Management of interstitial lung disease in systemic sclerosis

Interstitial lung disease (ILD) is very common in systemic sclerosis (SSc) and the leading cause of death. High-resolution computed tomography is a sensitive tool for the diagnosis of ILD in SSc and is abnormal in up to 90% of patients. The most common radiographic and histopathologic pattern seen in these patients is one of nonspecific interstitial pneumonia. Despite the high incidence of disease, the prognosis for most patients is good and those who progress tend to do so early in the course of disease. Treatment options are limited by a paucity of placebo-controlled trials. Data for use of cyclophosphamide and mycophenolate mofetil exist and there is an ongoing trial comparing these two treatments. Although there are limited data to guide us on how to care for these patients, this article proposes a management algorithm. There is ongoing research on new biological treatments as well as the use of biomarkers to predict the course of disease and response to treatment and these may shape the future management of SSc-ILD.

KEYWORDS: biomarkers ■ cyclophosphamide ■ interstitial lung disease ■ mycophenolate mofetil ■ nonspecific interstitial pneumonia ■ scleroderma ■ systemic sclerosis

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Learning objectives

Upon completion of this activity, participants should be able to:

- Distinguish appropriate initial tests for ILD among patients with SSc
- Assess how to follow the course of pulmonary disease in patients with SSc
- Analyze treatments for ILD among patients with SSc
- Evaluate the prognosis of ILD in the setting of SSc

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Systemic sclerosis (SSc) is a heterogeneous complex of diseases characterized by multiorgan involvement, endothelial dysfunction, excessive collagen production and immune system abnormalities [1]. Clinically, patients can have diverse systemic manifestations with any combination of skin, pulmonary, cardiac, renal, musculoskeletal and gastrointestinal involvement. SSc is an uncommon disorder that has an incidence of 18.7 new cases per million people per year and a prevalence of 242 cases per million people. It is a female predominant disease with a 3 to 4:1 female-to-male ratio and blacks have a higher incidence rate and more severe disease when compared with whites [2].

Our current understanding of the natural evolution of SSc has been facilitated by the 1980 SSc classification criteria, which provided uniform diagnostic criteria (**Box 1**) [3]. The disease is subdivided based on the pattern of skin involvement, with diffuse, limited and even absent skin manifestations.

SSc & lung involvement

Lung involvement in SSc is extremely common and clinically important. With improvement in the management of scleroderma renal disease, pulmonary disease has become the leading cause of death (it is the primary contributor in 33% of cases) [4]. In early autopsy series, up to 100% of patients had some type of pulmonary involvement [5,6]. When unselected patients are screened with high-resolution computed tomography (HRCT), up to 90% of patients will have SSc-associated interstitial lung disease (SSc-ILD) [7], while 40–75% will have physiologic abnormalities on pulmonary function testing (PFT) [8,9]. Clinically significant pulmonary disease appears early in the course of SSc, with 25% of patients developing lung disease within 3 years of diagnosis as defined by physiologic, radiographic or bronchoalveolar lavage (BAL) abnormalities [10].

Pulmonary involvement is associated with African–American ethnicity, skin score, serum creatinine and creatinine phosphokinase levels, hypothyroidism and cardiac involvement [10,11]. Other predictors include genetic factors [12], patterns of antibody positivity (antitopoisomerase antibodies predict lung involvement [11] and anticentromere and anti-RNA polymerase III antibodies appear protective [10,13]) and the pattern of skin disease (patients with diffuse SSc have a higher incidence of lung disease and those with limited SSc have a higher incidence of pulmonary hypertension [14–16]). African–American patients with SSc-ILD are particularly sensitive to the development of severe disease with a younger age of onset, higher antitopoisomerase levels, lower levels of forced vital capacity (FVC%) and diffusion capacity for carbon monoxide (DLCO%), and associated cardiac involvement at presentation when compared with white patients [8,11].

