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Systemic Sclerosis-Associated Interstitial Lung Disease: Lessons from Clinical Trials, Outcome Measures, and Future Study Design

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Abstract

Pulmonary involvement including interstitial lung disease (ILD) is the leading cause of mortality in patients with systemic sclerosis (scleroderma; SSc). This article reviews the current evidence based medicine regarding available therapies for SSc-ILD ; discusses the lessons learned from recent SSc-ILD randomized controlled trials (RCTs); and proposes outcome measures and recommendations for design of future RCTs for SSc-ILD.

Introduction

Pulmonary disease is the leading cause of morbidity and mortality in patients with systemic sclerosis (SSc)(1). Lung involvement in SSc is typically separated into two distinct entities: pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD) although many patient may have elements of both. This article will discuss only ILD in SSc, with a brief review on the pathogenesis and clinical measurements of SSc-ILD, followed by a focus on clinical trials of potential disease modifying therapies for this complication of SSc.

Pathogenesis and Therapeutic Implications

The pathogenesis of ILD in SSc involves a complex interplay of vascular injury, inflammation, and fibrosis and was recently reviewed (2). Microvascular injury and damage to the endothelial cells appear to be the initiating factors (3). Endothelial damage leads to the production of thrombin, endothelin-1, vascular endothelial growth factor, and adhesion molecules, which in turn may promote inflammation. Recent animal and human data also suggests that injury to epithelial cells may also play an important role in the pathogenesis. (4).

Interstitial and alveolar inflammation is present histopathologically in the earliest stages of SSc lung disease. Bronchoalveolar lavage (BAL) fluid samples obtained from SSc patients with ILD have increased total cell counts and higher percentages of neutrophils, eosinophils,

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and occasionally lymphocytes (5). Pro-inflammatory and profibrotic cytokines are overexpressed in lavage samples; including transforming growth factor-beta (TGF-β), connective tissue growth factor (CTGF), and platelet-derived growth factor (PDGF)(2).

Either inflammation or initial vascular damage leads to the local production of profibrotic factors such as thrombin and possibly endothelin-1. Thrombin promotes coagulation through the activation of fibrin and promotes the differentiation of fibroblasts into the more metabolically active myofibroblasts (6). Endothelin-1 is typically considered a local vasoconstrictor but has well established profibrotic effects as well (7).

In lung biopsies of SSc patients, TGF-β expression is increased in the fibrotic lung tissue (8) as is its key mechanism for presentation, integrin alpha(v_1)beta6 (9). TGF-β, endothelin-1 and other stimuli can induce connective tissue growth factor (CTGF) production, a cytokine that stimulates fibroblast growth and upregulates production of collagen and fibronectin (10). IL-13, a profibrotic cytokine, is a potent stimulator of fibroblast proliferation and collagen production(11). The overexpression of IL-13 in mice causes severe fibrosis in the lungs(12), and IL-13 neutralization inhibits fibrosis in murine models of bleomycin-induced lung injury. Recently, mice transgenic for the AP-1 family member Fra-2 have been shown to develop a severe SSc-like interstitial lung disease accompanied by both inflammation and proliferative vasculopathy.. The transcription factor Fra-2 is upregulated in lung tissues of ILD patients as well as in the skin(13).

Pathology

The most common pathological finding in lung biopsies of ILD in patients with SSc is nonspecific interstitial pneumonia (NSIP), although usual interstitial pneumonitis (UIP) is also occasionally found (14). In a biopsy series of 80 consecutive consenting patients, 77.5% had NSIP while the remaining patients had UIP/end-stage lung fibrosis or other patterns (14). Five-year mortality in this series did not differ between patients with NSIP or UIP/end-stage lung fibrosis. The lack of survival differentiation between connective tissue patients with NSIP pattern versus UIP is supported by other studies, and therefore a surgical biopsy is not considered to offer prognostic value.

Clinical Trials of Potential Disease-Modifying Therapies in SSc-ILD

Cyclophosphamide

A variety of immunosuppressive agents have been evaluated as potential disease-modifying therapies in SSc-ILD with cyclophosphamide (CYC) being the only one shown by RCT to be effective.. Studies have generally used FVC% predicted as the primary measure of outcome.

