Current and future outlook on disease modification and defining low disease activity in systemic sclerosis

Vivek Nagaraja MD[1], Marco-Matucci Cerinic MD PhD[2], Daniel E. Furst MD[3,2], Masataka Kuwana MD Ph.D.[4], Yannick Allanore MD Ph.D.[5], Christopher P. Denton MD[6], Ganesh Raghu MD[7], Vallerie Mclaughlin MD[8], Panduranga S. Rao[9], James R. Seibold MD[10], John D. Pauling BMedSci BMBS Ph.D. FRCP[11], Michael L. Whitfield, PhD[12], Dinesh Khanna MD MSc[1]

[1] Division of Rheumatology and Scleroderma Program, University of Michigan, Ann Arbor, Michigan, USA

[2] Division of Rheumatology, University of Florence, Florence, Italy

[3] The University of California in Los Angeles, University of Washington, Seattle Washington

[4] Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan

[5] Paris Descartes University, INSERM U1016, Sorbonne Paris Cité, Rheumatology A department, Cochin Hospital, Paris, France

[6] Division of Medicine, Centre for Rheumatology, University College London, Royal Free Hospital, London, UK

[7] Center for Interstitial Lung Diseases, Department of Medicine, University of Washington, Seattle, Washington, USA

[8] Division of Cardiology and Pulmonary Hypertension Program, University of Michigan, Ann Arbor, Michigan, USA

[9] Division of Nephrology, University of Michigan, Ann Arbor, Michigan, USA

[10] Scleroderma Research Consultants, LLC, Litchfield, Connecticut, USA

[11] Royal National Hospital for Rheumatic Diseases (at Royal United Hospitals), Bath, UK

[12] Department of Biomedical Data Science, Geisel School of Medicine at Dartmouth, Hanover

Corresponding Author:

Dinesh Khanna, MD, MSc

Professor of Medicine,

Director, University of Michigan Scleroderma Program

Division of Rheumatology/Dept. of Internal Medicine

Suite 7C27, 300 North Ingalls Street, SPC 5422

Ann Arbor, MI 48109

khannad@med.umich.edu

Phone: +1 734-763-3110

Fax: +1 734-763-5761

The authors declare that there is no financial support or other benefits from commercial sources for the work reported on the manuscript.

D Khanna has ownership interest in Eicos Sciences; has received grants from the National Institutes of Health (NIAID and NIAMS); has received consulting fees from Actelion, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, ChemomAb, Corbus, CSL Behring, Cytori, GlaxoSmithKline, Horizon, Pfizer, Regeneron, Roche/Genentech, Sanofi Aventis, and UCB Pharma.

Dinesh Khanna is supported by NIH/NIAMS K24 AR063120 and NIH/NIAMS R01 AR-07047.

Abstract

Systemic sclerosis (SSc) is an autoimmune rheumatic disease with heterogeneous clinical manifestations and variable disease course in which the severity of pathology dictates the disease prognosis and course. Among autoimmune rheumatic diseases, SSc carries the highest mortality, but there are exciting new therapeutic targets that appear to halt the progression of manifestations like skin or lung fibrosis. In selected patients, high-intensity regimens with autologous stem cell transplantation can favorably modify the disease course. From what was once thought to be an untreatable disease, targeted therapies have now changed the outlook of SSc to a treatable condition. Our review discusses these targeted therapies that are modifying the outlook of selected organ involvement and creating opportunities for the future. We take this opportunity to define a framework of 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 in SSc is higher than any other rheumatic disease (4, 5). SSc can be classified into two major clinical subsets by the extent of skin fibrosis [limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc)] that differ in their frequency and pattern of autoantibodies, clinical characteristics, and overall disease progression (1).

Contrary to rheumatoid arthritis (RA), the concept and use of disease-modifying therapies (DMT) 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 the recent clinical trials in SSc. Autologous hematopoietic stem cell transplantation (HSCT) trials in dcSSc have demonstrated survival benefit including meaningful improvement in skin, lung fibrosis, and health-related quality of life (HRQoL) (6-9). In this review, we discuss specific treatments that have modified the course of organ-specific manifestations and start the conversation on defining low disease activity in SSc.

What is disease-modifying therapy?

We borrow the concept of DMT from the use of disease modifying anti-rheumatic drugs (DMARDs) and biological response modifiers in RA. In the past three decades, the

management of RA has evolved from symptom management to the implementation of regimens**,** that impact disease activity, to the advent of DMARDs or biological response modifiers**,** which slow or arrest joint structural damage. The early institution of DMARDs or biological response modifiers 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 DMT in SSc as therapies or medication regimens**,** that positively impact the disease course by stabilizing and preferably an improvement in organ(s) function that are related to improvement in HRQoL and reduction in morbidity and mortality (11).

Natural history of the disease

The understanding of the natural history of SSc disease process is vital to the concept of DMT in the context of timing and patient selection. The early clinical features include Raynaud's phenomenon (RP) and gastro-esophageal reflux disease (12). Skin fibrosis is a pathological 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 an SSc specific antibody, can be diagnosed with Very Early Diagnosis of Systemic Sclerosis (VEDOSS) (13, 14). Thereafter, patients may progress to one of three clinical disease subsets based on the extent of skin involvement into: those with skin involvement restricted involvement affecting the limbs distal to the elbows or knees, with or without face involvement, are classified as lcSSc; those with distal as well as proximal involvement (including torse) are classified as dcSSc; and a small subset with sine SSc who don't have skin involvement but have

scleroderma-specific antibodies and internal organ involvement (15-17). This differentiation is essential as dcSSc is associated with higher morbidity and mortality, mainly due to more severe internal organ involvement (18). However, this dichotomous differentiation of the clinical phenotypes is an over-simplification 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 4-5 and then improves both via deremodeling and atrophy(19). Only a minority of patients have a new emergence of progressive cutaneous involvement after five years of disease onset. There is an increased risk of the onset of internal organ involvement during the progressive skin phase. For example, in dcSSc, most of the internal organ involvement (lung, renal, cardiac, and gastrointestinal) occurs in the first 3-4 years of the disease onset (Figure 1)(16). Internal organ involvement – although clinically silent – may evolve at the same time as progressive skin disease in the early phase. There are exceptions– for example, the pulmonary arterial hypertension (PAH) in generally a later complication and more common in lcSSc(20). Once fibrosis sets in, it can advance in a self-perpetuating manner and may not be driven solely by an immune-mediated process(21) for internal organ involvement.