Pulmonary function tests

Screening PFT will show a reduced FVC% in 40–75% of patients, with 15% having a severe reduction [8,9,17]. DLCO% is reduced in 96% of patients with any other physiologic abnormalities [18] and correlates with the extent of lung disease on HRCT [19]. Patients with the CREST variant of SSc (those with subcutaneous calcinosis [C], Raynaud's phenomenon [R], esophageal dysmotility [E], sclerodactyly [S] and telangiectasias [T]) have a higher FVC% and lower DLCO%, reflecting the higher incidence of pulmonary vascular disease [20]. Both FVC% and DLCO% are markers of disease severity with lower values associated with

Box 1. Systemic sclerosis diagnostic criteria.

- Patient must have:
  - Proximal scleroderma
  - Or two or more of the following:
    - Sclerodactyly
    - Digital pitting scars of the fingertips or loss of substance of the distal finger pad
    - Bilateral basilar pulmonary fibrosis

shorter survival [8,21]. A declining DLCO% is the single most significant marker of poor outcome [18].

Bronchoalveolar lavage

An abnormal BAL count is defined as a neutrophil count of ≥3% or an eosinophil count of ≥2%, and 38–72% of selected patients with SSc will have abnormalities [22,23]. Even in patients with a normal HRCT of the chest, close to 50% of patients will have abnormal BAL cell counts [24]. Early studies suggested that patients with a neutrophilic BAL had a more rapid decline in their FVC% and DLCO% when compared with those with a normal BAL [25,26]. Owing to this early association with disease progression, as well as uncontrolled data suggesting improved survival in patients with a neutrophilic BAL who received cyclophosphamide (CYC) [26], BAL was frequently recommended during the evaluation of SSc-ILD patients and was an inclusion criteria for the Scleroderma Lung Study I (SLS I), a multicenter, randomized double-blinded study of CYC in SSc-ILD [27]. However, additional well-controlled studies determined that this prior association between BAL cellularity and progression was likely an epiphenomena, with neutrophilia representing more extensive disease, as seen on chest imaging. The findings from BAL counts do not appear to add to the prognostic information when noninvasive testing such as pulmonary physiology and HRCT are available [28,29]. However, BAL is useful in excluding infection when it is clinically suspected, and although limited to the research setting at present, BAL may have future utility in the measure of biomarkers present in the alveolar lining fluid.

High-resolution computed tomography

High-resolution computed tomography is the standard method for noninvasive diagnosis of SSc-ILD. The true incidence of HRCT abnormalities is difficult to determine as most studies use patients who are referred for respiratory symptoms, introducing a significant bias. Up to half of the HRCTs conducted in patients with normal lung volumes and mild reductions in DLCO% show abnormalities [14]. Even in patients with limited SSc and anticentromere antibodies (and thus have a low risk of developing ILD), a third will have abnormalities on HRCT [14]. Although 55–91% of patients will have imaging abnormalities [7,14,30–32], the extent is generally limited, with an average of 13% of the lung parenchyma involved [31,33].

Despite its sensitivity for locating lung disease, HRCT has limitations. HRCT can be normal in patients with PFT abnormalities and an abnormal chest exam (i.e., crackles), and a number of these patients go on to develop abnormal HRCT scans at follow-up [14]. Patients can have histopathologic evidence of disease (inflammation and fibrosis) in areas of 'normal' lung when using HRCT [34]. Despite these limitations, the presence of a normal HRCT at baseline predicts a good prognosis, with 85% of these patients still having a normal HRCT at a mean follow-up of 5 years [14].

Specific patterns of HRCT abnormalities are recognized and, similar to the patterns seen in the idiopathic interstitial pneumonias, these patterns can generally predict the underlying histopathology. SSc patients most frequently will have a nonspecific interstitial pneumonia (NSIP) pattern [33], characterized by a greater proportion of ground-glass opacity (GGO) and a lesser degree of coarse reticulation with rare honeycomb cystic change [35]. This pattern was seen in 59% of patients in a large series [18].

