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Evolution of Systemic Sclerosis–Associated Interstitial Lung Disease One Year After Hematopoietic Stem Cell Transplantation or Cyclophosphamide

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Objective. Hematopoietic stem cell transplantation (HSCT) and cyclophosphamide (CYC) are treatment options for progressive systemic sclerosis associated with interstitial lung disease (SSc-ILD). The aims of our retrospective observational study were to evaluate: 1) the evolution of SSc-ILD in SSc patients treated with HSCT (assessed by high-resolution computed tomography [HRCT]; a group of patients treated with CYC was included as frame of reference); 2) how results of pulmonary function tests (PFTs) are associated with HRCT findings; and 3) which factors predict ILD reduction.

Methods. We semiquantitatively scored total ILD extent, reticulations, and ground-glass opacities (GGO) scores at baseline and at the 1-year HRCTs of SSc patients treated with HSCT or CYC. Linear association between changes in HRCT scores and PFT results and predictors of ILD improvement were studied.

Results. We included 51 patients (those treated with HSCT [n = 20] and those treated with CYC [n = 31]). The mean change in total ILD score was –5.1% (95% confidence interval [95% CI] –10.2, 0.0) in the HSCT treatment group ($P = 0.050$), and –1.0% (95% CI –4.3, 2.3) in the CYC treatment group ($P = 0.535$). For all patients, the evolution of HRCT scores was weakly associated with relative changes in PFT results. In univariate logistic regression, higher ground-glass opacities, higher total ILD, and lower single-breath diffusing capacity for carbon monoxide scores at baseline predicted improvement of ILD extent after treatment, but a multivariable model could not be built to assess independency of predictors.

Conclusion. One year after treatment with HSCT, a nonsignificant but clear reduction of SSc-ILD extent was observed. Changes in PFT results were associated with changes in HRCT scores but the correlation was weak and cannot be considered conclusive.

INTRODUCTION

Systemic sclerosis (SSc) is a complex connective tissue disease characterized by autoimmunity, vasculopathy, and fibrosis of skin and internal organs (1). Prevalence of SSc associated with interstitial lung disease (SSc-ILD) is estimated to be between 35% and 52% of SSc patients (2), but presence of lung abnormalities assessed by high-resolution computed tomography (HRCT) of the thorax has been described in up to 80% of SSc patients (3).

Complementarily to pulmonary function tests (PFTs), HRCT is the recommended screening tool to detect ILD in patients with SSc (4). With HRCT, ground-glass opacities (GGO), reticulations, subpleural nodules, and honeycombing, which are the characteristic features of ILD, can be recognized. It is also possible to identify the ILD pattern that, in SSc, is predominantly nonspecific interstitial pneumonia (5,6). Moreover, distinguishing patients with or without extensive lung involvement has significant treatment implications, underlining the prognostic relevance of HRCT (7).

In general, there are 2 treatment regimens most frequently adopted for SSc-ILD. Based on the results of Scleroderma Lung Study I (SLS-I) and II (SLS-II) (8,9), an induction phase with cyclophosphamide (CYC) that is followed or not followed by maintenance therapy with mycophenolate mofetil (MMF) or azathioprine (10), or, alternatively, MMF alone, are often chosen. The role of

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No potential conflicts of interest relevant to this article were reported.

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SIGNIFICANCE & INNOVATIONS

- Analyzing patients with systemic sclerosis (SSc) who were followed in our cohort through serial high-resolution computed tomography (HRCTs), we observed a clear reduction in the extent of interstitial lung disease (ILD) 1 year after hematopoietic stem cell transplantation (HSCT).
- Literature on HSCT in SSc mainly derives from randomized controlled trials. Our work contributes real-world data about the evolution of SSc-associated ILD after HSCT.
- Our findings suggest a weak correlation between changes in HRCT and modifications of pulmonary function tests.

biologic therapies, such as tocilizumab (11) or rituximab (12), is not yet supported by strong evidence, and the advent of antifibrotic agents promises to enrich the narrow armamentarium for SSc-ILD (13). According to the latest update of the European Alliance of Associations for Rheumatology (EULAR) recommendations for the treatment of SSc (14) and after 3 positive randomized controlled trials (RCTs) (15–17), hematopoietic stem cell transplantation (HSCT) is the other option to be considered for SSc-ILD in selected patients with rapidly progressive disease who are at risk of organ failure (after thorough screening).

