Clinical Course of Lung Physiology in Patients With Scleroderma and Interstitial Lung Disease

Analysis of the Scleroderma Lung Study Placebo Group

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Objective. Patients with systemic sclerosis–associated interstitial lung disease (SSc-ILD) are thought to have the greatest decline in lung function (forced vital capacity [FVC] % predicted) in the early years after disease onset. The aim of this study was to assess the natural history of the decline in FVC % predicted in patients receiving placebo in the Scleroderma Lung Study and to evaluate possible factors for cohort enrichment in future therapeutic trials.

Methods. Patients randomized to receive placebo (n = 79) were divided into 3 groups based on the duration of SSc (0–2 years, 2–4 years, and >4 years). Descriptive statistics and a mixed-effects model were used to analyze the rate of decline in the FVC % predicted over a 1-year period. Additional analyses stratified according to the severity of fibrosis on high-resolution computed tomography (HRCT) were performed, and interactions between disease severity and disease duration were explored.

Results. The mean ± SD decline in the unadjusted FVC % predicted during the 1-year period was 4.2 ± 12.8%. At baseline, 28.5%, 43.0%, and 28.5% of patients were in the groups with disease durations of 0–2 years, 2–4 years, and >4 years, respectively. The rate of decline in the FVC % predicted was not significantly different across the 3 disease groups (P = 0.85). When stratified by baseline fibrosis on HRCT, the rate of decline in the FVC % predicted was statistically significantly greater in the group with severe fibrosis (mean annualized decline in the FVC % predicted 7.2% versus 2.7% in the groups with no or moderate fibrosis; P = 0.008). The decline observed in the group with severe fibrosis was most pronounced in those with a relatively short disease duration (0–2 years; annualized decline 7.0%).

Conclusion. Among patients with SSc-ILD in the Scleroderma Lung Study, the rates of progression of lung disease were similar irrespective of disease duration. The baseline HRCT fibrosis score is a predictor of a future decline in the FVC % predicted in the absence of effective treatment.

Pulmonary disease is the leading cause of hospitalization and mortality in patients with systemic sclerosis (SSc) (1). Approximately 40% of patients with SSc develop moderate to severe restrictive lung disease (2). Longitudinal cohorts have provided important informa-
tion on the natural history of lung disease in SSc. Most of the decline in pulmonary function occurs during the first 3–4 years after the onset of non-Raynaud’s symptoms of SSc (2,3), and the course of pulmonary involvement is indolent after that. However, there is intraindividual variability in the changes in pulmonary physiology tests over time in patients with SSc. In addition, recent data suggest that the presence of moderate-to-severe fibrosis at baseline predicts poor survival in patients with SSc-associated interstitial lung disease (SSc-ILD) (4).

Results from the recently concluded Scleroderma Lung Study (SLS-I) (5), a randomized, placebo-controlled clinical trial, showed that a regimen of oral cyclophosphamide administered daily for 12 months was better than placebo for stabilizing lung function as measured by the forced vital capacity (FVC) % predicted and improving health-related quality of life (6,7) in patients with SSc-ILD during the treatment period. This large study recruited 158 patients with SSc-ILD, of whom 79 received placebo for a period of 1 year. Based on previous studies (2,8), the SLS-I investigators hypothesized a 9% annualized decline in the FVC % predicted (5). However, the study noted a decline of 2.6% over the 1-year treatment period in the patients assigned to receive placebo. Therefore, we sought to evaluate the variables associated with a greater decline in the FVC % predicted, because such characteristics could be useful for cohort enrichment in future therapeutic trials in SSc-ILD.

PATIENTS AND METHODS

Subjects. The study group comprised patients with SSc who participated in SLS-I and were considered to have SSc-ILD as defined by evidence of alveolitis on bronchoalveolar lavage (neutrophils ≥3%, eosinophils ≥2%) and/or ground-glass opacification on high-resolution computed tomography (HRCT). Other inclusion criteria were onset of the first non-Raynaud’s phenomenon manifestation <7 years prior to entry (based on data described by Steen et al [2]), FVC between 45% and 85% of the predicted value, and at least grade 2 dyspnea according to the baseline dyspnea index (BDI) described by Mahler et al (e.g., shortness of breath when climbing ≥2 flight of stairs) (9,10). Further details of the inclusion and exclusion criteria have been described previously (5).