Radiographic progression occurs; there is replacement of ground-glass abnormalities by traction bronchiectasis/bronchiolectasis and/or honeycomb change over time [14]. Up to two-thirds of patients with GGO will progress to fibrosis [24]. The reason for progression in areas of GGO may be that they actually represent a fine intralobular fibrosis below the resolution of HRCT [21], as surgical biopsies of these areas show fibrosis in up to 50% of cases, usually associated with traction bronchiectasis or bronchiolectasis on HRCT [36]. Prognosis depends not only on the extent of ground-glass abnormalities, but also the amount of associated reticulation, and stability or progression in HRCT pattern, in spite of treatment, is common.

Pathology

Early reports of the pathologic changes in SSc-ILD show a mixed pattern of fibrosis and inflammation in the majority of cases. The pattern consisted of interstitial and alveolar cellular inflammation with alveolar wall fibrosis. When compared with cryptogenic fibrosing alveolitis in older studies, the only noted differences were more lymphoid aggregates in patients with SSc [34]. After Katzenstein and Fiorelli described the features of NSIP in 1994 [37], a re-evaluation of patients with SSc-ILD revealed a significant number with features consistent with a diagnosis of NSIP [38]. In the largest study to date, 77% of patients with SSc-ILD had a histological pattern of NSIP, the majority of which were fibrotic NSIP [18]. More recently, in a minority of patients with a usual interstitial pneumonia (UIP) pattern on biopsy, more germinal centers and inflammation and fewer fibroblast foci were seen when compared with subjects with idiopathic pulmonary fibrosis [39].

Biomarkers

There has been interest in finding biomarkers that could predict the development of fibrosis, the clinical course and the response to therapy. A number of small studies have evaluated a few potential biomarkers that can be measured in biologic fluids. Krebs von den Lungen 6 antigen and surfactant proteins A and D are produced by type II alveolar cells in the lung, are measurable in the blood and BAL, and have been correlated with the presence of ILD in patients with SSc [40,41]. Elevated serum levels of pulmonary and activation-regulated chemokine were correlated with ILD severity in SSc and levels of this chemokine in BAL fluid were negatively correlated with total lung capacity and DLCO% [42,43].

Treatment

Because of the presence of significant amounts of inflammatory cell infiltrate in patients with SSc-ILD, a number of anti-inflammatory agents have been investigated. Corsticosteroids have historically been used but their efficacy has never been proven, and their use has been associated with the development of scleroderma renal crisis in higher doses [44,45]. D-penicillamine was traditionally used in the 1970s and 1980s and a retrospective analysis suggested that D-penicillamine led to an improvement in DLCO% [46], although its efficacy has not been confirmed with prospective placebo-controlled trials. IFN-γ, which has been evaluated in many open-label studies, was studied in a prospective trial and no effect on patients with SSc-ILD was noted [47]. The endothelin antagonist bosentan was recently evaluated in a prospective, double-blind, multicentered treatment trial and was found not to be useful in the treatment of SSc-ILD [48].

There is significantly more robust data examining the use of CYC. Studies dating back to 1993 showed that SSc-ILD patients treated with CYC and prednisone had a significant improvement in FVC% at 6 and 12 months, and the improvement seen with CYC was suggested to be superior to other immunosuppressive medications [49–51]. In 2000, a retrospective cohort study found that patients with a neutrophilic BAL who were treated with CYC were more likely to have stabilization or improvement in FVC% and DLCO% than those who were not treated [26]. This preliminary data led to two prospective, randomized, placebo-controlled trials that have shed light on the role of CYC in the treatment of SSc-ILD. The first was SLS I, a 13-center, double-blind, placebo-controlled trial looking at oral CYC in patients with active symptomatic SSc lung disease [27]. After 1 year of treatment, a small but significant treatment effect on FVC% as well as significant improvements in dyspnea scores and skin thickness were seen. More adverse events were seen in the CYC group but no significant increase in serious adverse events was seen. Patients with more fibrotic lung disease (as defined by chest imaging) at baseline noted a greater benefit, and may have been under-represented in the trial [52]. The beneficial effects returned to placebo levels 1 year after cessation of therapy with the exception of the improvements in dyspnea [53]. A second trial (Fibrosing Alveolitis in Scleroderma Trial [FAST]) in which subjects received 6 months of intravenous CYC followed by oral azathioprine suggested a trend towards an FVC% benefit, but no statistically significant difference in FVC%, DLCO%, HRCT appearance or dyspnea scores was demonstrated [54].

