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## Journal
Journal of Scleroderma and Related Disorders, 4(1)

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## Publication Date
2019-02-01

## DOI
10.1177/2397198318816915

Peer reviewed

*Original Research Article*

JSRD Journal of Scleroderma and Related Disorders

Journal of Scleroderma and Related Disorders
2019, Vol. 4(1) 62–70

DOI: 10.1177/2397198318816915
journals.sagepub.com/home/jso
SAGE

# Determining progression of scleroderma-related interstitial lung disease

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**Abstract**

Interstitial lung disease occurs in the majority of patients with systemic sclerosis. Although interstitial lung disease is the number one cause of death in systemic sclerosis, interstitial lung disease progression rates vary considerably among patients with systemic sclerosis. Some patients with systemic sclerosis–associated interstitial lung disease have subclinical disease and may not derive benefit from immunosuppression, while others have a more aggressive interstitial lung disease phenotype. Reliable predictors of interstitial lung disease progression are lacking. The present review describes our current approach to monitoring systemic sclerosis–associated interstitial lung disease progression in clinical practice. To illustrate the marked heterogeneity that exists in interstitial lung disease progression rates in systemic sclerosis, this review presents the individual disease course of five unique patients with systemic sclerosis–associated interstitial lung disease who participated in the Scleroderma Lung Study II. These cases illustrate that treatment response rates vary in systemic sclerosis–associated interstitial lung disease and more research is needed to determine how to predict treatment response in systemic sclerosis–associated interstitial lung disease and to develop personalized treatment approaches for patients with this devastating disease.

**Keywords**

Systemic sclerosis, interstitial lung disease, treatment, survival

Date received: 8 November 2018; accepted: 9 November 2018

## Introduction

A workshop focused on determining progression of systemic sclerosis–associated interstitial lung disease (SSc-ILD) was presented at the 2018 Systemic Sclerosis World Congress in Bordeaux, France. Here, we review the major elements of this workshop, including selected cases illustrative of varying degrees of progression of SSc-ILD derived from participants in the Scleroderma Lung Study (SLS) II. SLS II was the first randomized controlled trial (RCT) comparing mycophenolate (MMF) versus oral cyclophosphamide (CYC) for treatment of symptomatic SSc-ILD.[1]

Interstitial lung disease (ILD) is a leading cause of morbidity and mortality in patients with systemic sclerosis (SSc) and accounts for the highest percentage of the deaths in this disease.[2] Characteristic features of ILD on high-resolution computed tomography (HRCT) in scleroderma patients include fibrotic changes (reticulations with architectural distortion) along with ground-glass opacification with or without honeycombing.[3] Based on reports mainly from specialty centers, evidence of ILD is found in approximately 70%–90% of patients with SSc.[4] In contrast, according to a recent

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study from Norway in which HRCT scans obtained in all patients with confirmed SSc whose data were included in national electronic registries (N = 815), approximately 50% of patients had HRCT evidence of ILD.[4] Patients with HRCT-defined evidence of ILD at baseline may have a preserved forced vital capacity (FVC), although the single-breath diffusing capacity of the lung for carbon monoxide (DLCO) in such cases is often modestly reduced.[5] Consequently, HRCT is a more sensitive and specific diagnostic measure for the detection of SSc-ILD than pulmonary function tests (PFTs). Among PFTs, abnormalities in DLCO correlate best with extent of ILD on HRCT.[6]

## Risk factors for progression of SSc-ILD

The natural history of SSc-ILD is markedly heterogeneous, and a variety of clinical features and biomarkers at the time of disease presentation may predict progression. These predictive factors include both clinical features and a number of biomarkers. Factors predictive of a greater likelihood of progression include the following: low baseline FVC and/or DLCO; extent of ILD on HRCT; male gender; African American race; and a number of biomarkers, including anti-topoisomerase 1 antibody, interleukin-6, C-reactive protein, monocyte chemoattractant protein-1 (MCP-1), CCL18, CXCL4, Krebs von den Lungen-6 (KL-6), and surfactant protein D.[7] In contrast, the presence of anti-centromere antibody appears to have a protective effect.[8] ILD can occur in patients with both diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc), although the rate of progression of ILD is typically more rapid in patients with dcSSc.