Pulmonary function tests. Baseline measures of FVC, total lung capacity, and single-breath diffusing capacity for carbon monoxide (DLco) were obtained at the time of study entry and then every 3 months for the duration of the study. Pulmonary function tests were performed on study-certified equipment in accordance with recommended standards (11,12), and the quality of the tests was carefully monitored by centralized overreading, as previously described (5). All spirometric and DLco procedures had to be carried out on equipment that met the performance standards of the American Thoracic Society. All tests were carried out in University-based pulmonary function laboratories, and all sites were visited by the Director of the Pulmonary Function Quality Control Core for SLS-I (DPT). Moreover, as part of the overall pulmonary function quality control process, printouts of calibration curves and of all numerical and graphic results were submitted on a regular basis to the Pulmonary Function Quality Control Core for quality assessment. The overall quality of the test results, while varying somewhat from site to site in this 13-center study, was judged to range from satisfactory to excellent.

High-resolution computed tomography. HRCT scans were obtained with the subject in the prone position, without contrast, from the lung apices to the bases (13). Two independent radiologists who were blinded to the treatment assignment (cyclophosphamide or placebo for 12 months) carried out the scoring based on semiquantitative visual assessment. Lung images were divided into 3 zones for each lung. The upper lung zone extended from the lung apices to the aortic arch, the middle lung zone consisted of the area from the aortic arch to the inferior pulmonary veins, and the lower lung zone was assigned to the area from the inferior pulmonary veins to the diaphragm. Each of the 6 zones (except for 20 patients who were not scanned in the upper lung zone) from the right and left lungs was scored for ground-glass opacification (opacity through which normal lung markings could be seen), fibrosis (reticular opacity, traction bronchiectasis, and/or bronchiolectasis), and honeycomb cysts (14). Because SSc-ILD predominately affects the lower lung zones, we believed that an average score across all lung zones would dilute the effect of the most severely affected zones. Therefore, we used the score from the zone with the worst extent of abnormality (maximum score) in our analyses. In all patients (except for 1), the maximum fibrosis score at baseline was represented by the lower lung zones. Therefore, although the lung apices were not scanned in 14% of the patients, it is unlikely that we missed zones with the true maximum score in these patients. Scoring for the extent of involvement in each lung zone was as follows: 0 = absence of any pulmonary abnormality, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, and 4 = 76–100%.

Autoantibodies. Autoantibody data were available for 55 patients and included anti–Scl-70, anti–RNA polymerase III, and anticientromere antibodies, which were analyzed by enzyme-linked immunosorbent assays from Alpco Diagnostics (Scl-70 and anticientromere) and MBL International (anti–RNA polymerase III).

Statistical analysis. Based on the previous analysis by Steen and colleagues (2), we divided the patients in the placebo group into 3 subgroups based on the duration of SSc prior to study entry, as follows: 0–2 years (group A), 2–4 years (group B), and >4 years (group C). Disease duration was defined as the duration from the onset of the first non-Raynaud’s sign or symptom attributed to SSc as determined by direct interview of participating patients during screening and was captured in the case report form. The outcomes of interest were the annual rates of decline in the FVC and DLco % predicted. Due to baseline differences in physiologic measures in the 3 disease-duration groups, the outcomes were examined as the change in the FVC or DLco % predicted over the 1-year period divided by the baseline FVC or DLco % predicted.
Because our goal was to evaluate variables associated with a greater decline in FVC for cohort enrichment in future therapeutic trials, we examined the influence on the observed rate of decline in patients assigned to placebo of prespecified variables that were previously shown to be associated with a decline in the FVC % predicted or mortality in SLS-I and other cohorts (4). Summary statistics for baseline demographic and clinical data among the 3 disease-duration groups were generated. Analysis of variance was used to compare continuous variables among the 3 groups, and Fisher’s exact test or the chi-square test was used to compare categorical variables. Two-year data were not included due to discontinuations during the second year.