Open label studies by Silver et al (15) and White et al (16) ●● suggested that oral CYC may lead to stabilization of FVC% predicted in patients with SSc-ILD. The Scleroderma Lung Study (SLS) was designed as a multi-center, double-blind, randomized controlled study to evaluate the effectiveness and safety of oral CYC (upto 2.0 mg/kg/day) administered for one year in 158 patients with symptomatic SSc-ILD. Study design accepted the then current standards of definition of “active alveolitis” based on either analysis of BAL (≥3% neutrophils and/or ≥2% eosinophils) or presence of any ground glass opacification on thoracic HRCT. Ground glass appearance may represent fine fibrosis rather than inflammation(17). The SLS showed that CYC was associated with reduced loss of lung function (FVC and TLC), relative to placebo, at the end of the one-year treatment period (18) ●●. The physiologic benefits of CYC compared to placebo were modest (2.53% and 4.09% improvements in % predicted FVC and TLC, respectively, at 12 months; $p<0.03$).

These results were paralleled by improvement in patient-reported outcomes, including breathlessness, function and health-related quality of life measures (19). These measures met criteria for "minimally clinically important differences" in these measures and strongly supported the more modest physiological responses (19–21) The effect on FVC% and TLC % predicted was durable for an additional 6 months after CYC was discontinued but had disappeared at the 24 month evaluation. Effects on skin score and transition dyspnea index continued to favor CYC at end of 24 months but were no longer statistically significant (p=0.07 for TDI and 0.23 for skin) (22).

In a supportive study, CYC was administered by intravenous infusion monthly for 6 months followed by azathioprine (N=23), compared with placebo infusions and oral placebo (N=22), in patients with active SSc-ILD (23)●●. Intravenous therapy was chosen due to its better safety profile compared to oral CYC(24). This study attempted to induce a "remission" with CYC followed by a "maintenance" immunosuppressive regimen with lower potential toxicity. Results trended toward a favorable outcome in the actively treated group (FVC= + 4.19%, p=0.08). and are considered supportive of the SLS study. Neither study showed a statistically significant effect in DLCO%.

In the SLS, 1-year course of treatment with CYC was associated with treatment-related changes in fibrosis scores on HRCT scans, which correlated with measures of treatment response (FVC, TLC, and dyspnea)(25). A recent meta analysis of 3 RCTs and 6 additional prospective observational studies showed that CYC therapy was associated with a mean change of 2.83% (95% confidence interval = 0.35 to 5.31) in the FVC% and 4.56% (95% confidence interval = −0.21 to 9.33) in DLCO%(26).

Mycophenolate mofetil

Mycophenolate mofetil has been tested in several uncontrolled clinical studies and retrospective analyses in SSc-ILD and appears to favorably affect ILD. In the largest open label experience, Nihtyanova et al (27) treated 109 patients in whom 12% receiving MMF developed progression of ILD versus 19% of controls on other therapies. ($p<0.04$). Other SSc-related signs and symptoms also improved; 5 y survival (95.4%) on MMF versus 85.7% on other therapies (p=0.027). MMF was given for 12 months in 79% and for 12–36 months in 59% of patients. Based on this and other encouraging results from small case series, (27–31) and the rationale for its potential efficacy in SSc-ILD, a 12-center, double-blind, randomized controlled clinical trial (Scleroderma Lung Study II, SLSII) has recently started to evaluate the efficacy and safety of MMF (up to a target dose of 1.5 g twice daily for 2 years) in comparison with oral CYC (up to 2 mg/kg daily given for 1 year, followed by matching placebo for another year) in 150 patients with symptomatic SSc-ILD and evidence of any ground glass opacification on thoracic HRCT. The primary endpoint is change in FVC % predicted at 2 years, but the supportive measures which were so important in the first NIH lung study (see above) will be included as well.

Methotrexate

Oral methotrexate (MTX) has been examined in 2 double blind controlled trials (32;33). Skin change was the primary response measure in both trials (and showed that MTX had a modest favorable effect on skin). The Pope et al study showed a trend toward less deterioration in the DLCO, favoring MTX (DLCO% change= −3.7% change on MTX vs. −7.7% in the placebo, p=0.2) concomitantly with trend towards an improvement in skin score. FVC% was not reported in this study. The van den Hoogen et al study used a combined response measure which included change in DLCO and which favored MTX ($p<0.03$) but it was not possible to assess the results of the lung changes per se. While these

data are more credible than open experience, there is minimal support for the use of MTX for SSc-ILD. One should be aware of rare idiosyncratic reaction to MTX in the lungs.