The effect of CYC on the evolution of ILD assessed through HRCT (HRCT-ILD) in SSc patients has been evaluated in 2 analyses of the SLS trials (18,19), while the potential of HSCT to modify the progression of ILD extent has been investigated in 2 studies involving a limited number of patients (15,20). The main purpose of our research is to contribute additional real-world data retrospectively describing the evolution of SSc-ILD in patients treated according to the latest EULAR recommendations (14). Specifically, we are interested in the course of ILD in patients treated with autologous HSCT. Patients who received conventional immunosuppressive therapy with CYC were included as frame of reference to evaluate whether the changes in ILD that were observed after HSCT are different from what can be expected with intravenous CYC. The secondary objectives were to investigate the strength of correlation between HRCT evolution and changes in PFT results and which patient-related factors can predict ILD reduction in response to immunosuppressive therapy.

PATIENTS AND METHODS

Patients. The studied population was composed of adult patients enrolled in the Leiden Combined Care in SSc (CCISS) cohort (21). Data were collected between 2004 and 2019. To be included in the study, all participants had to meet the following criteria: 1) fulfill the 2013 American College of Rheumatology/EULAR classification criteria for SSc (22); 2) have evidence of ILD on baseline HRCT; 3) have been treated either with autologous HSCT or with intravenous CYC for at least 6 months; and 4) have high-quality HRCT images at baseline and after treatment completion available for scoring.

Research on the CCISS cohort is approved by the Ethics Committee of Leiden University Medical Center (LUMC) (approval number P09.003), and all patients gave written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki.

HRCT scoring. Baseline and follow-up HRCT scans were acquired in supine position and at maximal inspiration, using a standardized protocol at the radiology department of the LUMC. In all patients, HRCT scans were obtained contiguously with a slice thickness of 1–2 mm. Baseline HRCTs performed less than 6 months before the start of therapy and follow-up HRCTs obtained from 6 to 18 months after HSCT procedure or after first CYC pulse were selected for scoring. These HRCTs were performed as standard annual evaluation in the context of the dedicated SSc care pathway (21).

Two investigators (1 thoracic radiologist [LJMK] and 1 rheumatologist [AAS]), who are experienced in evaluation of chest imaging in patients with connective tissue diseases, independently scored all HRCTs blinded for patients' clinical characteristics, treatment history, and pulmonary function. For each patient, baseline and follow-up HRCTs were directly compared. Scoring of total ILD extent was performed according to the simple visual semiquantitative system described by Goh et al (7). The following 5 levels were examined: 1) origin of great vessels, 2) main carina, 3) pulmonary venous confluence, 4) halfway between the third and fifth section, and 5) immediately above the right hemi-diaphragm. In each of the 5 sections, total ILD extent was estimated at the nearest 5% approximation. The method proposed by Goh et al (7) would then provide separate estimations of GGO and reticular pattern (RET) extents, multiplying the relative proportions of GGO and RET by the total ILD extent in each level. In order to be more adherent to what is observed in clinical practice, we decided not to evaluate GGO and RET in the 5 levels as relative proportions but rather as extents at the nearest 5% approximation. Considering that the GGO and RET may overlap in the same portion of lung parenchyma, a single area could be scored as involved by both. As a consequence, the ILD extent would not necessarily correspond to the mere summation of the 2 components. Global scores for each of the 3 variables were calculated as the mean of the scores obtained at the 5 levels. The mean of the 2 global scores of each variable, computed by the 2 readers (LJMK and AAS), resulted in the total scores, namely GGO, RET, and total ILD scores. Discrepancies above 10% in any of the variables' global scores were discussed between the 2 readers to reach consensus. Changes at follow-up were computed as absolute percentages compared to baseline scores.

