forced vital capacity; MRSS = modified Rodnan skin score; HAQ = Health Assessment Questionnaire.

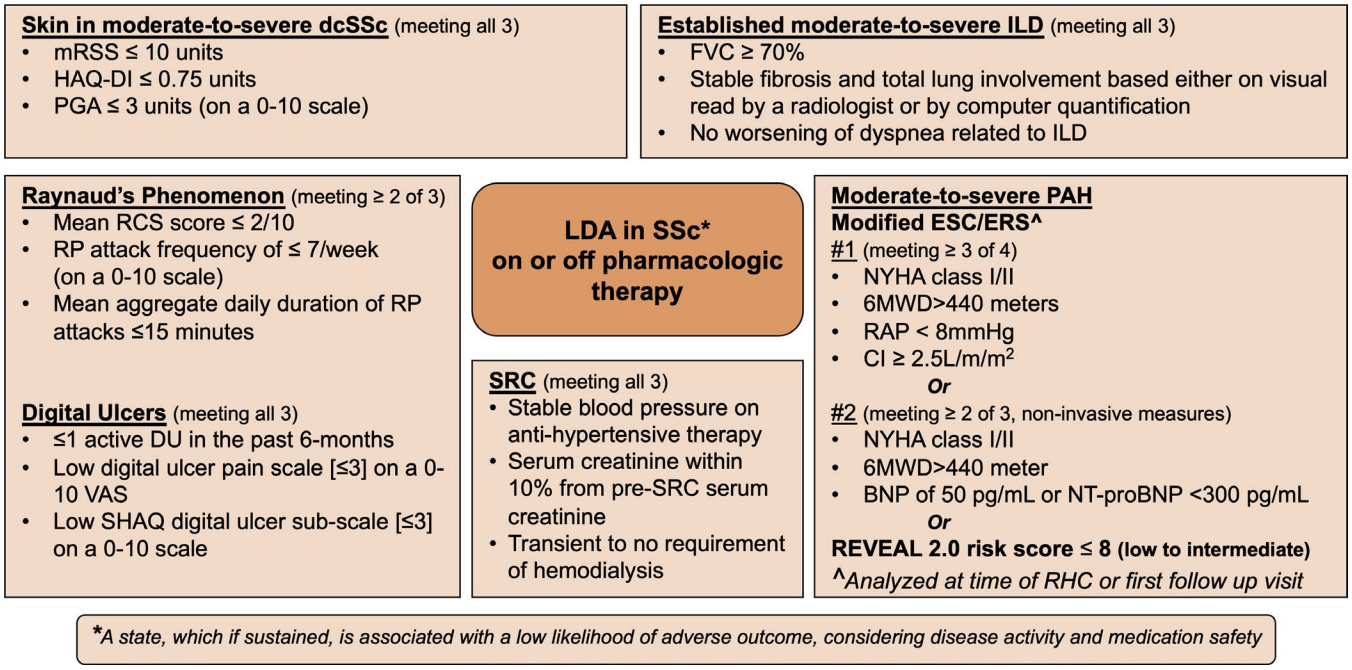

Figure 3. Suggested parameters for low disease activity state (LDA) in systemic sclerosis (SSc). These are author-driven preliminary proposals, influenced by data from randomized control trials and observational studies, which will need further testing and validation in future investigations. dcSSc = diffuse cutaneous SSc; MRSS = modified Rodnan skin score; HAQ DI = Health Assessment Questionnaire disability index; PGA = patient global assessment of disease activity; ILD = interstitial lung disease; FVC = forced vital capacity (percent predicted); RCS = Raynaud's Condition Score; RP = Raynaud's phenomenon; DU = digital ulcer; VAS = visual analog scale; SHAQ = Scleroderma Health Assessment Questionnaire; SRC = scleroderma renal crisis; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; ESC/ERS = European Society of Cardiology and European Respiratory Society; NYHA = New York Heart Association; 6MWD = 6-minute walking distance; RAP = right atrial pressure; CI = cardiac index; BNP = B-type natriuretic peptide; NT-ProBNP = N-terminal proBNP; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; RHC = right heart catheterization.

Another example is the global rank composite score used in the SCOT trial, which utilized a hierarchical combined measure of response. In SSc-ILD, a combination of objective measures (FVC, DL_{CO}, and lung imaging scores of fibrosis) and a patient-reported measure of dyspnea demonstrated responses and, in combination, could be utilized to increase sensitivity and discrimination. At this point, FVC currently appears to be a valid end point that could be used in these types of clinical trials if given regulatory approval (65,66). In PAH, recent successes have been achieved with clinically meaningful end points such as time to clinical worsening, which is a combined end point influenced by morbidity (such as worsening performance on 6-minute walk distance, worsening of New York Heart Association functional classification, requirement of additional PAH therapy, and hospitalizations due to PAH) or all-cause mortality as a valid end point in PAH (88).

How should we define remission and low disease activity in SSc?

Based on our current understanding and constraints with testing, disease remission, which we define as the absence of disease activity, may not be achievable in the setting of SSc due to the heterogeneity of the disease and the few positive trials that have been conducted to this effect. Buoyed by the outcomes in PAH and HSCT trials, it is time to start creating a framework for the conceptual definition for low disease activity in SSc.

First, low disease activity in SSc should be an individual disease state (on or off therapy). Second, low disease activity (when sustained over a period of time) should be associated with better outcomes and positive effects on HRQoL (89). Future studies should define the time period of low disease activity that demonstrates a favorable impact on outcomes and HRQoL, although this will differ based on organ involvement. Third, the distinction between what represents disease activity and what represents damage is a challenge that is currently an area of investigation (36). Activity is defined as the component of disease severity that is largely reversible and may result in little or no damage in the future. Damage is the component of severity that is largely irreversible. In Figure 3, we lay out a preliminary proposal to define low disease activity for the different manifestations in SSc (65,66,80,90–93). This is an author-driven preliminary proposal, influenced by data obtained from RCTs and observational studies. This proposal will need rigorous testing and validation using a consensus methodology in future studies.

Conclusions

Using data and outcome measures from recent clinical trials in SSc, we propose a conceptual framework on how to define low disease activity for different organ-specific manifestations in SSc. Disease-modifying therapies (such as HSCT in dcSSc, for example) and their effect on SSc should be considered in future investigations.

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AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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