In our opinion, SSc can be conceptualized as a family of similar diseases, an idea that is supported by molecular subsets identified by whole genome gene expression profiling with distinct clinical and serological features and recognized phases within some of the sub-types (22). The delayed emergence of new organ involvement and gradual progression of the disease provides 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 amongst the clinical subsets, as already outlined (5, 23-25). Patients usually present with predominately significant vasculopathic complications (such as RP, DU, PAH, SRC), predominately significant fibrotic complications (such as skin fibrosis, lung fibrosis, cardiac fibrosis), and for a small subset, a combination of these. Within each cutaneous subgroup, there is heterogeneity in the internal organ involvement(18). Second, there are molecular differences in the gene expression data in patients with a similar phenotype. Four subsets have been identified based on skin gene expression data**:** normal-like, inflammatory, fibroproliferative, and limited (22, 26). These subsets identify patients at risk for internal organ involvement, such as ILD, and response to current therapies (26, 27). Measuring gene expression subsets in clinical trials, and possibly even in routine clinical care, can breakdown and clarify patient heterogeneity, and provides a window through which to understand patient response to therapy. Third, the predictors of disease status at a specific time point (incidence or severity of organ-based

complications; largely influenced by autoantibodies) may differ from predictors of disease progression (28, 29).

Unlike the disease activity score (DAS-28), clinical disease activity index (CDAI), or others in RA, we lack reliable tools with which we can define the achievement of remission in SSc. In dcSSc, modified Rodnan skin score, and recently, a combined responder index in dcSSc (ACR CRISS - a composite end point that captures cardio-pulmonary-renal involvement and change in mRSS, HAQ-DI, patient global assessment, physician global assessment, and FVC% predicted) are used as outcomes to measure the efficacy of drugs (30). These measures have not been validated in lcSSc and may not perform well (31) . Further, clinical heterogeneity of the disease does not allow precise definition of global disease activity. Composite scores like the revised European Scleroderma Research Group Activity Index have been proposed**,** but have not been widely accepted in the evaluation of disease activity(28). Novel approaches for assessing disease activity in SSc are currently under development(32).

Are there currently DMTs 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 material, Table 1). This concept can be approached by categorizing SSc manifestations into vasculopathy, immunological or inflammatory involvement, and tissue fibrosis.

Vasculopathy

The predominant vascular complications in SSc are PAH, SRC, RP, and digital ulcers (DU). The morbidity and mortality are high in patients with PAH and SRC. RP and DU are chronic complications that can limit hand function, increase morbidity and disability,(33) and impact HRQOL. The 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 (34).

One of the relevant vasculopathic manifestation, which is associated with significant mortality and morbidity in SSc patients, is PAH. The prevalence of PAH measured by right heart catheterization in large cohorts of SSc patients ranges from 5 to 12% (35, 36). 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 PH, pulmonary venoocclusive disease, SSc myocardial disease, and later age of onset (37, 38). Greater emphasis has been put on early screening and detection of SSc-PAH with composite algorithms, allowing for the earlier institution of PAH-specific therapy(39-41). There is a growing body of evidence that this approach may improve the morbidity outcomes although the effect on long term mortality is unclear(42). The lower incidence of SSc-PAH in patients on dihydropyridine calcium antagonists offers a tantalizing glimpse into the potential disease-modifying actions of fairly modest vasodilator therapy on long-term outcomes in SSc (43). There are multiple approved therapies for the management of IPAH that target one of the three pathogenic pathways: (1) endothelin

antagonists; (2) nitric oxide (NO) /soluble guanylate cyclase (GC) agonists/ stimulators**;** and (3) prostacyclin analogs (44). High quality randomized controlled trials have shown that upfront or sequential combination therapies delay time to clinical worsening in IPAH patients. Similar approaches with combination therapies have suggested efficacy in SSc-PAH. In a recent meta-analysis, combination therapy targeting PAH conferred therapeutic efficacy compared with monotherapy in patients with SSc-PAH as suggested by reduction in the risk of clinical worsening by 27% (pooled relative risk of 0.73, 95% confidence interval (CI) [0.60–0.89], p=0.002) and a probable improvement of exercise capacity in these patients (45). Current trials are exploring the addition of immune modulating therapies [such as Rituximab (NCT01086540) and tocilizumab (NCT02676947)] in addition to currently approved therapies

In SSc, common and burdensome vascular manifestations include RP and Digital Ulcer (DU). RP is the harbinger of SSc and usually precedes tissue fibrosis(46). RP is a manifestation of abnormal cutaneous vessel function involved in thermal regulation of blood flow (47). The presence of RP and the loss of normal regulation of cutaneous vascular tone is a predictor of developing SSc, although it is not specific, cannot be used alone as a predictor, and may be long delayed (46, 48). DU disease is a significant cause of morbidity with around 50% of SSc patients developing DUs during their disease history (18). DU can be a sporadic phenomenon**;** but, for some patients, they are recurrent, continuous, and/or refractory (49). DUs 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. PDE-5 inhibitors, especially sildenafil, can reduce the frequency of RP attacks in SSc(50). A recent RCT comparing the use of oral sildenafil (20 mg three times daily) to placebo favored sildenafil in significantly decreasing the number of DUs at week-12, but did not meet the primary end-point of time to healing(51). In SSc patients with refractory and recurrent DUs, bosentan (an endothelin-1 receptor antagonist; 62.5 mg twice a day for four weeks**,** then 125 mg twice a day) can reduce the number of new DUs in those with >4 previous DUs, without any effect on healing existing DUs and is approved in Europe (52, 53). Intravenous prostanoid therapy improves DU healing and reduces the number of new DUs. In two multicenter, double-blind~~,~~ randomized trials, i.v. prostanoid therapy (0.5–2.0 ng/kg/min over six hours, on consecutive 5 days) was associated with significant improvement in the frequency of RP attacks and greater DU healing(54, 55). There is preliminary evidence that iloprost can prevent new DUs in patients with a history of DUs.