Targeted therapies

Bosentan—Bosentan, a non-selective endothelin receptor antagonist licensed for the treatment of pulmonary arterial hypertension, was studied in patients with SSc-related ILD in the BUILD 2 (Bosentan in Interstitial Lung Disease in Systemic Sclerosis 2) trial. After 12 months, patients who received bosentan did not separate from placebo, either with regard to the primary endpoint (six-minute walk distance) or a number of secondary end-points including FVC, DLCO, and time to desaturation. There were no differences in rate of occurrence of significant physiologic deterioration (FVC or DLCO) between active drug and placebo(34). Six minute walk test was found to be reproducible in the short term but lacked construct validity with pulmonary function testing and exhibited poor reproducibility at a time interval of one year(35).

Bosentan was also studied in idiopathic pulmonary fibrosis (IPF) where it did not show difference from placebo in 6-minute-walk distance (primary outcome) up to Month 12(36). However, post hoc exploratory analysis showed a trend in favor of bosentan in the secondary endpoint of time to death or disease progression (hazard ratio [HR], 0.613 95% confidence interval [CI], 0.328–1.144), which was more pronounced in the subgroup diagnosed using surgical lung biopsy (HR, 0.315 95% CI, 0.126–0.789) but no trend in the other group. Based on these results, a large study was designed to assess the effect of bosentan vs. placebo in patients with biopsy proven IPF (Clinical Trial Registration Number: NCT00391443). The preliminary results were recently reported and there was no significant difference between bosentan and placebo. It remains possible that endothelin antagonists of higher receptor avidity and selectivity may offer therapeutic potential.

Tyrosine kinase inhibitors—TGF-β and platelet derived growth factor (PDGF) are thought to be a key mediators of fibrosis in SSc. Signaling through tyrosine kinases is critical to transmission of signals from TGF-β and PDGF. Imatinib mesylate (Gleevec) is a tyrosine kinase inhibitor that binds to the c-abl and blocks efficiently its tyrosine kinase activity; c-abl is an important downstream signaling molecule of TGF-β(37;38). In addition, imatinib mesylate interferes with PDGF signaling by blocking the tyrosine kinase activity of PDGF receptors. In an *in vitro* model of bleomycin-induced pulmonary fibrosis, c-Abl inhibition by imatinib prevented TGF-beta induced extracellular matrix gene expression, transformation and proliferation of fibroblasts (38). An ongoing open-label study is assessing oral daily imatinib in patients with SSc-ILD (Clinical Trial Registration Number: NCT00512902). Preliminary data from 15 patients with SSc-ILD was recently reported(39). The inclusion/ exclusion criteria were similar to SLS-I. Of 15 patients, 7 completed the study and 8 dropped due to side effects. In patients who completed the study, statistically significant improvements were seen in total lung capacity and skin score. Side effects such as lower extremity and generalized edema, nausea/ vomiting, and diarrhea led to drop out in this trial. The majority of these adverse events can be managed with lowering the dose of imatinib, giving divided dose, or addition of a diuretic. Other ongoing open label studies of imatinib for skin disease in SSc will provide preliminary data for possible future RCTs.

A trial is in progress to study dasatinib (a tyrosine kinase inhibitor with targets similar to imatinib (c-abl, c-kit and PDGFR)but which also inhibits src-kinase (src-kinase plays an important role in regulating the deposition of extracellular matrix proteins by dermal fibroblasts (40) and has in addition pro-inflammatory effects)) (Clinical Trial Registration Number: NCT00764309).

Anti-IL-13 antibody—IL-13, a profibrotic cytokine, is a potent stimulator of fibroblast proliferation and collagen production(11). SSc is associated with an excess of fibroblast activation and collagen production, as well as increased production of IL-13 (41). The overexpression of IL-13 in mice causes severe fibrosis in the lungs(12), and IL-13 neutralization inhibits fibrosis in murine models of bleomycin-induced lung injury. There are currently 2 phase II, double-blind, placebo-controlled RCTs ongoing in SSc-ILD and IPF of a fully human monoclonal antibody against human IL-13 (Clinical Trial Registration Number: NCT00581997). Little is known regarding safety or efficacy of this medication and results are awaited with interest.