Mycophenolate mofetil (MM) has been used with increasing frequency in patients with SSc-ILD. An uncontrolled small study looking at 13 patients with recent onset SSc-ILD treated with antithymocyte globulin followed by MM showed improvement in skin scores and stable PFTs (FVC% and DLCO%) over the year of treatment [55]. MM with low-dose prednisone improved pulmonary function and HRCT findings in a small prospective, open-label trial with five [56] and nine patients showing improvement in PFTs with minimal side effects in a recent retrospective review [57]. Another review of 17 patients with SSc-ILD treated for up to 2 years with MM showed stable pulmonary

function in the majority of patients [58]. A retrospective analysis of patients with SSc treated with MM found a lower incidence of pulmonary fibrosis and better survival when compared with other immunosupressive regimens [59]. Finally, a retrospective analysis of 13 patients treated with MM found a reversal in the pretreatment FVC% decline and a stabilization of the pretreatment DLCO% decline after 12 months of treatment [60]. Owing to this preliminary data with MM and the lack of sustained improvement seen with CYC, the Scleroderma Lung Study II (SLS II) is an ongoing prospective, multicentered, placebo-controlled trial investigating the effects of 1 year of treatment with CYC versus 2 years of treatment with MM.

Other agents have been evaluated in smaller trials. Owing to their ability to affect profibrotic pathways through inhibition of both TGF-β and PDGF signaling, the tyrosine kinase inhibitors are an attractive treatment option for SSc. In two open-label trials of the tyrosine kinase inhibitor imatinib, a total of 36 patients with SSc-ILD had stable FVC% over 12 months of therapy with imatinib (with one trial showing a significant improvement in DLCO%) [61,62]. Owing to the possible pathogenic role of B cells in SSc, anti-CD20 therapy has been tried. Three small, open-label trials in a total of 32 patients with SSc treated with rituximab (a monoclonal antibody against CD20) showed no signficant decline in physiologic variables over 6 months of follow-up [63–65]. In an open-label, randomized trial of 14 patients with SSc-ILD, treatment with rituximab resulted in significant improvements in FVC% and DLCO% while patients treated with standard therapy (consisting of a combination of prednisone, bosentan, CYC and MM) showed a decline in these indices [66]. Finally, basiliximab (a monoclonal antibody against CD25) stabilized the PFTs of ten patients with SSc, eight of whom had ILD [67]. These promising results will hopefully translate to future larger, prospective, randomized controlled trials.

When medical therapy fails to stem progressive loss of lung function, lung transplantation can be lifesaving. Although there is a perception among some physicians that patients with SSc-ILD will have poor post-transplant outcomes due to concomitant gastroesophageal disease, renal disease or skin fibrosis, comparative studies show the 2- and 5-year outcomes in these patients to be similar to those who have undergone a lung transplant for other conditions (survival rates of 72 and 55%, respectively) [68,69]. Relative contraindications include significant skin breakdown from severe cutaneous disease, a creatinine clearance of less than 50 ml/min, severe reflux disease with aspiration and cardiac involvement with arrhythmias [69].

Prognosis

Patients with SSc-ILD have an estimated survival of 85% at 5 years [70]. Progression to respiratory failure is an uncommon but dreaded complication. End-stage lung disease, defined as death or leading to a need for oxygen or continuous medication for pulmonary arterial hypertension, is seen in only 4% of patients at 5 years [21], while severe restrictive lung disease, defined by a FVC% of ≤50%, is seen in 13% [8].