## When to initiate treatment for SSc-ILD

The decision to initiate treatment with potentially disease-modifying anti-rheumatic drugs (DMARDS) for SSc-ILD (as opposed to simply observing the patient over time) may be influenced by the likelihood of progression based on one or more of the above-mentioned features in an effort to spare patients with a low risk of progression from the potential toxicity of these agents. For example, Steen et al.[9] observed that survival over 10 years from disease onset was related to the baseline FVC%-predicted. Survival was the best (~87%) in those with an initial FVC of >75% predicted, the worst (~55%) in those with severe ventilator restriction (FVC < 50% predicted), and intermediate (~74%) in those with a baseline FVC of 50%–75% predicted.[9]

Goh et al.[10] explored the risk of survival and progression-free survival in an observational cohort of 215 patients with SSc followed for up to 10 years by dividing their patients into two groups, those with limited or extensive ILD, based on a combination of extent of ILD on HRCT and FVC% predicted at baseline. Patients were followed with serial PFTs (at 2- to 12-month intervals) following the baseline HRCT scan, and survival (as well as progression-free survival) was assessed within each of the groups. Progression was defined as a decline in FVC of >10% or in DLCO of >15% from baseline. Limited disease was defined by an extent of ILD on HRCT of ⩽10% or the combination of an extent of ILD on HRCT of 11%–30% ("indeterminate") plus an FVC ⩾ 70% predicted, while extensive disease was defined by an ILD extent on HRCT of >30% or an indeterminate HRCT scan plus an FVC < 70% predicted. Both overall survival and progression-free survival were markedly reduced in those with extensive disease compared to those with limited disease, with the latter group demonstrating a low risk for progression.[10]

Roth et al.[11] used data from the SLS I (oral CYC vs placebo in symptomatic SSc-ILD) to develop a model for predicting responsiveness to immunosuppressive therapy. HRCT scans were visually assessed for extent of fibrosis in the most involved lung zone (usually a lower lung zone) with division of the patients into four grades of ILD severity: Grade 1 (1%–25% extent); Grade 2 (26%–50% extent); Grade 3 (51%–75% extent); and Grade 4 (>75% extent).[12] In patients assigned to placebo, those in Grades 3 and 4 showed a markedly greater rate of decline in FVC over 12 months than those with lesser degrees of fibrosis.[11,13] In contrast, the course of FVC in patients receiving CYC was independent of the extent of fibrosis on the baseline HRCT, indicating that a favorable response to immunosuppressive therapy was largely confined to those with more extensive disease at baseline.[14] Depending on availability, computer-aided diagnostic (CAD) techniques can be used instead of or in addition to visual assessment to more precisely quantify the extent of fibrosis or total ILD (fibrosis + ground glass opacity + honeycombing) on HRCT within either the whole lung or the most severely affected lobe.[15,16]

## How to monitor patients with SSc-ILD

Based on the foregoing, physicians may or may not decide to initiate a DMARD (usually an immunosuppressive agent) in patients with SSc-ILD who appear to be at low risk of progression of their ILD. However, whether or not one decides to initiate immunosuppressive therapy after diagnosing SSc-ILD, patients will need to be monitored carefully to assess possible progression of their ILD. Evidence of progression in a patient in whom therapy was not initiated would be an indication to initiate therapy, while progression in the face of immunosuppressive therapy might be an indication to modify the therapeutic regimen, either by switching to another DMARD or adding an anti-fibrotic agent on top of the immunosuppressant. Moreover, in patients without evidence of SSc-ILD on the initial HRCT scan, a decline in lung function suggestive of the development of ILD would warrant obtaining a follow-up HRCT to confirm the development of SSc-ILD, thereby providing a justification for initiating therapy.

Progression of SSc-ILD is generally assessed using serial measurements of lung function (FVC and DLCO). Among 890 SSc patients followed at one institution, the FVC dropped below 75% predicted in approximately 40% of the patients, usually in the first 5–6 years after diagnosis of SSc, and a much smaller percentage of patients (10%–15%) lost at least half of their FVC (i.e. to <50% predicted) in the first 5–10 years.[9] HRCT can be used to confirm progression of SSc-ILD, particularly when changes in lung function are equivocal. In a Norwegian cohort, 53% of patients had HRCT evidence of progression (42.4% and 16.5% of patients had a >2% and >10% increase, respectively, in the extent of fibrosis in the whole lung on HRCT).[5]

The Outcome Measures in Rheumatology (OMERACT)–Connective Tissue Disease (CTD) working group has recommended the following as indicators of SSc-ILD progression: a relative decline in FVC over a year from baseline of ⩾10% or a relative decline in FVC of 5% to <10% plus a relative decline in DLCO of ⩾15%.[17] It is important to recognize, however, that measurements of FVC and DLCO are associated with considerable variability over time due to technical factors, diurnal or seasonal variability, or patient-related factors separate from true pathobiologic changes. Consequently, strict attention needs to be paid to ensuring that the tests are performed in accordance with published quality standards.[18,19]