Antithrombin Agents and other novel approaches—Bogatkevich et al have previously reported that thrombin induces a myofibroblast phenotype in normal lung fibroblasts resembling the phenotype of scleroderma lung myofibroblasts. A selective direct thrombin inhibitor, dabigatran, reversibly binds to the active site of thrombin and prevents the conversion of fibrinogen to fibrin. In a recent study, Bogatkevich et al showed that dabigatran inhibits thrombin-induced cell proliferation, α--smooth muscle cell (SMA) expression and organization, and the production of collagen and CTGF in normal lung fibroblasts. In addition, when treated with dabigatran, scleroderma lung myofibroblasts produced significantly less α-SMA, CTGF, and type I collagen compared with untreated cells.

B-cell depletion with rituximab (RTX) may also be a successful future therapeutic agent, based on recent data. In an SSc mouse model, anti-mouse CD-20 monoclonal antibody treatment depleted circulating and tissue B-cells and suppressed skin fibrosis in newborn mice(42). In a safety study of RTX, 15 patients with diffuse SSc were treated with two 1000 mg IV doses of RTX administered two weeks apart, and were followed up at six months(43). Overall, treatment was safe and well tolerated. Circulating B-cells and dermal B-cells were depleted, but RTX did not appear to result in a significant beneficial effect on skin disease. More recently, in an open-label study of 14 patients with SSc, eight patients were randomized to receive two cycles of RTX at baseline and 24 weeks (each cycle consisted of four weekly infusions at 375 mg/m2-fix this) while receiving standard treatment, while six control patients received standard treatment only(44). After one year, the RTX group had significant increases in FVC and DLCO compared to controls. In addition, skin thickening in the RTX group improved significantly (46). Larger scale, multicenter, RCT's are needed to confirm these possible beneficial effects of rituximab in SSc.

Prognostic information in SSc-ILD—In a recent analysis of 215 SSc patients followed for 10 years (45) ●●, baseline PFTs and HRCTs were predictive of mortality risk. An increased extent of disease (as defined by presence of ground glass opacity OR fibrosis) on HRCT >20% correlated with an increase in mortality (hazard ratio[HR] 2.48, P< 0.0005). Patients with a decreased baseline FVC <70% also had increased mortality risk (HR 2.11, *P*=0.001). When the two modalities were combined in a simple dichotomous staging system, patients with extensive disease (HRCT extent >20% on rapid evaluation OR FVC <70% when HRCT extent was intermediate) had a much higher mortality risk (HR 3.40 – 3.80 for four observers, P< 0.0005) than patients with mild disease (HRCT extent obviously <20%, or FVC >70% when HRCT extent was intermediate.

After summarizing the recently completed pivotal RCTs and observational data, Table 1 summarizes lessons learnt from recent SSc-ILD RCTs.

Outcome measures for SSc-ILD (Table 2)

Before discussing the design of future RCTs, it would be appropriate to understand the measures used in SSc-ILD trials. Whether a particular measure is appropriate for inclusion in RCTs is based on meeting the OMERACT filters of truth, feasibility, and discrimination(46). **Pulmonary function tests (PFTs)** in patients with SSc-ILD usually demonstrate a restrictive lung defect with decreased FVC and DLCO. The FVC is a validated measure for trials in SSc(47). PFTs are feasible in large RCTs of SSc-ILD(18;23). FVC has been used as the main parameter measuring restrictive lung disease. FVC was able to differentiate between active drug (CYC) and placebo in the SLS-I as detailed above. Low FVC predicts morbidity and mortality associated with SSc-ILD (48) and is responsive to change in multicenter RCTSs (18;23). DLCO is sensitive but not specific for parenchymal versus vascular damage and can decline in both forms of lung disease. It did not differentiate between active vs. placebo groups in 2 SSc-ILD studies. Even in IPF, a relatively "pure" interstitial lung disease, it is now clear that serial FVC is a better surrogate for mortality than serial DLCO, even though DLCO is the superior severity measure at a single point in time.