For patients who develop restrictive lung disease, a decline in lung function occurs earlier; the greatest decline in lung function in these patients occurs within the first 2 years [8]. Predictors of severe restrictive lung disease include male gender, PFTs at diagnosis (FVC% and DLCO%) and age (a higher incidence in younger patients) [8,21]. Furthermore, survival does not differ between those with a pathologic pattern of NSIP and those with UIP, a notable difference from patients with an idiopathic interstitial pneumonia. Both groups have an 82–90% 5-year survival rate and 29–69% 10-year survival rate [18]. It also appears that neither the subtype of SSc (limited versus diffuse) nor the degree of fibrosis on HRCT affects the likelihood of progression [35]. Mortality is higher in African–Americans [8] and those with a lower FVC% and DLCO% at presentation [18]. Patients presenting with a FVC% of ≤50% have a 10-year survival rate of 40–50% [8]. When followed over time, changes in DLCO% at 3 years was associated with a decreased survival, an association not seen with changes in FVC% or DLCO% at 1 year [18].

Recently, Goh *et al.* developed a prognostic algorithm for patients with SSc-ILD (Figure 1) [31]. The algorithm relies solely on HRCT scoring cases with minimal or extensive disease, with recourse to a FVC% cutoff in cases of an indeterminate extent of disease. This staging system was shown to be easy to use and predictive of mortality.

Evaluating patients for lung disease

Clinicians should consider PFTs and a HRCT scan of the chest in all patients with SSc to help with the early identification of those at risk for the development of clinically significant respiratory disease. Normal initial testing portends a good prognosis; only 15% of those with a normal HRCT will develop clinically significant lung involvement at 5 years.

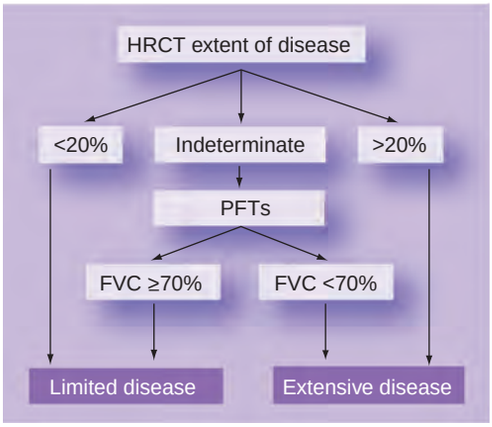

Figure 1. Stratification of systemic sclerosis-associated interstitial lung disease patients. A simple scheme by Goh *et al.* to stratify patients based on HRCT extent of disease with FVC% as a recourse in cases where the extent of disease is indeterminate. HRCT: High-resolution computed tomography; FVC: Forced vital capacity; PFT: Pulmonary function test.
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However, if HRCT or PFTs are abnormal, referral to a pulmonologist is warranted as not all changes will have clinical relevance. Further evaluation might then include indices of oxygenation at rest and with exertion (e.g., resting arterial blood gas and 6 min walk test). In patients at increased risk for pulmonary arterial hypertension (i.e., limited SSc) or those with indirect evidence of its presence (isolated reduction in DLCO%, DLCO% reduced out of proportion to FVC%, desaturation or symptomatology out of proportion to pulmonary disease, or suggestive findings on HRCT [71]), further evaluation should be considered. Transthoracic echocardiography has significant limitations but is often performed because of its convenience and ease of performance. However, right heart catheterization is often necessary to confirm or exclude the presence of pulmonary arterial hypertension. Esophageal disease (e.g., gastroesophageal reflux with dysmotility or esophageal stricture) should also be considered as its presence can be associated with considerable thoracic symptoms.

Who & when to treat

While respiratory symptoms, and physiologic and especially imaging abnormalities are common in patients with SSc [8], only a subset of patients will develop clinically significant, progressive disease. As all of our available therapies carry a risk of adverse reactions, attempts to minimize this risk by focusing treatment on those patients with a high risk of disease progression appears appropriate.