To further ensure that changes larger than the above-cited thresholds represent true biologic alterations, the tests should be repeated after a relatively brief interval to document that they are sustained. Moreover, if there is doubt as to the clinical significance of any observed changes in lung function (e.g. if a discordance exists between the apparent deterioration in lung function and the absence of any worsening of symptoms of dyspnea), then consideration should be given to obtaining a follow-up HRCT scan for confirmation of true ILD progression. Conversely, if a patient exhibits worsening of breathlessness in the absence of any significant decrements in lung function, a repeat HRCT scan should likewise be considered since progression of fibrosis has been noted on serial HRCT scans in patients with idiopathic pulmonary fibrosis (IPF) in the absence of observable changes in lung function.[20]

### *Distinguishing changes in lung function due to progression of ILD from changes due to the development or progression of pulmonary hypertension*

Pulmonary hypertension (PH) develops in approximately 20% of patients with SSc-ILD and, in the absence of ILD, in approximately 8% of patients with SSc.[21,22] Thus, it is important to identify the presence or development of PH in patients with SSc-ILD both at the time of diagnosis and during follow-up. Echocardiography (ECHO) or right heart catheterization (RHC) is recommended for evaluating PH in SSc.[23] Findings of an estimated systolic pulmonary artery pressure of ⩾40 mm Hg on ECHO should be a strong indication for RHC in a dyspneic patient. A mean pulmonary artery pressure of ⩾25 mm Hg on RHC demonstrates the presence of PH. Comparison of the FVC with the DLCO results may also be useful in evaluating the presence of development of PH. A decrement in DLCO without a corresponding decrease in FVC (resulting in an FVC%/DLCO% ratio > 1.6) could be attributable to the development or worsening of PH.[22] In the latter case, RHC or ECHO should be considered for the assessment of possible PH. In any case, a yearly ECHO has been recommended for the detection of the development of PH.[23]

### *Ancillary measures of progression of ILD*

In addition to pulmonary function measurements, other methods for evaluating possible progression of SSc-ILD include assessments of progressive dyspnea (e.g. a visual analog scale)[24] or exercise capacity (e.g. the 6-min walk test[25] and oxygen saturation, especially during exercise[26]). Worsening of dyspnea or exercise tolerance may or may not accompany a decline in lung function or might be disproportionate to the latter. If uncertainty exists regarding the clinical significance of a decrement in lung function or an increase in breathlessness, the HRCT scan can be repeated to determine whether a worsening of structural evidence of ILD (fibrosis; ground glass opacity) accompanies the physiologic decline or increase in symptoms.

## Selected cases illustrating variations in the disease course of SSc-ILD from SLS II

### *Brief overview of SLS II*

As already described, SLS II was a double-blind RCT comparing MMF administered for 24 months with CYC administered for 12 months followed by an additional 12 months of placebo in patients with symptomatic SSc-ILD. Details concerning the design and results of SLS II have already been published.[1] Briefly, the course of ILD was monitored by serial measurements of FVC and DLCO at 3-month intervals. Additional measures of ILD progression included computer-assisted quantitative radiographic measures of the extent of fibrosis (QLF) and total ILD (QILD) in both the whole lung (WL) and the lobe of maximal involvement (LM) on volumetric HRCT scans obtained at total lung capacity at baseline and 24 months, QLF and QILD are expressed as a percentage of fibrosis and total ILD, respectively, within the whole lung or lobe of maximal involvement. In addition, self-reported breathlessness was measured by the Mahler Baseline Dyspneic

**Table 1.** Progression of SSc-ILD in Case 1. The baseline FVC%-predicted and DLCO%-predicted were 79.4% and 85.2%, respectively.

| Month | Relative ΔFVC, % | Relative ΔDLCO, % | BDI/TDI |
|---|---|---|---|
| 0 | | | 7 |
| 3 | −6.79 | −16.5 | |
| 6 | −8.68 | −20.9 | −6.5 |
| 9 | −13.6 | −16.0 | |
| 12 | −14.4 | −18.9 | −6 |
| 15 | −18.1 | −20.6 | |
| 18 | −19.3 | −26.8 | |
| 21 | | | |
| 24 | −33.8 | −25.8 | −8 |

SSc-ILD: systemic sclerosis–associated interstitial lung disease; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; BDI: Baseline Dyspneic Index; TDI: Transitional Dyspnea Index.