A major~~,~~ life-threatening vasculopathic manifestations of SSc is SRC**,** once the most common cause of death in SSc(56). SRC is a rare complication that affects 2–15% of patients with SSc (11% of dcSSc and 4% of lcSSc patients) (36). SRC typically presents in patients with early, rapidly progressive~~,~~ dcSSc and predominantly having anti-RNA polymerase III antibodies(57). The prognosis of SRC substantially improved in the 1980s with the introduction of angiotensin-converting-enzyme inhibitors (ACE-i) for rapid blood pressure control, with additional antihypertensive agents as required(56). Current patient survival is 70–82% at one year but decreases to 50–60% at five years despite

dialysis support. In a prospective analysis of 108 patients with SRC in a single center, patients on ACE-i [captopril (n=47) and enalapril (n = 8)] had significantly better survival rate at 1 year (76%) and 5 years (66%) compared to patients~~,~~ not on ACE-i (1 year 15% and 5 years is 10%)(56). In another prospective trial, 145 patients with SRC treated with ACE-i demonstrated survival rates of 90% and 85% at five and eight years~~,~~ respectively, after the onset of SRC(58). Furthermore, treatment with ACE-i decreased the need for permanent dialysis(16).

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 or practices.

Immuno-inflammatory 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 i.v. cyclophosphamide (CYC) in symptomatic established SSc-ILD has a significant**,** although modest beneficial effect on lung function, thickening of the skin, dyspnea, and HRQOL (59, 60); it has no impact on long term survival (61, 62). Three major prospective trials were initiated to examine the role of HSCT in SSc treatment - ASTIS (7), ASSIST (8) and the Scleroderma: Cyclophosphamide or Transplant [SCOT](6). These studies compared autologous HSCT (± radiation) to various i.v. CYC regimens. All studies included early dcSSc patients with moderate-to-severe skin thickness and internal organ involvement (lung involvement largely accounted for the

vast majority of the cases). Although there were substantial differences in the study design among these trials, the results of the three studies allow one to draw valid conclusions regarding the effect of HSCT in early SSc patients with progressive skin and/or lung involvement. The following are the notable observations in the transplant arms: 1) clinically meaningful improvement in the skin thickness, 2) overall stabilization of lung function, 3) clinically meaningful improvement in the HRQOL, 4) overall survival benefit although short term higher mortality in the transplant arm during the first year post-transplant in ASTIS trial, and 5) SSc heart disease (myocardial involvement and PAH) seems to be the main driver of transplantation-related mortality (6-8, 63).

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

Tissue fibrosis

Three important manifestations of tissue fibrosis include skin fibrosis, interstitial lung disease, and myocardial fibrosis.

Skin fibrosis is a cardinal manifestation and is seen in most SSc patients, although a small minority have no skin involvement (systemic sclerosis sine scleroderma)(17, 64). Skin fibrosis is associated with significant morbidity due to pruritis, DU, skin tightness, and skin ulcers at other sites. A rapidly progressive phenotype of skin fibrosis is associated with higher mortality due to progressive internal organ involvement (65).

Recently, immunosuppressive therapies such as CYC, mycophenolate mofetil (MMF), and biological 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), CYC and MMF showed clinically meaningful improvements in mRSS in dcSSc compared to placebo (66). In a recent RCT, abatacept (vs placebo) showed clinical meaningful change in ACR-CRISS despite non-significant change in mRSS. Decline in mRSS over 12 months was clinically and significantly higher in abatacept vs. placebo for the Inflammatory and Normal-like skin gene expression subsets(67). In another RCT, subcutaneous tocilizumab showed trends in improvement in mRSS but also highlighted a marked heterogeneity in individual response (68).

SSc-ILD is present in 70-80% of patients with SSc, but approximately 20-25% develop symptomatic ILD(69, 70). ILD is the leading cause of death in SSc**,** which accounts for over one-third of SSc-related deaths(25). Immunosuppressive therapies have been consistently explored for the treatment of SSc-ILD**,** with different results. In the SLS I, patients with SSc-ILD received oral CYC or matching placebo for 12-months and were followed, double-blind, for an additional 12-months(59). At the end of 12-months, significant, albeit modest, treatment effects of CYC vs. placebo were observed on FVC and total lung capacity (TLC), but not on DLCO. The effect on FVC persisted at 18-months in the CYC group but was no longer present at 24-months. Additionally, CYC improved dyspnea, HRQOL, and functional ability. CYC treatment did not change long-term survival(62). In SLS II, patients with SSc-ILD were randomized to receive either

daily oral MMF at 3 grams/day for 24-months or daily oral CYC for 12-months (followed by placebo for 12-months)(71). No significant differences were observed in the long-term survival or organ failure for patients randomized by CYC versus MMF. In a recently conducted long-term follow-up of patients in SLS~~,~~ I and II, the majority of patients died of complications related to SSc; respiratory failure from end-stage lung disease was one of the leading causes of death(62). In phase III clinical data, IL-6 inhibiton in early SSc with elevated CRP led to stabilization of FVC% in the tocilizumab group vs. a clinically meaningful decline in the placebo group over 48 weeks [treatment difference of 4.2%; p = 0.0002] (68). The mean [SD] FVC% was 82.1% [14.8%] at baseline which highlights the benefit of treating patients with subclinical ILD with high-risk features (early dcSSc, and elevated CRP). Rituximab (RTX) therapy in SSc has shown promising effects on both ILD and skin thickening. A recent open-label, randomized, controlled trial of RTX (1000 mg x 2 doses) vs. monthly pulse CYC analyzed a population of 60 early, treatment naïve, anti-SCL-70+, dcSSc patients with ILD (72). The RTX group improved their FVC% at the end of 6 months [RTX group +5.8% vs. CYC group -1.2%] suggesting that RTX needs to be tested in a double-blind RCT. These data suggest that targeted biological therapies may have disease-modifying effect in ILD with preservation of lung function(68, 73). Recently, in a 52-week placebo-controlled RCT, treatment with nintedanib - a tyrosine kinase inhibitor - slowed the progression of SSc-ILD and led to approval by the Food and Drug Administration (74). The adjusted annual rate of decline in forced vital capacity 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 were observed. Overall, about half of the patients were on

baseline MMF; these patients had lower FVC decline if in the placebo group and lower magnitude of the nintedanib treatment effect on FVC. The rate of gastrointestinal adverse events was higher in the nintedanib than in the placebo group. Currently, there is an ongoing double-blind RCT (SLS III) comparing the upfront combination of MMF with pirfenidone (an anti-fibrotic agent approved for idiopathic pulmonary fibrosis) vs. MMF alone in the treatment of SSc-ILD is ongoing (NCT03221257).