It is recognized that many patients with only mild physiologic or imaging abnormalities will remain clinically stable indefinitely, while those with more severe disease are likely to show measurable progression [31]. Therefore, the decision to treat should be made on a case-by-case basis where clinical significance of the disease (severity) and the likelihood of future progression are also considered.

Patients can be stratified on the basis of physiologic and imaging abnormalities according to the simple scheme described by Goh *et al.* (Figure 1) [31]. As patients who develop progressive disease tend to do so early in the course of their illness, patients with mild and stable radiographic or physiologic derangements should be followed up by querying symptoms and physiology at least every 3–6 months for the first 5 years. After stability is confirmed, yearly evaluations seem reasonable (Figure 2). The frequency of radiographs needs to weigh the risk of radiation exposure with the risk of missing evidence of disease progression and delaying treatment. Pulmonary physiology is relatively risk free. Changes in physiologic variables such as declines in FVC% or DLCO% should prompt radiographic evaluation to document progression of interstitial disease and evidence of disease progression should prompt treatment.

In contrast to those with limited disease, patients with extensive lung disease are at increased risk of disease progression and mortality and treatment should be considered.

What should not be used to determine treatment

The presence of 'alveolitis' (defined by a neutrophil count of ≥3% or an eosinophil count of ≥2% on BAL) should not be used to determine which patients with SSc-ILD should be treated. Although suggested to be useful in previous studies [25,26], in the prospective study of CYC in the treatment of SSc-ILD (SLS I) it was found to be a marker of disease severity and not an independent risk factor of disease progression [29]. For now, BAL appears most warranted in a clinical setting to rule out infection and in a research setting to evaluate for biomarkers that may predict the development or clinical course of lung disease.

While the extent of fibrotic disease seen on HRCT has clear prognostic significance, other commonly held beliefs about chest imaging in SSc may not be true. The presence of GGO has

traditionally been felt to be associated with the presence of cellular inflammation and therefore potentially reversible disease. Unfortunately, this is not a clear cut relationship in SSc-ILD. When patients undergo surgical lung biopsy, it is clear that GGO represents fibrosis in half of patients and progression of GGO occurs in spite of treatment in two-thirds of patients.

Given the ability of HRCT to provide an imaging pattern diagnosis that correlates well with the pathologic pattern, routine surgical lung biopsy does not appear necessary. Beyond this, the clinical course and outcome appear to be similar between the major histopathologic subsets (i.e., NSIP and UIP). As of today, surgical lung biopsy is generally not necessary in the evaluation of patients with typical HRCT findings, and provides its major benefit in the evaluation of those with atypical presentations or where the diagnosis is unclear.

Treatment & monitoring

In those patients in whom treatment is initiated, currently available data mostly support the use of CYC and secondarily MM. As this is an area of ongoing investigation, one might consider whether the patient qualifies for a treatment trial.

Our usual approach to therapy is to select a cytotoxic agent based on the severity of disease. In those with mild disease, MM is generally recommended while those with severe or rapidly progressive disease are generally treated with CYC. Treatment duration is planned for 12 months, with the total duration of therapy dictated by the clinical response. In those in whom therapy must be stopped because of adverse effects an alternative cytotoxic is considered. Because of cumulative toxicity, treatment with CYC is generally limited to 12 months with MM or azathioprine added after that point for those that need continued therapy.

Regardless of the medication chosen, in those patients in whom treatment is initiated, regular medication-specific monitoring for drug-related complications is necessary. In those with acute signs or symptoms, infection and drug reaction must always be actively considered as a potential cause.

When monitoring for beneficial treatment effects, querying symptoms, physiology and gas exchange every 3–6 months appears reasonable. In light of the currently available data from prospective treatment trials, stability in lung function should be considered a success.