We used a linear mixed-effects model to evaluate the association between the outcome variables (rate of decline in the FVC and DLCO % predicted) and covariates with a random intercept to account for within-subject correlation of the outcome variables across multiple visits. First, we generated 3 models to assess the associations between the maximum scores for HRCT fibrosis, ground-glass opacification, and honeycombing at baseline on the rates of decline in the FVC and DLCO % predicted, including variables of time, disease duration, and interactions among time, disease duration, and HRCT scores. If there was a significant association, we used linear mixed-effects models to assess the relationships between primary outcome measures (rate of decline in the FVC and DLCO % predicted) and the following covariates: disease duration, maximum HRCT scores at baseline (fibrosis, honeycombing, ground-glass opacification), age, sex, baseline BDI scores, autoantibody status (anti–Scl-70 versus anti–RNA polymerase III versus anticientromere and others), smoking status, and the modified Rodnan skin thickness score. We also performed sensitivity analyses after reclassifying disease duration by including Raynaud’s phenomenon in the definition of the first sign or symptom of SSc.

All analyses were performed using SAS software. P values less than 0.05 were considered significant. Because this was an exploratory analysis, we did not account for multiple comparisons.

### RESULTS

Seventy-nine of 158 eligible patients were randomly assigned to receive placebo; 77 of these patients had a known baseline disease duration and were included in the current analysis. Of these 77 patients, 66 completed the 12-month study visit; 55 of these 66 patients completed all clinic visits, and the remaining 11 patients had withdrawn from randomized treatment or had been considered treatment failures at some time during the treatment year but returned to complete the 12-month study visit. At baseline, 22 patients (28.5%) were in group A, 33 patients (43.0%) were in group B, and 22 patients (28.5%) were in group C.

Table 1 presents the baseline characteristics of patients in the placebo group according to the 3 catego-
ries of disease duration. Patients in group A were significantly older at baseline compared with patients in the other 2 groups (mean age 56.2 years for group A versus 46.4 years and 43.4 years for patients in groups B and C, respectively), there was a trend toward a higher proportion of female patients in group C, and the BDI focal scores were significantly higher in group A than in groups B and C. Autoantibody data were available in 55 patients. Of these, 19 patients (35%) had anti–Scl-70 antibodies, 5 patients (9%) were positive for anti-RNA polymerase III and anticientromere antibodies, and 31 (56%) had other antibodies that were not characterized (Table 1). Patients in group A had slightly lower baseline FVC and DlCO % predicted values compared with the other 2 groups, but these differences were not statistically significant (P = 0.6 for both the FVC and DlCO % predicted). No significant differences in health-related quality of life measures or in the HRCT-defined disease extent were observed across the 3 groups.

Rate of decline in the FVC and DlCO % predicted, stratified by disease-duration groups. For all groups considered together, the mean ± SD decline in the unadjusted FVC % predicted was 4.2 ± 12.8% (Table 2), and the mean ± SD decline in the unadjusted DlCO % predicted was 8.2 ± 18.6%. The change in the FVC % predicted over 12 months was not correlated with the baseline FVC % predicted (r = –0.08, P = 0.54). No significant differences in the unadjusted rates of decline in the FVC % predicted were observed across the 3 groups (P = 0.85) (Figure 1A and Table 2). No between-group differences were observed in the rate of decline in the FVC % predicted adjusted for the baseline FVC % predicted (Figure 1B). For DlCO % predicted values, group A had a greater mean ± SD decline (17.9 ± 26.3%) over 12 months compared with groups B and C (P = 0.03) (additional information is available from the corresponding author).