Cardiac involvement is frequently encountered in SSc patients, is often asymptomatic, and is associated with higher mortality (23, 36, 57). Myocardial fibrosis is the pathological hallmark and has been reported in >50% of autopsies(75). 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 like implantable cardioverter defibrillator, dual chamber pacing, or cardiac transplantation may be necessary. Immunosuppressive therapy is generally needed to treat the myocardial involvement and evolution to fibrosis.

In summary, data suggests that the improvement in skin involvement may not be an achievable end point in trials (due to individual heterogeneity), but biologics and recently – tyrosine kinase inhibitor - may play an important role in modulating the immune system in early disease and targeting ILD.

Other unmet needs

There are other disabling manifestations in SSc where the pathogenesis is poorly understood and/ or don't have validated outcome measures. The gastrointestinal tract is involved in up to 95% of patients with SSc and is a presenting feature in about 10% of patients(76)**.** It causes substantial morbidity and is responsible for 6% to 12% of mortality in SSc patients. Calcinosis, characterized by the deposition of insoluble calcium salts in the skin and subcutaneous tissue, is seen in about 25% of patients with SSc (77). In SSc, arthritis and joint contractures (small and large joints) are commonly seen in about one-third of patients, with large joint contractures predictive of mortality (78, 79). Telangiectasias, while themselves harmless, can be a major source of body image dissatisfaction in addition to being harbingers of pulmonary vascular disease that could make them valuable markers of disease progression. These manifestations are often unaccounted as a disease outcome in pharmacological 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 to measure it?

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

Reliable, valid, and responsive outcome measures are needed to assess the effect of DMT. Based on the RCTs conducted for key clinical manifestations in SSc (shown in Supplementary material Table 1) the researchers have learned lessons about the

outcome measures. mRSS – a measure of skin thickeness – has shown natural regression, despite enrichment for early disease, low mRSS at enrollment, and/or elevated acute phase reactants (67, 68, 80). In the RCTs of abatacept and tocilizumab in dcSSc, mRSS was not able to separate active therapies from placebo but there were statistically significant and clinically meaningful improvements in the ACR-CRISS, a measure designed to capture the global or holistic evaluation in early SSc. In tocilizumab, ACR CRISS was driven by improvement in FVC% where as the HAQ-DI and physician global assessments were statistically significant in the abatacept trial. ACR-CRISS core set measures should be included in forthcoming clinical trials. Another example is the global rank composite score used in the SCOT trial. In SSc-ILD, a combination of objective measures (FVC, DLCO, and lung imaging scores of fibrosis) and patient reported measure of dyspnea are key outcomes in clinical trials, although FVC is an approvable regulatory endpoint(59, 60). In PAH, recent successes have been achieved with clinically meaningful endpoints such as time to clinical worsening, that is influenced by morbidity (such as worsening of 6MWD, worsening of NYHA Class, requirement of additional PAH therapy, and hospitalizations due to PAH) or all-cause mortalit and is an approvable endpoint in PAH(81). Outcome measures targeting other organ involvement, such as RP and DU, will require positive trials before

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

Based on our current understanding and constraints with testing, disease remission, which we define as the absence of disease activity, may not achievable in the setting of SSc due to the heterogeneity of the disease and few positive trials to this effect. Buoyed

by the outcomes in PAH and HSCT trials, it is time to start laying a framework for conceptual definition for LDA in SSc. First, LDA in SSc is an individual disease state (on or off therapy) and is distinctly different along the spectrum of disease activity. Second, LDA when sustained over a period of time should be associated with better outcomes and positive effects on HRQOL (82). The future studies should define the time period that has a favorable impact on outcomes and HRQOL although this will differ based on organ involvement. Third, the distinction between what represents 'activity' vs. 'damage' is a challenge which currently is an area of investigation(32). Activity is defined as that component of disease severity that is largely reversible and may result in little or no damage in the future. Damage is that 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. These definitions are opinion of the authors, influenced by the data from RCTs and observational studies but need to be validated in future studies.

In conclusion, we summarize the data from recent RCTs, review the outcome measures used in recent RCTs, and propose LDA for different organ involvement in SSc.

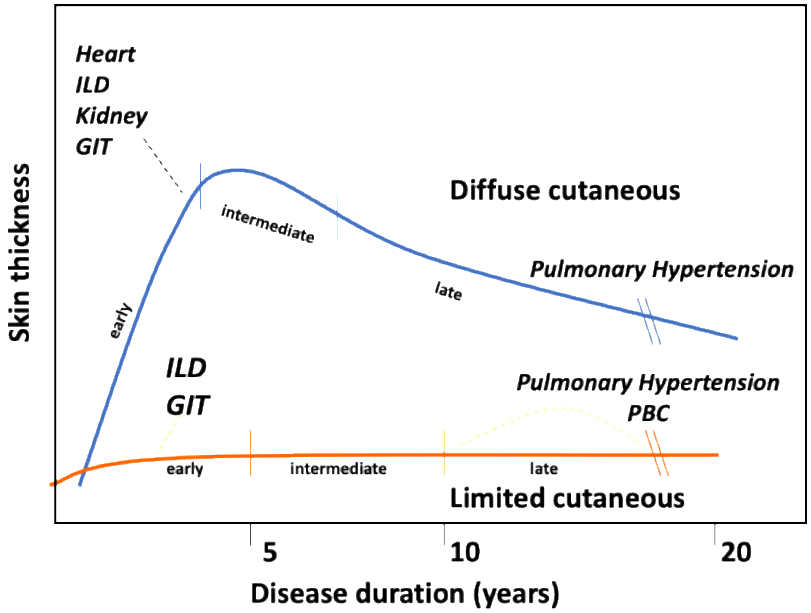
Author contributions

Drs Vivek Nagaraja and Dinesh Khanna wrote the initial draft and all authors were involved in or revising the manuscript for important intellectual content, and all authors approved the final version to be published.