High-resolution computer tomography of lungs (HRCT) aims to characterize and quantify the degree of inflammation and fibrosis, thus supporting its face and content validity. The feasibility of HRCT for multicenter RCTs was demonstrated in 2 recent studies in SSc-ILD (18;23). The reliability of HRCT was demonstrated in the SLS trial (18) where there was good inter-reader agreement for determination of the absence or presence of pure ground-glass (Kappa=0.76) and fibrosis (Kappa=0.74) and fair agreement for honeycombing (Kappa=0.29). In the SLS, a higher degree of baseline extent of fibrosis seen on baseline HRCT scan was predictive of the rate of decline in FVC in subjects on placebo, as well as the response to CYC therapy. Patients with the most extensive fibrosis seen on baseline HRCT scan responded best to CYC treatment. In a recent analysis of 215 patients with SSc followed for 10 years (45), extent of reticular change but not ground glass on the HRCT was predictive of mortality risk. A clinically meaningful change has not yet been defined for HRCT. Therefore, HRCT should not be used as a primary outcome but can be used for cohort enrichment and as a secondary/ exploratory measure.

The Six Minute Walk Test (6MWT)-An Outcome Measure for SSc-ILD

The 6MWT measures the distance a person can walk in 6-minutes in carefully prescribed manner. It has been extensively used as an outcome measure in various cardiac and pulmonary diseases. The 6MWT was found to be feasible and reliable in a one year, multicenter, double-blind, randomized control trial comparing bosentan to placebo in 163 patients with SSc-ILD (35) but lacked construct validity and responsiveness to change in SSc-ILD. Limitations of the 6MWT were recently highlighted by various groups, showing that pain and musculoskeletal involvement can influence the walking test and that the 6MWT is not always solely reflective of changes in the lung when used in SSc(49;50), raising doubts about its specificity in this systemic disease and its relevance to monitoring therapy. We believe there are sufficient data to justify elimination as a candidate outcome measure.

Exercise oxygen desaturation

Recent data has assessed peripheral oxygen saturation (SpO2) in patients with SSc-ILD. SpO2 had a high agreement with arterial oxygen saturation during rest and exercise (SaO2) (51). In addition, the desaturation in exercise was associated with increased mortality. The hazard of death during the median 7.1 years of follow-up was 2.4 times greater for subjects whose SpO2 fell below 89% (p=0.02) or when SpO2max fell by 4 points from baseline (p=0.02). In addition, SpO2 desaturation(52) and heart rate recovery(53) during 6MWT in

IPF predicts mortality. It should be mentioned that oxygen saturation in SSc is subject to technical problems as finger or ear oximetry may be falsely low in the setting of SSc-related peripheral vascular disease. The recommended technique is forehead oximetry in SSc patients.

Dyspnea Indices

The Mahler dyspnea index (54) was used in the SLS and assesses the level of dyspnea. Baseline scores depend on ratings for 3 different categories: functional impairment, magnitude of task, and magnitude of effort. Baseline scores were able to discriminate between moderate and severe physiological parameters of breathing (FVC and DLCO) and correlated well with the baseline breathing visual analog scale (r=0.61) (55). Mahler's transition dyspnea score was able to differentiate between patients on CYC and placebo in SLS at 1-year, demonstrating its sensitivity to change.

The breathing VAS scale in the Scleroderma Health Assessment Questionnaire (S-HAQ) allows patients to assess their degree of difficulty in performing daily activities due to shortness of breath on a continuous 100 mm scale (56). The VAS discriminates between moderate and severe reductions in lung function, correlates well with the Mahler dyspnea index (r=0.61) and was shown to be sensitive to change in a SSc cohort (56); it did not differentiate between CYC vs. placebo in the SLS. Having discussed lessons learned from RCTs and observational studies and the outcome measures, Table 3 provides preliminary proposed recommendations for design of future SSc-ILD RCTs.

Conclusion

Recent well-designed trials in SSc-ILD have provided useful information regarding the metrics of outcome measures and trial design. This is coupled with an increase understanding about pathogenesis of SSc-ILD. As evident by ongoing open label studies of anti-IL13, tyrosine kinase inhibitors, and anti-CD20 inhibitors, there is a renewed interest in assessing targeted therapies in SSc-ILD and there will likely be placebo-controlled RCTs in near future. With that in mind, we propose recommendations for design of future SSc-ILD studies.