A study by Goldin et al (19) demonstrated that decreases or increases of at least 4% in quantitative ILD scores in the lobe of

maximal involvement and of 2% or more in the whole lung were considered to respectively identify significant worsening or improvement in ILD extent in SSc patients, while scores that remained within these limits represented stable disease; however, those thresholds were based on quantitative HRCT texture-based computer-aided analysis. By contrast, the scoring method proposed by Goh et al (7) is visual and, to our knowledge, no study has validated its longitudinal application. Therefore, we collegially agreed that a difference of 5% between pre- and posttreatment HRCTs, corresponding to the approximated minimum change visually identifiable at each HRCT level, could be reliable to distinguish patients with different ILD evolution. Improvement or progression were thus defined, respectively, as absolute reduction or increase above 5% in total ILD score, while stability was defined as those patients in whom no more than 5% ILD extent modification was identified at follow-up.

Finally, since the differential diagnosis of GGO is wide-ranging, other possible causes of ILD were always considered for all patients with SSc. In Leiden, all SSc patients are assessed for pulmonary arterial hypertension (PAH) at least annually. The screening is based on the European Society of Cardiology/European Respiratory Society recommendations (23), and, since 2013, the DETECT algorithm (24) is systematically applied to all patients in order to identify individuals that should proceed to right-sided heart catheterization. Moreover, since opportunistic and nonopportunistic infections can cause GGO, all HRCTs were evaluated with a multidisciplinary approach involving thoracic radiologists, pulmonologists, rheumatologists, and, in case of suspicion of infectious processes, also infectious disease specialists. Bronchoalveolar lavage, however, was performed only in patients with symptoms suggestive of respiratory tract infection. Although lung biopsy would provide a definitive diagnosis, the procedure is not routinely performed in SSc patients at the LUMC.

Clinical and laboratory data. Demographic data and clinical characteristics were collected at baseline, including disease subset, autoantibody positivity, presence of PAH, and mean modified Rodnan skin thickness score. Screening for PAH and HRCTs were preformed contextually as part of the 2-day care pathway for the follow-up of SSc patients. Disease duration was defined as time since the onset of the first sign or symptom attributable to SSc that was different from Raynaud's phenomenon. Results of baseline and follow-up PFTs that were closest to the corresponding HRCT dates were collected, provided that the time interval between HRCTs and PFTs did not exceed 3 months. All measurements were obtained at the pulmonology department of the LUMC. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and single-breath diffusing capacity for carbon monoxide (DLco) corrected for hemoglobin were included in the study. All physiologic values were reported as percentages of the predicted reference values, in accordance with published standards (25,26). Patients receiving 6 or 12 CYC pulses were analyzed as a single group because they were comparable in terms of demographic characteristics and HRCT scores at baseline, and at follow-up there was no statistically significant difference in mean changes of HRCT scores and PFT results.

Table 1. Characteristics of patients*

Baseline characteristics	HSCT (n = 20)	CYC (n = 31)	*P*
Female sex, no. (%)	10 (50)	24 (77)	0.043†
Age, years	46.5 ± 10.1	51 ± 12.8	0.189
Disease duration, median (IQR) years	2.5 (1.2–5.4)	1.8 (0.7–4.4)	0.380
dcSSc, no. (%)	18 (90)	19 (61)	0.025†
ATA, no. (%)	14 (70)	17 (55)	0.279
ILD, no. (%)	20 (100)	31 (100)	1
PAH, no. (%)	0	1 (3)	0.417
MRSS	23.2 ± 12.2	13.5 ± 10.4	0.003†
HRCT scores, %			
Ground-glass score	20.3 ± 13.6	21.5 ± 12.7	0.737
Reticular pattern score	13.9 ± 10.8	14.8 ± 10.3	0.772
Total ILD score	26.8 ± 14.6	25.1 ± 13.9	0.679
Pulmonary function tests, % predicted ‡			
FVC	77.8 ± 18.1	80.2 ± 16.7	0.633
FEV_1	75.7 ± 15.3	82.1 ± 15.8	0.165
DLco	53.4 ± 19.2	53.3 ± 11.6	0.985

* Values are the mean ± SD unless indicated otherwise. ATA = anti–topoisomerase I antibodies; CYC = cyclophosphamide; dcSSc = diffuse cutaneous systemic sclerosis; DLco = single-breath diffusing capacity for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high-resolution computed tomography; HSCT = hematopoietic stem cell transplantation; ILD = interstitial lung disease; IQR = interquartile range; MRSS = modified Rodnan skin thickness score; PAH = pulmonary arterial hypertension.
† Significant.
‡ In 2 patients, baseline FVC and FEV_1 (n = 1 in CYC group) or DLco (n = 1 in CYC group) were not available, while at follow-up FVC and FEV_1 had not been obtained in 1 patient in the CYC group.