Acknowledgments

We would like to acknowledge Dr. Thomas A. Medsger Jr, MD (Professor of Medicine, Division of Rheumatology, University of Pittsburgh Medical Center, Pittsburgh, USA) for his thoughtful input on a previous version of the submitted manuscript.

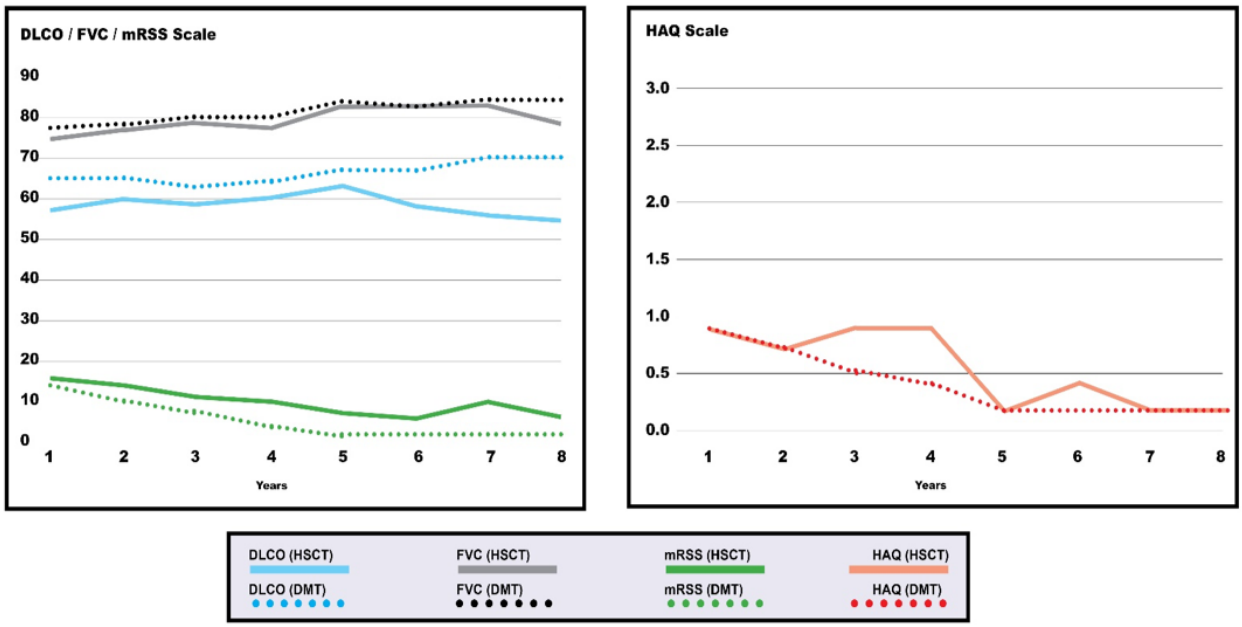
Figure 1: The usual timing of organ-specific manifestations in systemic sclerosis



ILD Interstitial Lung Disease, GIT gastrointestinal tract, PBC Primary Biliary Cirrhosis

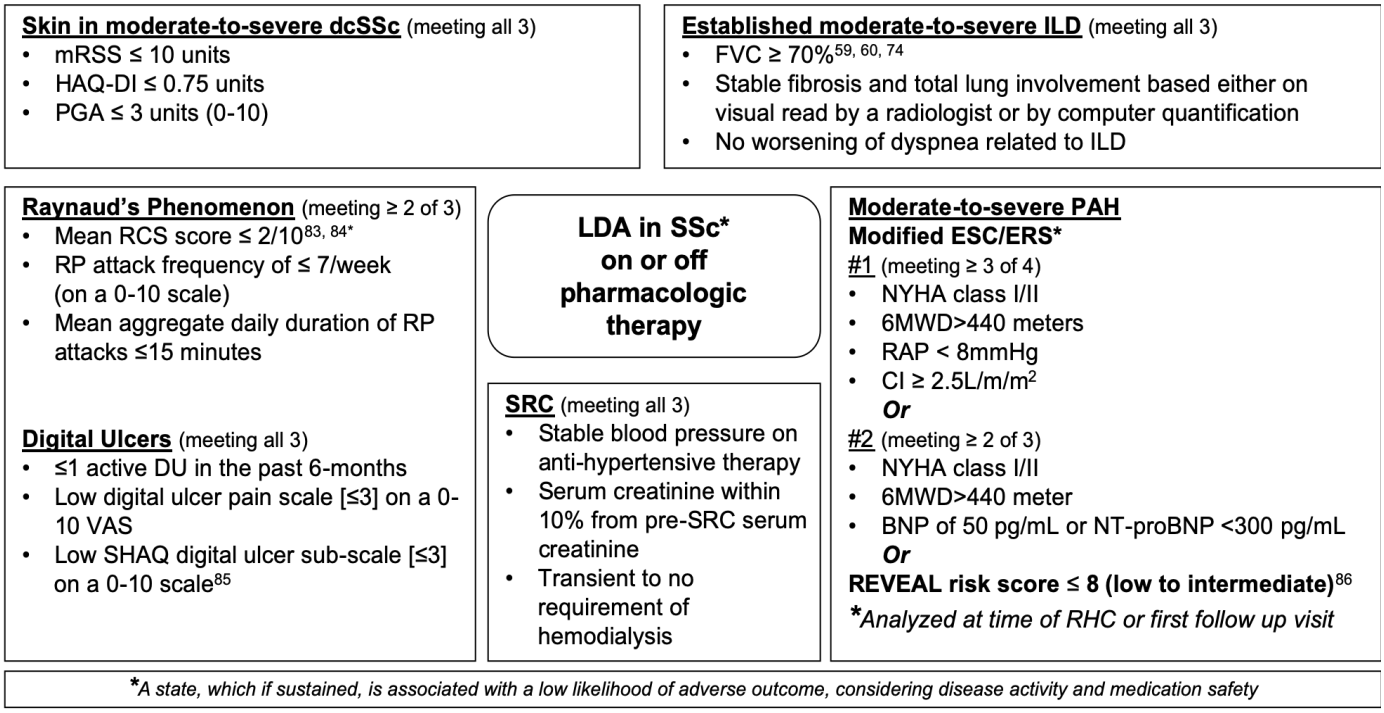
(Adapted from Steen V, Medsger TA. Systemic Sclerosis: Lippincott Williams & Wilkins; 1996)