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Table 1

Lessons learned from recent studies(18;23;45)

1	Multicenter 1-year RCTs in SSc-ILD are feasible.
2	FVC% predicted is responsive to change in a 1 year RCT.
3	Patient reported outcomes are feasible and are responsive to change.
	a. Mahler's transition dyspnea index (TDI) is responsive to change in a 1 year RCT and minimally important difference estimate for improvement and worsening of TDI, which is 1.5 units(21).
	b. The Health Assessment Questionnaire Disability Index for SSc is a responsive tool in SSc-ILD over 1 year (difference of 0.16 favoring cyclophosphamide; p<=0.009), with changes greater than the minimally clinically important change for SSc(which is 0.14 for SSc(20)).
4	Patients who had baseline FVC% predicted < 70% have a greater placebo-corrected improvement in their FVC% predicted (placebo corrected improvement= 4.62%, p=0.007) with CYC than other patients(22)
5	Change in FVC is a superior end-point to change in DLCO or the six minute walk distance and can be regarded as the preferred primary end-point for future studies.
6	Change in DLCO did not mirror treatment effects on FVC and other variables and is an unsatisfactory primary end-point, influenced equally by changes in interstitial and vascular disease.
7	Change in the six minute walk distance exhibited striking long-term variability in the BUILDS studies and is an unsatisfactory primary end-point.
8	Extent of fibrosis on the *baseline* HRCT scan is a significant predictor of worsening FVC in the placebo group and of response to CYC in the SLS(18) ••.
9	Extent of ground glass appearance on the *baseline* HRCT scan is not a significant predictor of response to CYC in the SLS •• and in the UK observational cohort.
10	BAL cellularity at baseline is not a predictor of response in the SLS −1(57;58)••.
11	Presence of placebo group may lead to a selection bias where a less severe population is enrolled in the study. In the SLS, mean (SD) decline in the FVC% predicted in the placebo group was −2.9 (8.3) over 12 months, likely leading to a small treatment effect.

Table 2

Summary of Outcome measures in SSc-ILD

Outcome measures	Ready for RCTs in SSc-ILD	Recommendations as an outcome measure
FVC% predicted	Y	Primary
DLCO% predicted	N	No
TLC% predicted	Y	Secondary
HRCT	Y	Secondary/ Exploratory
6MWT	N	Not applicable
Dyspnea Indices		
Mahler Dyspnea Index	Y	Secondary
Breathing VAS from S-HAQ	Y	Secondary
Progression-free survival	Y	Secondary

***S-HAQ= Scleroderma-Health Assessment Questionnaire**

Table 3

Proposed recommendations for future SSc-ILD studies:

1)	Limited or diffuse cutaneous SSc(59).
2)	1-year placebo (or active) controlled RCT.
3)	The presence of ILD should be based upon the detection of appropriate abnormalities on HRCT, with this process subject to quality control.
4)	Presence of dyspnea should not be required as an inclusion criterion since there is lack of dyspnea in some patients with moderate-severe loss of lung function/advanced fibrosis on HRCT and presence of dyspnea in SSc may be related to cardiopulmonary deconditioning and pulmonary hypertension. Dyspnea should be included as a secondary outcome measure in SSc-ILD trials and currently Mahler Dyspnea Index meets the OMERACT filter (19;21).
5)	The primary goal of RCT should be to prevent disease progression as defined by stabilization of FVC% predicted (rather than to achieve regression of fibrotic abnormalities)
6)	Progression-free survival is an important secondary end-point. In the IPF trials (pirfenidone and BUILD-1), progression free survival showed a trend towards pirfenidone and bosentan. However, it lacks data in SSc-ILD.
7)	A systematic attempt should be made to enhance the sensitivity of this end-point by means of:
a)	Rigorous quality control in the accuracy of PFT estimation
b)	**Cohort enrichment:** Cohort enrichment: The selection of patients at greater risk of progression, based upon disease severity, observed progression or a short duration of systemic disease. Although cohort enrichment might be based on any single one of the criteria, it is recommended that patients attain severity threshold based on HRCT and FVC %. Currently, the published severity threshold (45), incorporating HRCT and FVC measures, is appropriate although this or other staging systems may be refined in the near future. In addition, they should meet one of the two criteria: a) short duration of systemic disease (defined as first 6 years after onset of signs or symptoms attributable to SSc from first non- Raynaud's signs or symptoms) or b) observed progression (> 10% of FVC over the past 3–12 months).
c)	Exploratory analyses in which marginal reductions in FVC (5–10%) are evaluated alone and in combination(as a composite measure) with a) changes in dyspnea; and b) changes in HRCT extent.
8)	Evaluation of biomarker signal, to inform subsequent study design to establish a) whether biomarker signal at baseline predicts a treatment effect; b) whether short term improvement in biomarker signal predicts a longer term treatment effect