Table 2. Difference of pretreatment and 12-month posttreatment HRCT scores and PFTs within 2 groups*

	Changes within groups			
	Pretreatment	Posttreatment	Difference (95% CI), %†	*P*
HSCT				
HRCT scores, %				
Ground glass opacities score	20.3 ± 13.6	14.1 ± 8.7	−6.2 (−11.0, −1.4)	0.015‡
Reticular pattern score	13.9 ± 10.8	13.5 ± 10.3	−0.4 (−1.7, 0.9)	0.542
Total ILD score	26.8 ± 14.6	21.7 ± 11.8	−5.1 (−10.2, 0.0)	0.050
PFTs, %				
FVC	77.8 ± 18.1	84.7 ± 19.2	+6.9 (3.5, 10.4)	<0.001‡
FEV_1	75.7 ± 15.3	82.2 ± 15.9	+6.5 (2.6, 10.4)	0.002‡
DL_{CO}	53.4 ± 19.2	55.1 ± 15.0	+1.7 (−2.8, 6.3)	0.431
CYC				
HRCT scores, %				
Ground glass opacities score	21.5 ± 12.7	19.8 ± 12.3	−1.7 (−5.0, 1.6)	0.301
Reticular pattern score	14.8 ± 10.3	16.2 ± 10.9	+1.4 (0.0, 2.8)	0.053
Total ILD score	25.1 ± 13.9	24.1 ± 13.8	−1 (−4.3, 2.3)	0.535
PFTs, %				
FVC	80.2 ± 16.7	84.6 ± 19.7	+4.4 (−0.5, 9.4)	0.077
FEV_1	82.1 ± 15.8	86.5 ± 17.6	+4.4 (−0.2, 9.0)	0.061
DL_{CO}	53.3 ± 11.6	55.6 ± 13.1	+2.3 (−1.4, 6.0)	0.209

* Values are the mean ± SD unless indicated otherwise. 95% CI = 95% confidence interval; PFTs = pulmonary function tests (see Table 1 for other definitions).
The posttreatment period was 12 months after HSCT or CYC treatment initiation.
† The reported differences are absolute percentages.
‡ Significant.

Minimum clinically important difference (MCID) for FVC changes in SSc-ILD has been estimated using data from the SLS trials. It corresponds to a range from 3.0% to 5.3% for improvement and from –3.0% to –3.3% for worsening (27). However, this MCID was obtained at group level in the SLS trials, whereas in the present study we primarily aimed at assessing changes in individual patients. Therefore, we applied a more stringent 5% cutoff also to FVC changes, in order to identify patients with improved, stable, or worsened ventilatory function.

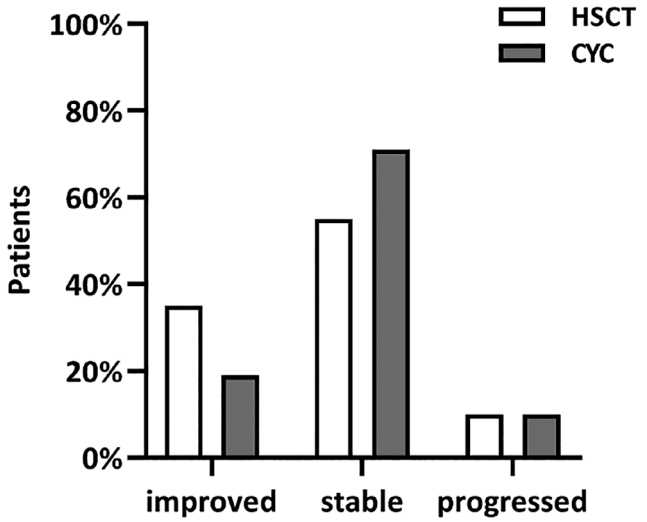

Figure 1. Proportion of improved, stable, or progressed patients 1 year after treatment with hematopoietic stem cell transplantation (HSCT) or cyclophosphamide (CYC). Improvement or progression were defined as absolute changes >5% in total interstitial lung disease (ILD) score, while stability identified patients with no more than 5% ILD extent modification at follow-up.