Figure 2: The long-term impact of ideal disease-modifying therapy in predominately fibrotic phenotype on SSc outcomes (in comparison to HSCT)



DMT Disease Modifying Therapy, HSCT Hematopetic Stem Cell Therapy, DLCO diffusion capacity for carbon monoxide, FVC forced vital capacity, MRSS Modified Rodnan Skin Score, HAQ Health Assessment Questionnaire

Figure 3: Low disease activity state in systemic sclerosis



LDA = low disease activity, SSc = systemic sclerosis, mRSS = modified Rodnan skin score, HAQ-DI Health Assessment Questionnaire Disability Index, PGA = patient global assessment, ILD = interstitial lung disease, FVC% pred = forced vital capacity percentage predicted, TLC% pred = total lung capacity percentage predicted, RP = Raynaud's phenomenon, RCS = Raynaud's Condition Score, DU = digital ulcers, VAS = visual analog scale, SHAQ = Scleroderma Health Assessment Questionnaire PAH = pulmonary arterial hypertension, PAP = pulmonary arterial pressure, PVR = pulmonary vascular resistance, BNP = brain natriuretic peptide, NT-Pro-BNP = N-terminal pro brain natriuretic peptide, RV = right ventricle, NYHA = New York Heart Association, REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management, SRC = scleroderma renal crisis

*Chosen arbitrarily as mid-point between P Khanna et al's estimate of the PASS and Pauling et al's seasonal data

References: (59, 60, 74, 83-86)

References:

1. Denton CP, Khanna D. Systemic sclerosis. Lancet (London, England). 2017.
2. Allanore Y, Simms R, Distler O, Trojanowska M, Pope J, Denton CP, et al. Systemic sclerosis. Nat Rev Dis Primers. 2015;1:15002.
3. Varga J, Trojanowska M, Kuwana M. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. Journal of Scleroderma and Related Disorders. 2017;2(3):137-52.
4. Nihtyanova SI, Tang EC, Coghlan JG, Wells AU, Black CM, Denton CP. Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study. QJM. 2010;103(2):109-15.
5. Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis. 2017;76(11):1897-905.
6. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, McSweeney PA, Pinckney A, Welch B, et al. Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma. N Engl J Med. 2018;378(1):35-47.
7. van Laar JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA. 2014;311(24):2490-8.
8. Burt RK, Shah SJ, Dill K, Grant T, Gheorghiade M, Schroeder J, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. Lancet. 2011;378(9790):498-506.
9. Nash RA, McSweeney PA, Crofford LJ, Abidi M, Chen CS, Godwin JD, et al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study. Blood. 2007;110(4):1388-96.
10. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;388(10055):2023-38.
11. St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004;50(11):3432-43.
12. van den Hombergh WM, Carreira PE, Knaapen-Hans HK, van den Hoogen FH, Fransen J, Vonk MC. An easy prediction rule for diffuse cutaneous systemic sclerosis using only the timing and type of first symptoms and auto-antibodies: derivation and validation. Rheumatology (Oxford). 2016;55(11):2023-32.
13. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013;65(11):2737-47.
14. Minier T, Guiducci S, Bellando-Randone S, Bruni C, Lepri G, Czirják L, et al. Preliminary analysis of the very early diagnosis of systemic sclerosis (VEDOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign for suspicion of systemic sclerosis. Ann Rheum Dis. 2014;73(12):2087-93.

15. Wirz EG, Jaeger VK, Allanore Y, Riemekasten G, Hachulla E, Distler O, et al. Incidence and predictors of cutaneous manifestations during the early course of systemic sclerosis: a 10-year longitudinal study from the EUSTAR database. Ann Rheum Dis. 2016;75(7):1285-92.
16. Steen VD, Medsger TA, Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum. 2000;43(11):2437-44.
17. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988;15(2):202-5.
18. Walker UA, Tyndall A, Czirjak L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis. 2007;66(6):754-63.
19. Merkel PA, Silliman NP, Clements PJ, Denton CP, Furst DE, Mayes MD, et al. Patterns and predictors of change in outcome measures in clinical trials in scleroderma: an individual patient meta-analysis of 629 subjects with diffuse cutaneous systemic sclerosis. Arthritis Rheum. 2012;64(10):3420-9.
20. Hachulla E, Launay D, Mouthon L, Sitbon O, Berezne A, Guillevin L, et al. Is pulmonary arterial hypertension really a late complication of systemic sclerosis? Chest. 2009;136(5):1211-9.
21. Bhattacharyya S, Midwood KS, Yin H, Varga J. Toll-like receptor-4 signaling drives persistent fibroblast activation and prevents fibrosis resolution in scleroderma. Advances in wound care. 2017;6(10):356-69.
22. Milano A, Pendergrass SA, Sargent JL, George LK, McCalmont TH, Connolly MK, et al. Molecular subsets in the gene expression signatures of scleroderma skin. PLoS One. 2008;3(7):e2696.
23. Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis. 2010;69(10):1809-15.
24. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis. 2007;66(7):940-4.
25. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford). 2012;51(6):1017-26.
26. Hinchcliff M, Huang CC, Wood TA, Matthew Mahoney J, Martyanov V, Bhattacharyya S, et al. Molecular signatures in skin associated with clinical improvement during mycophenolate treatment in systemic sclerosis. J Invest Dermatol. 2013;133(8):1979-89.
27. Martyanov V, Whitfield ML. Molecular stratification and precision medicine in systemic sclerosis from genomic and proteomic data. Curr Opin Rheumatol. 2016;28(1):83-8.
28. Nevskaya T, Baron M, Pope JE, Canadian Scleroderma Research G. Predictive value of European Scleroderma Group Activity Index in an early scleroderma cohort. Rheumatology (Oxford). 2017.
29. Nihtyanova SI, Sari A, Harvey JC, Leslie A, Derrett-Smith EC, Fonseca C, et al. Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. Arthritis Rheumatol. 2019.