Index (BDI) at baseline and the Transitional Dyspnea Index (TDI), representing the change in dyspnea from baseline, which was measured every 3 months thereafter. The BDI score can range from 0 to 12, with the lower scores indicating worse dyspnea. The TDI score can range from −9 to +9, with the more negative scores indicating progressively worsening dyspnea and the more positive scores indicating progressively improving dyspnea.

## *Case 1*

Case 1 was a 35-year-old female with dcSSc with a disease duration of 1.8 years from the onset of the first non-Raynaud's symptom of SSc. She had a positive antinuclear antibody (ANA) with a homogeneous pattern (negative Scl-70, negative centromere, and positive RNA Polymerase III antibodies). At the time of her enrollment, her baseline FVC%-predicted was 79.4% and her DLCO%-predicted was 85.2%. Her Baseline Dyspnea Index (BDI) score, a valid measure of breathlessness, was 7, which indicates moderate dyspnea. Her quantitative radiographic extent of ILD (QILD-LM) in the most severely affected lobe (left lower lobe) was 31.9%, and the extent of fibrosis in that lobe (QLF-LM) was 3.5%. In addition to her pulmonary features, this participant had a modified Rodnan skin score (mRSS) of 13.

The participant was randomized to treatment with oral CYC for 1 year followed by 1 year of placebo. Table 1 illustrates the course of her FVC, DLCO, and Transition Dyspnea Index (TDI) during the 24-month trial. After 1 year of CYC, the patient experienced a relative decline in the FVC%-predicted of 14% and a relative decline in the DLCO%-predicted of 19%. The patient was transitioned to placebo during year 2, and she continued to experience a decline in both pulmonary function parameters paralleling her increased self-reported dyspnea. Furthermore, her QILD-LM and QLF-LM scores substantially increased from 31.9% to 60.1% and from 3.5% to 21.2%, respectively (Figure 1(a)).

Five years after the patient was randomized, the patient was confirmed to be alive. However, she had started supplemental oxygen 1 year after randomization, and she was disabled and unable to work.

Based on her disease course (Table 1), the patient met the OMERACT-CTD working group definition of ILD progression.[17] Unfortunately, the treating physician did not start her on alternate immunosuppressive therapy during the study, despite failing treatment with CYC and continuing to experience disease progression on placebo. This case demonstrates the importance of serial PFT monitoring for assessing SSc-ILD progression. By year 1, and some may argue by month 6, the patient likely should have been transitioned to a different ILD-targeted therapy, such as MMF.

## *Case 2*

Case 2 was a 50-year-old female with dcSSc with a disease duration of 1.7 years from the onset of the first non-Raynaud's symptom of SSc. She had a positive ANA with a speckled pattern (negative Scl-70, negative centromere, and positive RNA Polymerase III antibodies). At the time of her enrollment, her baseline FVC%-predicted was 71.8% and her DLCO%-predicted was 61.7%. Her BDI score was 9, which indicates mild-to-moderate dyspnea. Her QILD-LM score (left lower lobe) was 28.0%, and the QLF-LM score was 2.4%. In addition to her pulmonary features, this participant had an mRSS of 33.

The participant was randomized to treatment with MMF for 2 years. Table 2 illustrates the course of her FVC, DLCO, and TDI during the 24-month trial. At month 6, the relative change in the FVC%-predicted was −11.9; however, at month 9, the relative change in the FVC%-predicted was +3.7. By the conclusion of the 2-year study, the relative change in the FVC%-predicted was +9.7, indicating overall improvement in the FVC%-predicted. This improvement fulfills the recently defined minimal clinically important difference (MCID) for improvement in FVC%-predicted in SSc-ILD (range of 3.0–5.3).[27] Because the MCID was derived from a research cohort, there are limitations in applying this threshold to clinical practice. The DLCO%-predicted also improved over the course of the study. The QLF-LM and QILD-LM scores demonstrated only a modest degree of progression (Figure 1(b)). Four years after the patient was first randomized, she was confirmed to be alive without the evidence of clinical progression or a need for supplemental oxygen.