The stratification method described by Goh et al (7) was applied to define, at baseline, patients with extensive or limited lung disease. In particular, patients with an ILD extent of ≤10% were categorized as having limited disease and patients with >30% as having extensive disease. For cases with an ILD extent of >10% and ≤30%, an FVC of ≥70% or <70% stratified the patient, respectively, in the limited or extensive disease group.

Statistical analysis. Statistical analysis was performed using SPSS, version 23. Baseline demographic, clinical, and laboratory characteristics were expressed using descriptive statistics, with mean ± SD or median (interquartile range [IQR]) reported when appropriate. Differences in baseline characteristics between patients treated with CYC or HSCT were analyzed. These characteristics were compared using the 2-sample *t*-test and Mann–Whitney U test, respectively, for normally and non-normally distributed continuous variables, and with the chi-square test for categorical variables. Pre- to posttreatment changes in HRCT scores and PFT results were compared within groups using paired sample *t*-tests, and differences in means were reported with 95% confidence intervals (95% CIs). In the combined population, Spearman's rho (ρ) was used to evaluate the correlation between absolute changes in HRCT scores and relative changes in PFT results, whereas univariate logistic regression was used to assess baseline characteristics predictive of improvement in ILD extent. *P* values less than 0.05 were considered statistically significant.

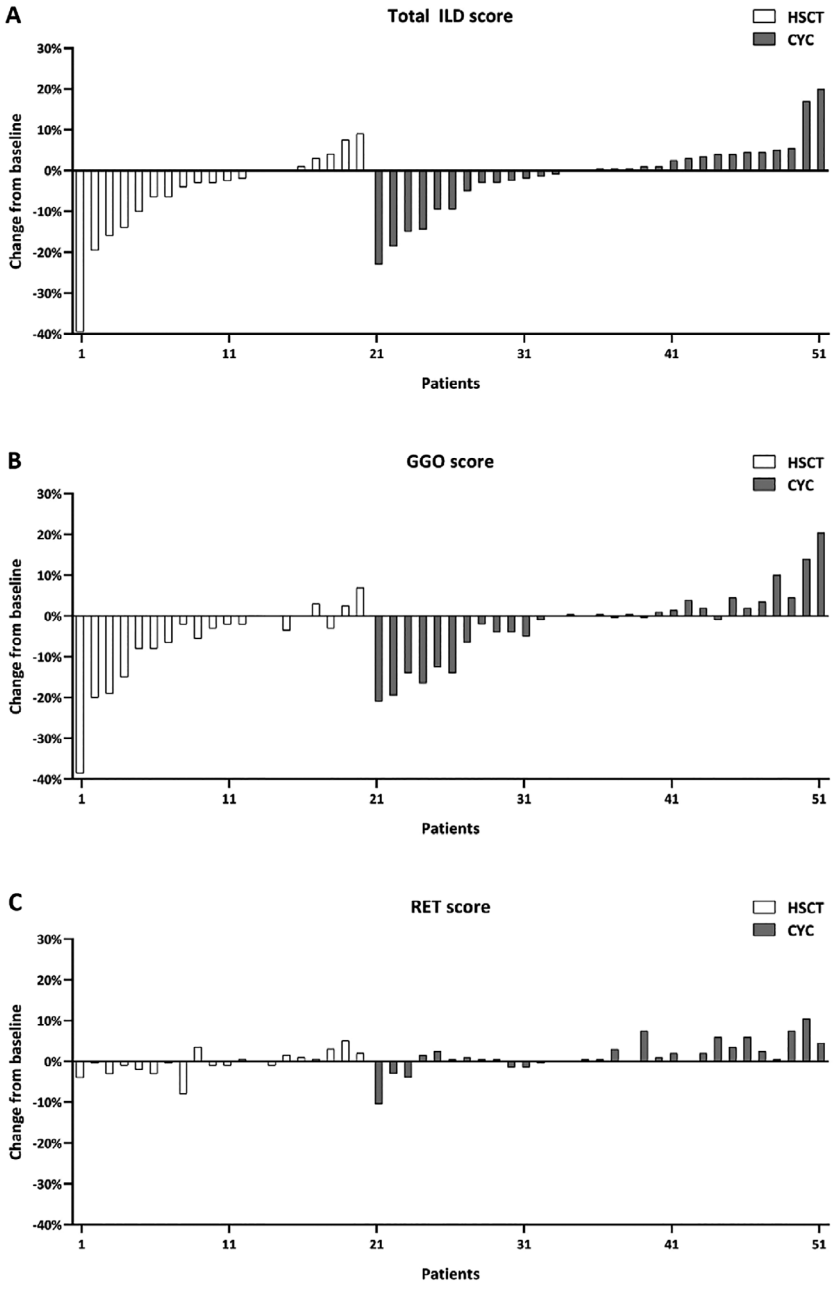