Rate of decline in the FVC and DlCO % predicted, stratified by maximum HRCT scores at baseline. We explored the impact of maximum HRCT scores for fibrosis, ground-glass opacification, and honeycombing at baseline on the rate of decline in the FVC and DlCO % predicted. The cut-off HRCT values for comparison were based on the distribution of the baseline HRCT variables. No differences in the rates of decline were observed among patients stratified according to the severity of ground-glass opacification or honeycombing (P not significant) (Table 2). In contrast, when patients were stratified according to the maximum HRCT fibrosis score, those with severe fibrosis showed a greater mean ± SD decline in the FVC % predicted (7.2 ± 11.8%) compared with the group with no or moderate fibrosis (2.7 ± 12.8%; P = 0.008) (Table 2 and Figure 2). The differences in the rates of decline in the DlCO % predicted between patients with severe fibrosis and those with no or moderate fibrosis were not significant (Figure 3) (additional information is available from the corresponding author).

We assessed the impact of disease duration on

Table 2. Decline in the FVC % predicted in the placebo group over 12 months*

<table>
<thead>
<tr>
<th>Disease duration, years</th>
<th>No. of patients</th>
<th>Decline in FVC % predicted</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>0–2</td>
<td>17</td>
<td>4.4 ± 18.8</td>
<td>0.85</td>
</tr>
<tr>
<td>2–4</td>
<td>29</td>
<td>4.4 ± 10.1</td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>18</td>
<td>3.5 ± 10.1</td>
<td></td>
</tr>
<tr>
<td>HRCT fibrosis score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2</td>
<td>40</td>
<td>2.7 ± 12.8</td>
<td>0.008</td>
</tr>
<tr>
<td>3–4</td>
<td>25</td>
<td>7.2 ± 11.8</td>
<td></td>
</tr>
<tr>
<td>HRCT ground-glass opacification score</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0–1</td>
<td>55</td>
<td>4.9 ± 13.0</td>
<td>0.61</td>
</tr>
<tr>
<td>2–3</td>
<td>10</td>
<td>1.8 ± 9.8</td>
<td></td>
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<tr>
<td>HRCT honeycombing score</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>38</td>
<td>3.8 ± 14.5</td>
<td>0.96</td>
</tr>
<tr>
<td>≥1</td>
<td>27</td>
<td>5.3 ± 9.2</td>
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</tr>
</tbody>
</table>

Autoantibody positivity

- Anti–Scl-70
- Anti–RNA polymerase III/anticentromere
- Anti–Scl-70
- Others

Overall

- 66

4.2 ± 12.8

* Except where indicated otherwise, values are the mean ± SD. FVC = forced vital capacity; HRCT = high-resolution computed tomography; anti–RNA polymerase III = anti–RNA polymerase III.
the decline in the FVC % predicted according to the HRCT fibrosis category. Patients in group A (disease duration 0–2 years) with HRCT fibrosis scores of 3–4 had a greater decline in the FVC % predicted (change of 7.04 [8.70%]) compared with group A patients with HRCT fibrosis scores of 0–2 (change of 0.94 [12.24%]) ($P = 0.03$). In contrast, among patients in group B (disease duration 2–4 years) and group C (disease duration >4 years), no significant differences in the rate of decline in the FVC % predicted according to the fibrosis scores were observed (Figure 4). In the linear mixed-effects model, an HRCT fibrosis score of $\geq 3$ was associated with a significant decline in the FVC % predicted ($P = 0.004$) after adjusting for covariates (additional information is available from the corresponding author). The models that included different degrees of ground-glass opacification and honeycombing did not show any significant association with the decline in the FVC % predicted, irrespective of disease duration.

We further assessed the statistical interaction between the HRCT fibrosis score and disease duration in the 3 patient groups. Patients in group A had a significant interaction between fibrosis (fibrosis score $\geq 3$) and the number of months of treatment ($P = 0.03$), demonstrating that patients with an HRCT fibrosis score of $\geq 3$ and a disease duration of 0–2 years had an increased decline in the FVC % predicted over 12 months of treatment compared with those with lesser degrees of fibrosis. In group A, the annualized rates of decline were 7.0% in patients with a fibrosis score of 3–4 and 0.9% in patients with a fibrosis score of 0–2. This interaction between fibrosis and months of treatment was not significant for other disease durations. No association was observed between HRCT scores (fibrosis, ground-glass opacification, and honeycombing) and the DLCO % predicted for any category of disease duration.