This case illustrates an example of a positive response to immunosuppressive therapy with MMF. Moreover, the variation in the course of the FVC%-predicted at month 6 highlights the importance of obtaining reproducible findings on

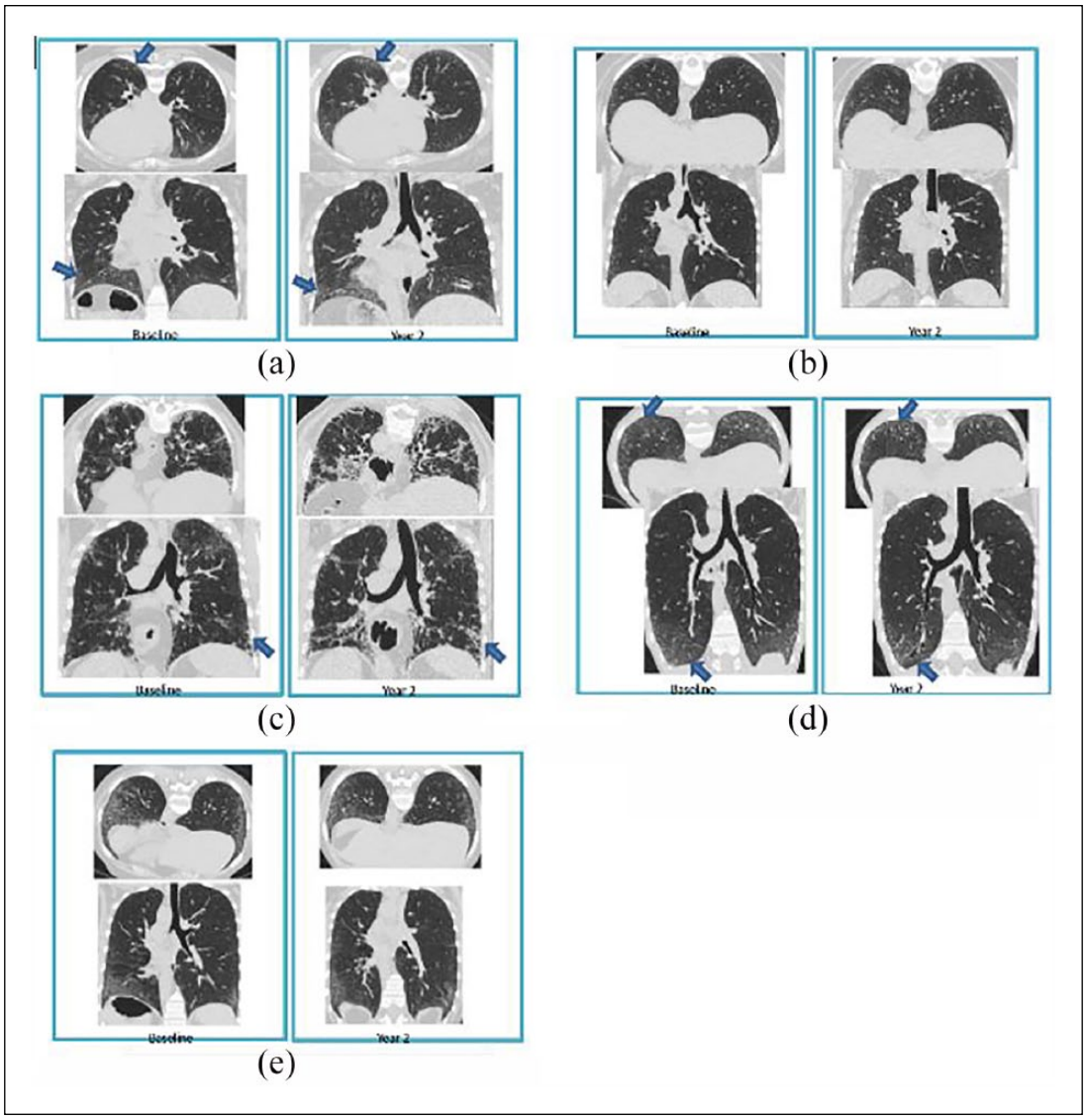


**Figure 1.** Changes in the radiographic extent of ILD for (a) Case 1: her QILD-LM and QLF-LM scores substantially increased from 31.9% to 60.1% and from 3.5% to 21.2%, respectively. (b) Case 2: her QILD-LM and QLF-LM scores increased from 28.0% to 2.4% and from 53.5% to 7.0%, respectively. (c) Case 3: his QILD-LM and QLF-LM scores increased from 44.1% to 68.0% and from 22.2% to 47.6%, respectively. (d) Case 4: his QILD-LM and QLF-LM scores increased from 30.5% to 42.0% and from 4.9% to 15.3%, respectively. (e) Case 5: her QILD-LM and QLF-LM scores increased from 23.6% to 24.5% and from 6.8% to 8.2%, respectively.