Figure 2. Evolution of high-resolution computed tomography scores 1 year after treatment shown in descending order from maximum improvement to maximum progression of interstitial lung disease (ILD) score. Individual changes from baseline to follow-up of total (ILD) score (**A**), ground-glass opacities (GGOs) score (**B**), and reticular pattern (RET) score (**C**) are shown. Bars represent individual patients. HSCT = hematopoietic stem cell transplantation; CYC = intravenous cyclophosphamide.

RESULTS

Patient characteristics. In order to have the 1-year follow-up HRCTs available, we included patients treated until May 2018. Of the patients enrolled in the CCISS cohort, 40 received HSCT. Of these patients who received HSCT, 20 were not included in the present study. The main reasons for exclusion were absence of ILD at baseline HRCT (n = 7) and unavailability of HRCT images stored in digital format and suitable for scoring (n = 9). Moreover, 3 patients died before the follow-up HRCT could be obtained (treatment-related complications, including sepsis and multiple organ failure [n = 2] and disease progression [n = 1]), and in 1 case scoring accuracy was compromised by the presence of radiation-induced pulmonary fibrosis. As a result, 20 patients (10 men, 10 women) treated with HSCT were included in the study. As frame of reference, 31 patients (7 men, 24 women) who were treated with 6 monthly pulses (n = 17) or 12 monthly pulses (n = 14) of CYC (750 mg/m^2) were studied. Baseline characteristics are

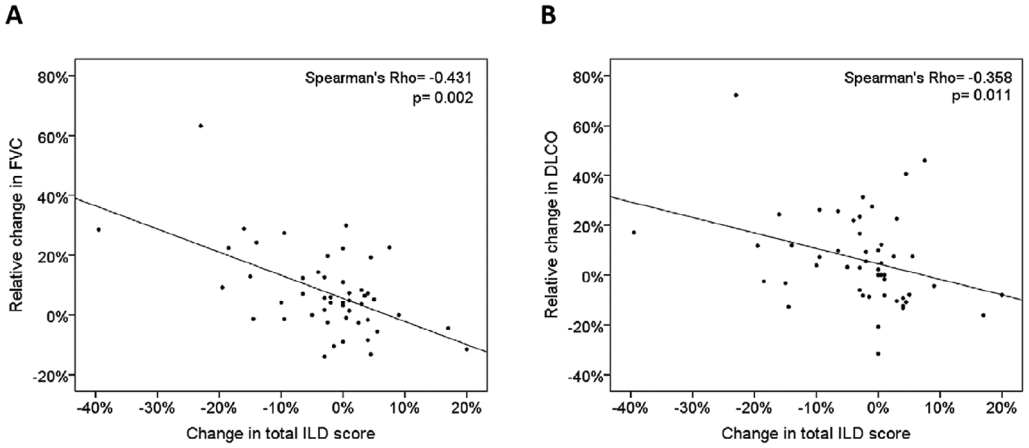

Figure 3. Correlations between evolution of interstitial lung disease (ILD) and changes in pulmonary function tests. Scatter plots of bivariate correlation, in the combined population, between changes in total ILD and relative changes in forced vital capacity (FVC) (**A**) or single-breath diffusing capacity for carbon monoxide (DLCO) (**B**). At follow-up compared with baseline, changes in total ILD score were calculated as absolute differences, and changes in FVC and DLCO were calculated as relative changes.