Treatment trials

There is a need for better treatments in SSc-ILD and these therapies will need to prove their efficacy in formal treatment trials. Future trials should enhance their cohorts by focusing on

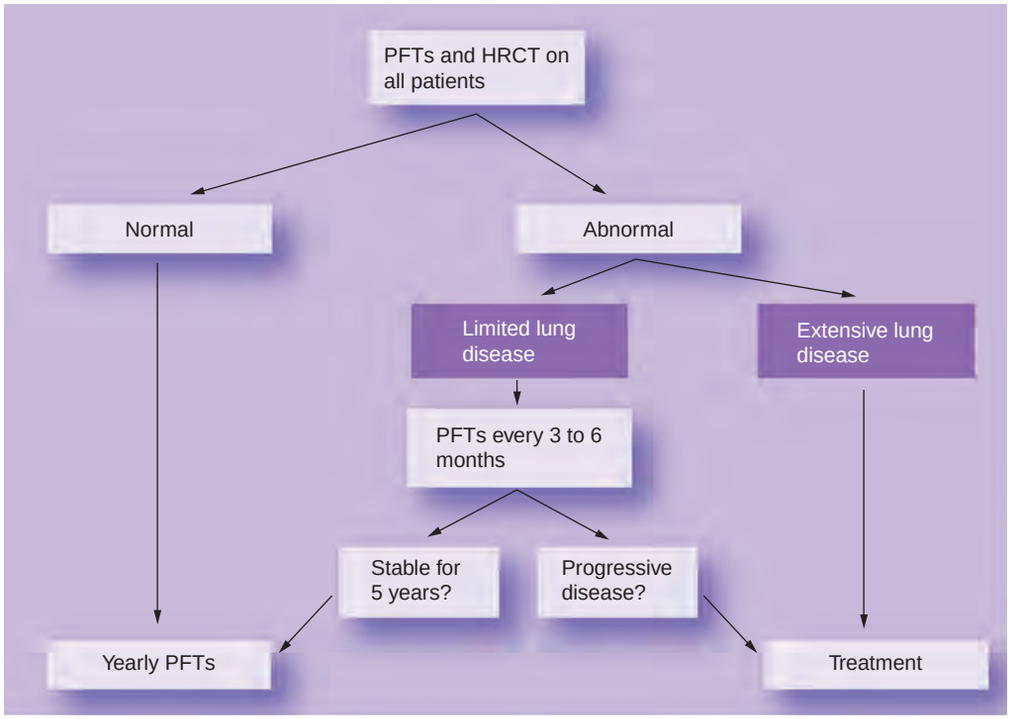

Figure 2. Management of systemic sclerosis-associated interstitial lung disease patients.
A proposed algorithm for the long-term follow-up of patients with systemic sclerosis.
HRCT: High-resolution computed tomography; PFT: Pulmonary function test.

patients at the greatest risk of progression. Based on what has been learnt from past trials, future investigations should have a trial duration of at least 1 year, use either placebo or CYC as their control, focus on HRCT as the primary diagnostic modality for the diagnosis of ILD and consider disease stability instead of improvement as an outcome [72]. Potential medications for future study include those currently being evaluated for the treatment of other ILDs and include anti-TGF-β and anti-CTGF approaches, pirfenidone and tyrosine kinase inhibitors.

Future perspective

Over the next 5–10 years, work will focus on understanding the pathogenesis of ILD in patients with SSc. We will evaluate new treatment modalities for SSc-ILD, including biologic agents. Studies will utilize enhanced cohorts and focus on different outcomes to measure the success of a treatment. We will have results from SLS II which will establish a standard treatment for SSc-ILD against which future treatments should be measured. There will be the identification of new biomarkers to help guide us in identifying the different clinical phenotypes of SSc-ILD as well as potentially predicting those at risk for progression and those most likely to respond to treatment. By improving our understanding of this complication of SSc, we can improve both the quality of life for these patients as well as their outcome.

Executive summary

Background

- Systemic sclerosis is a heterogeneous complex of diseases with multiorgan involvement and excessive collagen production.
- Systemic sclerosis is an uncommon disease with a female predominance.