PFTs. As described above, measurement variation exists for both the FVC and DLCO. To ensure that any changes in the FVC or DLCO are accurate, treating physicians should repeat these tests at no less than 3-month intervals when monitoring progression (or earlier if the observed result may prompt a change in therapy).

## *Case 3*

Case 3 was a 66-year-old male with dcSSc with a disease duration of 2.5 years from the onset of the first non-Raynaud's symptom of SSc. He had a positive ANA with a speckled and nucleolar pattern (negative Scl-70, positive centromere, and negative RNA Polymerase III antibodies). At the time of his enrollment, his baseline FVC%-predicted was 62.0% and his DLCO%-predicted was 51.6%. His BDI score was 6, which indicates moderate dyspnea. His QILD-LM score (right lower lobe) was 44.1%, and the QLF-LM score was 22.2%. In addition to his pulmonary features, this participant had an mRSS of 22.

The participant was randomized to treatment with MMF for 2 years. Table 3 illustrates the course of his FVC, DLCO, and TDI during the 24-month trial. During the first year of the study, there was relative stability of the FVC%-predicted;

**Table 2.** Progression of SSc-ILD in Case 2. The baseline FVC%-predicted and DLCO%-predicted were 71.8% and 61.7%, respectively.

| Month | Relative ΔFVC, % | Relative ΔDLCO, % | BDI/TDI |
|---|---|---|---|
| 0 | | | 9 |
| 3 | 0.5 | −2.8 | |
| 6 | −11.9 | 5.8 | 5.5 |
| 9 | 3.7 | 18.2 | |
| 12 | −8.1 | 5.6 | 7.5 |
| 15 | −2.1 | 10.7 | |
| 18 | −2.1 | 19.9 | |
| 21 | −2.1 | 19.0 | |
| 24 | 9.7 | 25.8 | |

SSc-ILD: systemic sclerosis–associated interstitial lung disease; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; BDI: Baseline Dyspneic Index; TDI: Transitional Dyspnea Index.

**Table 3.** Progression of SSc-ILD in Case 3. The baseline FVC%-predicted and DLCO%-predicted were 62.0% and 51.6%, respectively.

| Month | Relative ΔFVC, % | Relative ΔDLCO, % | BDI/TDI |
|---|---|---|---|
| 0 | | | 6 |
| 3 | 3.8 | −7.3 | |
| 6 | 0.7 | −4.7 | |
| 9 | 2.4 | −7.8 | |
| 12 | −8.8 | −15.3 | |
| 15 | −11.1 | −9.3 | |
| 18 | −18.0 | −22.7 | |
| 21 | | | |
| 24 | −18.0 | −46.8 | |

SSc-ILD: systemic sclerosis–associated interstitial lung disease; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; BDI: Baseline Dyspneic Index; TDI: Transitional Dyspnea Index.

however, the DLCO%-predicted declined. The disproportionate decline in the DLCO relative to the FVC should have prompted evaluation for PH. By the conclusion of the study, the FVC/DLCO ratio was 1.8 (49.6/27.4). The patient clearly experienced progression of his ILD in conjunction with the development of PH, as his QILD-LM and QLF-LM scores increased from 44.1% to 68.0% and from 22.2% to 47.6%, respectively, (Figure 1(c)). The patient unfortunately died 3 years after he was first randomized in SLS II. The cause of death was respiratory failure.

The present case illustrates the importance of screening for the development of PH as well as at the same time continuing to monitor FVC%-predicted in patients with SSc-ILD. PH is the second leading cause of death in SSc-ILD[28] and an important contributor to breathlessness. Most clinicians perform yearly echocardiograms for patients with SSc; however, it is important to recognize the limitations of the echocardiogram as a screening tool for SSc when used alone. In the case above, even if the echocardiographic findings did not suggest an elevated right ventricular systolic pressure (RVSP), the disproportionate decline in the DLCO relative to the FVC should have prompted a referral for an RHC.