presented in Table 1. In the population, the mean age at treatment was 49.2 ± 11.9 years and median disease duration was 1.9 years (IQR 0.9–4.4 years). In the HSCT group, there were more men ($P = 0.043$), more patients with diffuse cutaneous SSc ($P = 0.025$), and higher mean mRSS ($P = 0.003$). Thirteen of the 20 patients treated with HSCT had received ≥1 immunosuppressive therapies before HSCT (CYC [n = 7], methotrexate [n = 5], and glucocorticoids [n = 6]). In the CYC group, 18 patients had been treated with at least 1 immunosuppressant before CYC was administered (methotrexate [n = 10], MMF [n = 7], glucocorticoids [n = 12], azathioprine [n = 4], and rituximab [n = 2]). Although it cannot be excluded that these therapies had a long-term effect on ILD, all had already been discontinued when baseline HRCTs included in the present study were obtained and all patients had progressive ILD.

Baseline HRCTs and PFTs. In the whole population, at baseline, the mean total ILD score was 25.8% ± 14.0%, the mean GGO score was 21.0% ± 12.9% and the mean RET score was 14.4% ± 10.4%. According to the staging system proposed by Goh et al (7), which includes combining HRCT scores and PFT results, 12 patients in the HSCT group (60%) and 12 in the CYC group (39%) were classified as having extensive lung disease while, respectively, 8 (40%) and 18 (58%) had limited disease. In 1 patient in the CYC group, pretreatment FVC was missing, and the staging system could not be applied. In the studied population, the mean baseline FVC and DLCO were, respectively, 79.2% ± 17.2% and 53.3% ± 14.9%.

The HRCT scores and the results of PFTs at baseline in patients treated with HSCT or CYC were numerically comparable. No statistically significant difference was detected between the 2 groups (Table 1).

HRCT and PFT changes at follow-up. Follow-up HRCTs were obtained 11.4 ± 3 months after treatment initiation. In the HSCT group, the mean changes in HRCT scores were –5.1% (95% CI –10.2, 0.0; $P = 0.050$) for total ILD, –6.2% (95% CI –11.0, –1.4; $P = 0.015$) for GGO, and –0.4% (95% CI –1.7, 0.9; $P = 0.542$) for RET (Table 2). In the CYC group, mean changes in HRCT scores were –1.0 % (95% CI –4.3, 2.3; $P = 0.535$) for total ILD, –1.7% (95% CI –5.0, 1.6; $P = 0.301$) for GGO, and +1.4% (95% CI 0.0, 2.8; $P = 0.053$) for RET (Table 2). Using the defined cutoff of >5% change in HRCT score to define ILD extent improvement, stability, or progression, we found that 35% (n = 7) of patients in the HSCT group and 19% (n = 6) in the CYC group were categorized as improved, while ILD extent remained stable respectively in 55% of patients in the HSCT group (n = 11) and 71% (n = 22) in the CYC group, and showed progression in 10% of patients in both groups (n = 3 in CYC and n = 2 in HSCT) (Figure 1). Details regarding changes in each HRCT score at individual patient level are provided in Figure 2. The HRCT scan of a patient with marked ILD improvement after HSCT is shown (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24451/abstract).

One year after HSCT, the mean FVC increased by 6.9% (95% CI 3.5, 10.4; $P < 0.001$) and the mean DLCO by 1.7% (95% CI –2.8, 6.3; $P = 0.431$). In the CYC group, the mean FVC increased by 4.4% (95% CI –0.5, 9.4; $P = 0.077$) and the mean DLCO by 2.3% (95% CI –1.4, 6.0; $P = 0.209$). Data are presented in Table 2.