30. Khanna D, Berrocal VJ, Giannini EH, Seibold JR, Merkel PA, Mayes MD, et al. The American College of Rheumatology Provisional Composite Response Index for Clinical Trials in Early Diffuse Cutaneous Systemic Sclerosis. Arthritis Rheumatol. 2016;68(2):299-311.
31. Allanore Y. Limited cutaneous systemic sclerosis: the unfairly neglected subset. Journal of Scleroderma and Related Disorders. 2016;1(3):241-6.
32. Baron M, Kahaleh B, Bernstein EJ, Chung L, Clements PJ, Denton C, et al. An interim report of the scleroderma clinical trials consortium working groups. Journal of Scleroderma and Related Disorders. 2018:2397198318783926.
33. Mihai C, Landewe R, van der Heijde D, Walker UA, Constantin PI, Gherghe AM, et al. Digital ulcers predict a worse disease course in patients with systemic sclerosis. Ann Rheum Dis. 2016;75(4):681-6.
34. Matucci-Cerinic M, Kahaleh B, Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. Arthritis Rheum. 2013;65(8):1953-62.
35. Avouac J, Airo P, Meune C, Beretta L, Dieude P, Caramaschi P, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol. 2010;37(11):2290-8.
36. Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis Rheumatol. 2014;66(6):1625-35.
37. Lefevre G, Dauchet L, Hachulla E, Montani D, Sobanski V, Lambert M, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. Arthritis Rheum. 2013;65(9):2412-23.
38. Sobanski V, Giovannelli J, Lynch BM, Schreiber BE, Nihtyanova SI, Harvey J, et al. Characteristics and Survival of Anti-U1 RNP Antibody-Positive Patients With Connective Tissue Disease-Associated Pulmonary Arterial Hypertension. Arthritis Rheumatol. 2016;68(2):484-93.
39. Coghlan JG, Denton CP, Grunig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis. 2014;73(7):1340-9.
40. Khanna D, McLaughlin V. Screening and Early Detection of Pulmonary Arterial Hypertension in Connective Tissue Diseases. It Is Time to Institute It! Am J Respir Crit Care Med. 2015;192(9):1032-3.
41. Young A, Nagaraja V, Basilious M, Habib M, Townsend W, Gladue H, et al. Update of screening and diagnostic modalities for connective tissue disease-associated pulmonary arterial hypertension. Semin Arthritis Rheum. 2018.
42. Mihai C, Antic M, Dobrota R, Bonderman D, Chadha-Boreham H, Coghlan JG, et al. Factors associated with disease progression in early-diagnosed pulmonary arterial hypertension associated with systemic sclerosis: longitudinal data from the DETECT cohort. Ann Rheum Dis. 2018;77(1):128-32.
43. Steen V, Medsger TA, Jr. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. Arthritis Rheum. 2003;48(2):516-22.
44. Klinger JR, Elliott G, Levine DJ, Bossone E, Duvall L, Fagan K, et al. Therapy for Pulmonary Arterial Hypertension in Adults 2018: Update of the CHEST Guideline and Expert Panel Report. Chest. 2019.

45. Pan J, Lei L, Zhao C. Comparison between the efficacy of combination therapy and monotherapy in connective tissue disease associated pulmonary arterial hypertension: a systematic review and meta-analysis. Clinical and experimental rheumatology. 2018.
46. Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis. 2011;70(3):476-81.
47. Flavahan NA. A vascular mechanistic approach to understanding Raynaud phenomenon. Nat Rev Rheumatol. 2015;11(3):146-58.
48. Koenig M, Joyal F, Fritzler MJ, Roussin A, Abrahamowicz M, Boire G, et al. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis Rheum. 2008;58(12):3902-12.
49. Matucci-Cerinic M, Krieg T, Guillevin L, Schwierin B, Rosenberg D, Cornelisse P, et al. Elucidating the burden of recurrent and chronic digital ulcers in systemic sclerosis: long-term results from the DUO Registry. Ann Rheum Dis. 2016;75(10):1770-6.
50. Herrick AL, van den Hoogen F, Gabrielli A, Tamimi N, Reid C, O'Connell D, et al. Modified-release sildenafil reduces Raynaud's phenomenon attack frequency in limited cutaneous systemic sclerosis. Arthritis Rheum. 2011;63(3):775-82.
51. Hachulla E, Hatron PY, Carpentier P, Agard C, Chatelus E, Jego P, et al. Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo-controlled SEDUCE study. Ann Rheum Dis. 2016;75(6):1009-15.
52. Korn JH, Mayes M, Matucci Cerinic M, Rainisio M, Pope J, Hachulla E, et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum. 2004;50(12):3985-93.
53. Matucci-Cerinic M, Denton CP, Furst DE, Mayes MD, Hsu VM, Carpentier P, et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2011;70(1):32-8.
54. Wigley FM, Seibold JR, Wise RA, McCloskey DA, Dole WP. Intravenous iloprost treatment of Raynaud's phenomenon and ischemic ulcers secondary to systemic sclerosis. J Rheumatol. 1992;19(9):1407-14.
55. Wigley FM, Wise RA, Seibold JR, McCloskey DA, Kujala G, Medsger TA, Jr., et al. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. Ann Intern Med. 1994;120(3):199-206.
56. Steen VD, Costantino JP, Shapiro AP, Medsger TA, Jr. Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. Ann Intern Med. 1990;113(5):352-7.
57. Jaeger VK, Wirz EG, Allanore Y, Rossbach P, Riemekasten G, Hachulla E, et al. Incidences and Risk Factors of Organ Manifestations in the Early Course of Systemic Sclerosis: A Longitudinal EUSTAR Study. PLoS One. 2016;11(10):e0163894.
58. Steen VD, Medsger TA, Jr. Long-term outcomes of scleroderma renal crisis. Ann Intern Med. 2000;133(8):600-3.

59. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 2006;354(25):2655-66.
60. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4(9):708-19.
61. Volkmann ER, Tashkin DP, Li N, Roth MD, Khanna D, Hoffmann-Vold AM, et al. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II. Arthritis Rheumatol. 2017;69(7):1451-60.
62. Volkmann ER, Tashkin DP, Sim M, Li N, Goldmuntz E, Keyes-Elstein L, et al. Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts. Ann Rheum Dis. 2019;78(1):122-30.
63. Sullivan K, Pinckney A, Goldmuntz E, Welch B, Khanna D, Simms RW, et al. Myeloablative Autologous Hematopoietic Stem Cell Transplantation for Severe Scleroderma: Long-Term Outcomes 6-11 Years after Entry on a Randomized Study Comparing Transplantation and Cyclophosphamide. ARTHRITIS & RHEUMATOLOGY; 2018: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA; 2018.
64. Poormoghim H, Lucas M, Fertig N, Medsger TA. Systemic sclerosis sine scleroderma: demographic, clinical, and serologic features and survival in forty-eight patients. Arthritis Rheum. 2000;43(2):444-51.
65. Shand L, Lunt M, Nihtyanova S, Hoseini M, Silman A, Black CM, et al. Relationship between change in skin score and disease outcome in diffuse cutaneous systemic sclerosis: application of a latent linear trajectory model. Arthritis Rheum. 2007;56(7):2422-31.
66. Namas R, Tashkin DP, Furst DE, Wilhalme H, Tseng CH, Roth MD, et al. Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: Post-hoc analyses from the Scleroderma Lung Study I and II. Arthritis Care Res (Hoboken). 2017.
67. Khanna D, Spino C, Johnson S, Chung L, Whitfield M, Denton CP, et al. Abatacept in Early Diffuse Cutaneous Systemic Sclerosis - Results of a Phase 2 Investigator-Initiated, Multicenter, Double-Blind Randomized Placebo-Controlled Trial. Arthritis Rheumatol. 2019.
68. Khanna D, Lin CJ, Kuwana M, Allanore Y, Batalov A, Butrimiene I, et al. Efficacy and Safety of Tocilizumab for the Treatment of Systemic Sclerosis: Results from a Phase 3 Randomized Controlled Trial. ARTHRITIS & RHEUMATOLOGY; 2018: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA; 2018.
69. Launay D, Remy-Jardin M, Michon-Pasturel U, Mastora I, Hachulla E, Lambert M, et al. High resolution computed tomography in fibrosing alveolitis associated with systemic sclerosis. J Rheumatol. 2006;33(9):1789-801.
70. Hoa S, Bernatsky S, Steele RJ, Baron M, Hudson M. Association between immunosuppressive therapy and course of mild interstitial lung disease in systemic sclerosis. Rheumatology (Oxford). 2019.
71. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4(9):708-19.

72. Sircar G, Goswami RP, Sircar D, Ghosh A, Ghosh P. Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. Rheumatology (Oxford). 2018;57(12):2106-13.
73. Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet. 2016;387(10038):2630-40.
74. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. N Engl J Med. 2019;380(26):2518-28.
75. Kahan A, Allanore Y. Primary myocardial involvement in systemic sclerosis. Rheumatology (Oxford). 2006;45 Suppl 4:iv14-7.
76. Forbes A, Marie I. Gastrointestinal complications: the most frequent internal complications of systemic sclerosis. Rheumatology (Oxford). 2009;48 Suppl 3:iii36-9.
77. Herrick AL, Gallas A. Systemic sclerosis-related calcinosis. Journal of Scleroderma and Related Disorders. 2016;1(2):194-203.
78. Avouac J, Walker U, Tyndall A, Kahan A, Matucci-Cerinic M, Allanore Y, et al. Characteristics of joint involvement and relationships with systemic inflammation in systemic sclerosis: results from the EULAR Scleroderma Trial and Research Group (EUSTAR) database. J Rheumatol. 2010;37(7):1488-501.
79. Clements PJ, Wong WK, Hurwitz EL, Furst DE, Mayes M, White B, et al. The Disability Index of the Health Assessment Questionnaire is a predictor and correlate of outcome in the high-dose versus low-dose penicillamine in systemic sclerosis trial. Arthritis Rheum. 2001;44(3):653-61.
80. Distler O, Allanore Y, Denton C, Kuwana M, Matucci-Cerinic M, Pope J, et al. OP0183 EFFICACY AND SAFETY OF RIOCIGUAT IN PATIENTS WITH EARLY DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS AND INTERSTITIAL LUNG DISEASE (SSC-ILD): RESULTS FROM THE PHASE IIB RISE-SSC STUDY. Annals of the Rheumatic Diseases. 2019;78(Suppl 2):167-.
81. Sitbon O, Gomberg-Maitland M, Granton J, Lewis MI, Mathai SC, Rainisio M, et al. Clinical trial design and new therapies for pulmonary arterial hypertension. Eur Respir J. 2019;53(1).
82. van Vollenhoven R, Voskuyl A, Bertsias G, Aranow C, Aringer M, Arnaud L, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). Ann Rheum Dis. 2017;76(3):554-61.
83. Khanna PP, Maranian P, Gregory J, Khanna D. The minimally important difference and patient acceptable symptom state for the Raynaud's condition score in patients with Raynaud's phenomenon in a large randomised controlled clinical trial. Ann Rheum Dis. 2010;69(3):588-91.
84. Pauling JD, Reilly E, Smith T, Frech TM. Factors influencing Raynaud’s condition score diary outcomes in systemic sclerosis. The Journal of rheumatology. 2019:jrheum. 180818.
85. Steen VD, Medsger TA. The value of the Health Assessment Questionnaire and special patient-generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum. 1997;40(11):1984-91.
86. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, et al. Predicting Survival in Patients With Pulmonary Arterial Hypertension: The REVEAL Risk Score Calculator 2.0 and Comparison With ESC/ERS-Based Risk Assessment Strategies. Chest. 2019;156(2):323-37.