Systemic sclerosis & lung involvement

- Lung involvement is extremely common in systemic sclerosis and the leading cause of death.
- Clinically significant interstitial lung disease occurs early in the course of disease.
- Bronchoalveolar does not add to the prognostic evaluation.
- High-resolution computed tomography is abnormal in up to 91% of patients with systemic sclerosis.
- Nonspecific interstitial pneumonia is the most common histological pattern.

Treatment

- The first Scleroderma Lung Study found that oral cyclophosphamide had a significant improvement in forced vital capacity after 1 year of treatment with a return to placebo levels 1 year after discontinuation of medication.
- Mycophenolate mofetil has been shown to stabilize or improve pulmonary functions in retrospective reviews and uncontrolled or open-label trials.
- Scleroderma Lung Study II is an ongoing trial comparing 1 year of cyclophosphamide treatment with 2 years of mycophenolate mofetil treatment.
- Patients with systemic sclerosis-related interstitial lung disease who undergo transplant have outcomes similar to those transplanted for other conditions.

Prognosis

- Death is uncommon, with an estimated 5-year survival of 85%.
- Survival does not differ between those with nonspecific interstitial pneumonia and usual interstitial pneumonia.
- A recent prognostic algorithm has been designed that uses high-resolution computed tomography results and pulmonary function tests and is predictive of mortality.

Evaluation of patients for lung disease

- All patients should have an initial evaluation with computed tomography and pulmonary function tests.
- Clinicians should have a low threshold to evaluate patients for pulmonary hypertension and gastroesophageal reflux.

Who & when to treat

- Patients should be stratified into those with mild disease (who are followed closely) and those with extensive disease (who are treated).
- Significant changes in physiology should prompt radiographic evaluation.

What should not be used to determine treatment

- The presence of 'alveolitis' on bronchoalveolar lavage should not be used to determine treatment.
- Routine surgical lung biopsy is not necessary in most cases.

Treatment

- The data are most supportive for the use of cyclophosphamide or mycophenolate mofetil.
- In patients who are treated, regular medication-specific monitoring is necessary.

Future directions

- There needs to be more prospective treatment trials using either placebo or cyclophosphamide as a control.
- Biomarkers could serve as markers of disease severity and possibly predict response to treatment.

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- ▪▪ of considerable interest

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1. You are seeing a 45-year-old black man who was recently diagnosed with systemic sclerosis (SSc) after noting 5 months of skin changes. The extent of other organ involvement is unknown at this time. You consider whether his lungs might be affected by SSc, although he has no pulmonary symptoms at this time. Which of the following is the best course of action to assess for possible pulmonary disease in this patient?

- ☐ **A** No action until pulmonary symptoms develop
- ☐ **B** Pulmonary function tests (PFTs) only
- ☐ **C** PFTs plus high-resolution CT (HRCT) scan only
- ☐ **D** PFTs, HRCT, and serum levels of Krebs von den Lungen 6 (KL-6) antigen and surfactant proteins A and D (SP-A and SP-D)

2. The patient undergoes appropriate testing, which demonstrates limited disease. What is the best course of management at this time?

- ☐ **A** Repeat HRCT testing every 6 months
- ☐ **B** PFTs every 3 to 6 months
- ☐ **C** Initiation of treatment with mycophenolate mofetil
- ☐ **D** Initiation of treatment with rituximab

3. The patient wants to know more about his prognosis. What can you tell him?	
☐ **A**	The 5-year risk for mortality is approximately 15%
☐ **B**	The greatest risk for mortality occurs among patients with late progression of ILD
☐ **C**	The presence of "alveolitis" on bronchoalveolar lavage is the most significant factor to determine when to initiate treatment
☐ **D**	Findings on HRCT are not useful in predicting prognosis

4. The patient's ILD progresses to the point where medical intervention is recommended. What is the best choice for treatment?	
☐ **A**	Cyclophosphamide
☐ **B**	Gamma-interferon
☐ **C**	Bosentan
☐ **D**	No medical therapy; proceed directly to lung transplantation