**Table 4.** Progression of SSc-ILD in Case 4. The baseline FVC%-predicted and DLCO%-predicted were 78.9% and 49.6%, respectively.

| Month | Relative ΔFVC, % | Relative ΔDLCO, % | BDI/TDI |
|---|---|---|---|
| 0 | | | 10 |
| 3 | −3.3 | 11.5 | |
| 6 | −10.9 | −14.0 | 1 |
| 9 | −5.9 | −2.8 | |
| 12 | −18.8 | −11.1 | −1 |
| 15 | | | |
| 18 | | | |
| 21 | | | |
| 24 | −11.1 | 7.7 | 3 |

SSc-ILD: systemic sclerosis–associated interstitial lung disease; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; BDI: Baseline Dyspneic Index; TDI: Transitional Dyspnea Index.

## *Case 4*

Case 4 was a 38-year-old male with dcSSc with a disease duration of 0.4 years from the onset of the first non-Raynaud's symptom of SSc. He had a positive ANA with a speckled pattern (negative Scl-70, negative centromere, and negative RNA Polymerase III antibodies). At the time of his enrollment, his baseline FVC%-predicted was 79.5% and his DLCO%-predicted was 49.6%. His BDI score was 10, which indicates mild dyspnea. His QILD-LM score (right lower lobe) was 30.5%, and the QLF-LM score was 4.9%. In addition to his pulmonary features, this participant had an mRSS of 10.

The participant was randomized to treatment with oral CYC for 1 year followed by placebo for 1 year. Table 4 illustrates the course of his FVC, DLCO, and TDI during the 24-month trial. During the first year of the study, both the FVC%-predicted and the DLCO%-predicted declined (relative change from baseline of −18.8 and −11.1, respectively). Because the FVC%-predicted declined >15%, the patient was deemed a treatment failure as pre-specified by the SLS II protocol. He discontinued study treatment at that point, and was started by his treating physician on MMF. When he returned for his 24-month final study visit, the relative change in his FVC%-predicted from baseline was −11.1, while the relative change in DLCO%-predicted was +7.7, indicating that he had some improvement on alternate therapy. He had a relatively modest increase in his QILD-LM and QLF-LM (from 30.5% to 42.0% and

**Table 5.** Progression of SSc-ILD in Case 5. The baseline FVC%-predicted and DLCO%-predicted were 82.9% and 55.8%, respectively.

| Month | Relative ΔFVC, % | Relative ΔDLCO, % | BDI/TDI |
|---|---|---|---|
| 0 | | | 6 |
| 3 | 0.6 | −6.2 | |
| 6 | 3.9 | −27.8 | 0 |
| 9 | 0.3 | −31.7 | |
| 12 | −4.9 | −41.8 | −4 |
| 15 | −2.4 | −30.0 | |
| 18 | −8.3 | −32.3 | |
| 21 | 2.9 | −20.1 | |
| 24 | −0.7 | −14.3 | −2.5 |

SSc-ILD: systemic sclerosis–associated interstitial lung disease; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; BDI: Baseline Dyspneic Index; TDI: Transitional Dyspnea Index.

from 4.9% to 15.3%, respectively) (Figure 1(d)). Five and a half years after he was initially randomized to treatment in SLS II, he was confirmed to be alive without the evidence of clinical progression or a need for supplemental oxygen.

The present case exemplifies that some patients may preferentially respond to specific immunosuppressive therapy. This participant failed treatment with CYC, but experienced improvement with MMF. Fortunately, the decision to change therapy likely altered the trajectory of his disease course and improved his long-term survival.

### *Case 5*

Case 5 was a 54-year-old female with lcSSc with a disease duration of 2.1 years from the onset of the first non-Raynaud's symptom of SSc. She had a positive ANA (speckled and nucleolar patterns) and negative sub-serologies (negative centromere, negative Scl-70, and negative RNA Polymerase III). At the time of her enrollment, her baseline FVC%-predicted was 82.9% and her DLCO%-predicted was 55.8%. Her BDI score was 6, which indicates moderate dyspnea. Her QILD-LM score (left lower lobe) was 23.6%, and the QLF-LM score was 8.2%. In addition to her pulmonary features, this participant had an mRSS of 6.

The participant was randomized to treatment with oral CYC for 1 year followed by placebo for 1 year. Table 5 illustrates the course of her FVC, DLCO, and TDI during the 24-month trial. At month 6, her DLCO had declined disproportionately to the FVC. The FVC/DLCO ratio at that time was 2.06. Over the course of the study, the DLCO continued to decline disproportionately to the FVC. The patient was diagnosed with PH and started on PH-targeted therapy at month 12. By the conclusion of the study, the DLCO had improved. The QILD-LM and QLF-LM scores demonstrated relative stability (changes in QILD-LM from 23.6% to 24.5% and in QLF-LM from 6.8% to 8.2%, respectively) (Figure 1(e)). The dyspnea scores also improved. However, 3 years after her randomization, the patient died of respiratory failure due to ILD and congestive heart failure.