We reclassified disease duration by including Raynaud’s phenomenon in the definition of the first SSc sign or symptom. The median (interquartile range [IQR]) disease duration was 1.6 years (IQR 1.2–1.9) for...
group A, 2.5 years (IQR 2.5–4.4) for group B, and 6.7 years (IQR 5.5–8.2) for group C. When disease duration was reclassified from the date at which Raynaud’s phenomenon was identified to determine the onset of SSc, no differences were observed when compared with use of the date of the first non-Raynaud’s sign or symptom to define onset of SSc.

Rate of decline in the FVC and DLCO % predicted, stratified by the presence of autoantibodies. The rates of decline in the FVC % predicted were similar in patients with anti–Scl-70 autoantibodies versus those with other autoantibodies ($P = 0.88$) (Table 2). Similar results were observed for the DLCO % predicted (additional information is available from the corresponding author).

**DISCUSSION**

SLS-I was the first randomized controlled clinical trial in patients with SSc-ILD to demonstrate the efficacy of a pharmacologic intervention (5). Because daily administration of oral cyclophosphamide for 12 months affected the change in the FVC % predicted over 1 year, the placebo group was selected for analysis to avoid confounding by active treatment. The placebo group comprised a large number of patients, providing a unique opportunity to assess the natural history of SSc-ILD over a 1-year period.

In the current analysis, we showed that the placebo group had a decline in unadjusted FVC and DLCO % predicted values (4.2% and 8.2%, respectively) over a period of 12 months. The unadjusted rates of decline in the FVC and DLCO % predicted were similar across the categories of disease duration (0–2 years, 2–4 years, and >4 years). A greater extent of maximum fibrosis on HRCT at baseline was associated with a greater decline in the FVC % predicted, and this effect on the FVC % predicted was most evident during the first 2 years after disease onset. The reason why a greater extent of fibrosis at baseline predisposes to a greater rate of decline in a physiologic indicator of disease severity in patients with evidence of ILD is not clear. A possible explanation for these findings may be that a greater extent of fibrosis at baseline in such patients might represent more rapid progression from inflammation to lung fibrosis prior to study entry that continues during the ensuing year, as reflected by a greater rate of decline in the FVC % predicted over this period of time.

Previous published data on the decline in lung function come from a large observational cohort at the University of Pittsburgh. Steen et al (2) demonstrated that the major decline in FVC occurred within the first 4–6 years of SSc. Patients in whom severe restrictive disease developed (FVC ≤50% of predicted) had lost 32% of the remaining FVC each year for the first 2 years, 12% of the remaining FVC for each of the next 2 years, and 3% of the remaining FVC for each of the following 2 years. In another observational study from Greece, Plastiras and colleagues retrospectively analyzed patients with SSc (3) and observed that baseline FVC % predicted values measured in 60 patients within the first 3 years after disease onset predicted the subsequent rate of change in pulmonary function. Neither Steen et al (2) nor Plastiras et al (3) performed HRCT or bronchoalveolar lavage in their cohorts.

In a nonrandomized treatment study of patients with SSc-ILD and evidence of alveolitis on bronchoalveolar lavage, White et al (8) retrospectively compared patients who were treated with oral cyclophosphamide with those who refused therapy. Oral cyclophosphamide was administered for a median of 10.8 months, and the investigators noted a 4.3% improvement in the FVC % predicted among treated patients (compared with a 7.1% decline in those who refused treatment with cyclophosphamide) (8).

Based on results of the 2 observational studies and the study by White and colleagues (8), SLS-I was designed to capture patients with both a relatively short disease duration (defined as <7 years from the onset of the first non–Raynaud’s phenomenon manifestation) and evidence of presumed active ILD (defined by bronchoalveolar lavage and/or HRCT), with the assumption that these patients would have a greater decline in the FVC % predicted over a period of 1 year. However, in SLS-I, the rate of decline in the FVC % predicted was only 4.2% over a 12-month period and did not vary across the 3 disease-duration groups.