The present case illustrates an example of PH development in a patient with stability of ILD. In this scenario, PH-targeted therapy not only improved diffusing capacity but also led to improvement in breathlessness. The follow-up HRCT was particularly helpful in this case for demonstrating radiographic stability in the extent of lung disease. In SSc-ILD, the optimal timing for re-assessment of the HRCT scan is unclear. While some centers perform yearly evaluations in patients undergoing SSc-ILD therapy, others perform HRCT scans at 6 months. Some only perform follow-up HRCT scans when there is clinical uncertainty as to whether there has been progression.

## Conclusion

The disease course for patients with SSc-ILD is highly variable as demonstrated in the aforementioned selected cases from SLS II. We have herein presented illustrative cases showing ILD improvement, ILD worsening, and ILD stability, as well as the development of co-morbid PH. A striking feature of all of the cases is that traditional predictive factors were not consistently helpful in determining the prognosis for these patients. For example, in Case 1, the participant was a relatively young women with only mild impairment on her PFTs (FVC%-predicted was 79.4% and her DLCO%-predicted was 85.2%) at the time of her enrollment. She was Scl-70 antibody negative and was started on immunosuppressive therapy within 2 years of her disease onset. However, she experienced substantial progression of her ILD, despite the fact that she did not possess any of the factors traditionally thought to predict ILD worsening (e.g. FVC%-predicted $<70\%$, male gender, older age, and Scl-70 antibody positivity), except for the presence of diffuse cutaneous disease.

Similarly, in Case 5, the participant developed PH relatively early in the course of their disease. She did not possess an anti-centromere antibody and had mild ILD based on her HRCT scan. Although PH is typically thought to present at later disease stages in patients with lcSSc, this patient's PH manifested itself within the first 2 years of her disease onset. Fortunately, the treating physician diagnosed the PH promptly and initiated effective therapy in a timely fashion.

In addition, the present cases further demonstrate that treatment response rates also vary considerably. In Case 4, the participant failed treatment with CYC, but responded positively to treatment with MMF. At the time of his enrollment, his ILD was mild based on his PFTs, HRCT results,

and breathlessness scores; however, CYC treatment did not prevent worsening of his ILD. When he was started on MMF, his ILD improved. The timing of his improvement and the initiation of MMF could have been coincidental, but it is more than likely that MMF was more efficacious in this particular individual. At the present time, there are no reliable biomarkers, which predict whether a patient will preferentially respond to MMF over CYC, or vice versa.

Taken together, these cases illustrate that our knowledge of the factors that predict progression of ILD in SSc is still evolving. More research is needed to help clinicians identify patients with rapidly progressive ILD phenotypes that may benefit from a more aggressive treatment approach. More research is also needed to determine whether certain clinical and/or biological factors could be used to predict treatment response to specific ILD-targeted therapies. With the emergence of anti-fibrotics as a potential treatment option for patients with SSc-ILD, it is critically important for future studies to assess whether clinical and molecular signatures could be used to determine whether a patient may preferentially respond to one therapy over another.

While tremendous advances in SSc-ILD clinical care and research have occurred in the last 5 years, we still have a long way to go to offer SSc-ILD patients the personalized health care that they deserve. We cannot solely rely on the "traditional" predictive factors for determining progression of SSc-ILD, especially since many of these factors were originally identified from single-center, observational cohort studies where patients were receiving different or no therapies and for varying amounts of time. Data from SLS II and other clinical trials in this area can provide valuable information to researchers seeking to uncover the most important clinical and biological factors which predict progression of SSc-ILD and response to therapy.

## Declaration of conflicting interests

Dr E.R.V. reports research grants from Boehringer Ingelheim, Merck Serono, and consulting fees from Boehringer Ingelheim. Dr D.P.T. reports consulting fees from Boehringer Ingelheim and Merck Serono. Dr D.P.T. is also a consultant for an independent investigator-initiated trial of pirfenidone on a background of mycophenolate that is supported by Genentech. Dr G.H.K. reports no disclosures. Dr J.G. reports no disclosures. Dr P.J.C. reports no disclosures.

## Funding

This work was supported by grants from the NHLBI/NIH: R01 HL089758 (D.P.T.), the Scleroderma Foundation Young Investigator Award (E.R.V.), and the Rheumatology Research Foundation Scientist Development Award (E.R.V.).

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