We suspect that the lack of any demonstrable effect of disease duration on the rate of decline in our patient population might be attributable to inherent differences in patients enrolled in a randomized controlled trial versus patients followed up in observational studies. It is likely that patients with moderate-to-severe disease and rapidly declining lung physiology were likely underrepresented in SLS-I; patients with less extensive disease may be selectively enrolled in a placebo-controlled study, while those with more aggressive disease may be overrepresented in pilot studies of open-label treatments.

Previous analyses of data from SLS-I (which included both cyclophosphamide and placebo groups) (5) and the study by Goh et al (4) showed that moderate-
to-severe fibrosis on the baseline HRCT scan is an independent predictor of response to cyclophosphamide and poor survival, respectively. The results of our current analysis support previous findings that moderate-to-severe maximum fibrosis on the baseline HRCT (defined as ≥50% involvement of fibrosis in the lung zone with the maximum fibrosis score) is also an independent predictor of the decline in the FVC % predicted (Table 2) (P = 0.008). In contrast, baseline ground-glass opacification and honeycombing were not predictors of a decline in the FVC % predicted. One of the inclusion criteria for SLS-I was the presence of any ground-glass appearance on HRCT scans, with the notion that ground-glass opacification on HRCT scans represents reversible inflammation.

Studies on the validity of HRCT for idiopathic pulmonary fibrosis have been performed. In one study, the correlation of “ground-glass opacification” on HRCT with “inflammation” on lung specimens was weak (r = 0.27) (15). In another recent study (16), normal results of HRCT had a good association with normal pathology on lung specimens (r = 0.72). However, ground-glass opacification was not associated with any histologic pattern (r < 0.20). It has been suggested that ground-glass opacification on CT may represent fine (subresolution) fibrosis rather than reversible inflammation (17).

Our results have implications for the design of future therapeutic trials in SSc-ILD. Cohort enrichment can be attained by recruiting patients with a moderate-to-severe degree of baseline fibrosis on HRCT in the zone(s) with the greatest degree of fibrosis. Our findings complement those obtained in 215 patients with SSc who were followed up for 10 years (4), in whom the baseline FVC % predicted and findings on HRCT scans were predictive of the mortality risk. Also, based on recent studies showing a negative association between bronchoalveolar lavage findings and the FVC % predicted (4,18), bronchoalveolar lavage–identified cellularity should likely not be used as an inclusion criterion in future randomized controlled trials. HRCT is likely to be included in future SSc-ILD randomized controlled trials (12,13) for 1) cohort enrichment based on the extent of disease and 2) adjustment for baseline severity in key treatment-effect analyses (because it is likely that a treatment effect may differ in patients with mild rather than extensive lung disease). In addition, serial HRCT scans can provide a surrogate end point or more accurate measure of serial change in pulmonary fibrosis. Moreover, the baseline HRCT is important in excluding other significant thoracic disease not attributable to SSc (19).

A major limitation of the current study was that only 55 of the 77 patients completed the first 12 months of the trial. However, the present analysis of the natural history of SSc-ILD is based on the largest sample of patients with SSc examined to date. Second, this analysis was restricted to patients participating in a randomized controlled trial and is not necessarily applicable to patients in general clinical practice. Third, SSc-ILD trial designs continue to evolve (19), and the results of this analysis may not be applicable to other SSc-ILD studies with different inclusion/exclusion criteria. Last, our analysis was limited to a 1-year duration. However, current recommendations (19) propose a trial design with a minimum of 1 year; our 1-year data may inform the design of future trials.

In conclusion, we describe the natural course of SSc-ILD over a period of 1 year. Future SSc-ILD clinical trials can achieve cohort enrichment by enrolling patients with HRCT-defined moderate-to-severe fibrosis.

AUTHOR CONTRIBUTIONS
All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Khanna had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Khanna, Steen, Furst, Clements, Roth, Elashoff, Seibold, Tashkin.

Acquisition of data. Steen, Furst, Clements, Goldin, Elashoff, Seibold, Tashkin.


REFERENCES