Applying the defined cutoff of 5% change in FVC% to define improvement, stability, or progression of ventilatory function, we observed that 55% (n = 11) of patients in the HSCT and 36% (n = 11) in the CYC group experienced FVC% improvement after treatment, respectively 40% (n = 8) and 42% (n = 13) were

Table 3. Predictors of improvement in ILD extension at follow-up HRCT*

Variables	ILD improvement at follow-up HRCT	
	OR (95% CI)	*P*
Baseline GGO score	1.20 (1.08, 1.34)	0.001†
Baseline reticular pattern score	1.02 (0.95, 1.08)	0.662
Baseline total ILD score	1.12 (1.04, 1.21)	0.003†
Baseline FVC	0.96 (0.92, 1.01)	0.092
Baseline FEV_1	0.97 (0.93, 1.01)	0.150
Baseline DLco	0.91 (0.84, 0.97)	0.008†
Disease duration	0.76 (0.54, 1.07)	0.113
Age	1.02 (0.97, 1.08)	0.453
DcSSc	1.24 (0.31, 4.95)	0.756
Baseline mRSS	0.98 (0.93, 1.04)	0.540
ATA positivity	1.64 (0.43, 6.26)	0.472
Female sex	1.94 (0.46, 8.28)	0.368

* Univariate logistic regression in the combined population analyzing patients with >5% reduction in interstitial lung disease (ILD) assessed through high-resolution computed tomography (HRCT) extension (13 of 51 patients). 95% CI = 95% confidence interval; ATA = anti–topoisomerase I antibody; dcSSc = diffuse cutaneous systemic sclerosis; DLco = single-breath diffusing capacity for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GGO = ground-glass opacity; OR = odds ratio.
† Significant.

stable, while in 5% (n = 1) and 16% (n = 5) of cases FVC% worsened. Change in FVC% could not be calculated in 2 CYC patients due to missing data.

Correlation of HRCT and PFTs changes. In a pooled analysis of all patients, relative change in FVC was correlated with changes in the mean total ILD score ($\rho = -0.431$, $P = 0.002$), in the GGO score ($\rho = -0.354$, $P = 0.013$), and in the RET score ($\rho = -0.424$, $P = 0.002$). Also, relative changes in DLco were associated with changes in the mean total ILD score ($\rho = -0.358$, $P = 0.011$) and in the RET score ($\rho = -0.368$, $P = 0.009$), but not with the GGO score ($\rho = -0.266$, $P = 0.062$). Correlations between the evolution of ILD and changes in FVC or DLco are shown in Figure 3.

Predictors of improvement in the combined population. As predefined, 13 patients (n = 7 in HSCT and n = 6 in CYC group) were categorized as improved in the combined population. Baseline characteristics of improvers and nonimprovers are shown (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24451/abstract). Using HRCT-ILD improvement as the dependent variable, we assessed baseline characteristics that were predictive of a more favorable response to immunosuppression. In univariate logistic regression (Table 3), the baseline GGO score (OR 1.20 [95% CI 1.08, 1.34], $P = 0.001$), total ILD score (OR 1.12 [95% CI 1.04, 1.21], $P = 0.003$), and pretreatment DLco (OR 0.91 [95% CI 0.84, 0.97], $P = 0.008$) predicted improvement in total ILD score at follow-up. As only 13 patients were categorized as improvers (and also taking into consideration the multicollinearity between predictors), a multivariable logistic regression model could not be built, thus precluding the possibility to analyze the independency of the improvement predictors.

DISCUSSION

We performed a retrospective observational study to describe the evolution of ILD for 1 year in SSc patients receiving HSCT. A group of patients treated with intravenous CYC was included as frame of reference. The main finding of our study is that the mean ILD extent, which was evaluated through HRCTs of the thorax, decreased in both groups. In particular, the mean ILD extent decreased by 5.1% in the HSCT group and by 1.0% in the CYC group. Secondly, we showed an association between modifications of HRCT-ILD and changes in PFT results. However, although statistically significant, the correlations between the evolution of ILD and variations of PFT results, and in particular of DLco, were weak in all analyses. Thirdly, studying which baseline factors might influence reduction of ILD extent in response to immunosuppressive therapy, the independency of improvement predictors could not be assessed and results cannot be considered conclusive.

Our findings indicate that, when SSc patients are treated in accordance with current recommendations (14), stabilization or even improvement of ILD is a reachable goal in the majority of cases. Only 10% of patients showed progression of HRCT-ILD, and, in our opinion, the mean reduction in ILD extent observed after HSCT is indicative of a clear effect. Conversely, the minimal change in total ILD extent observed after CYC can conceivably be explained by measurement variability. Comparing the findings in the HSCT group in our study with previous research, in a small RCT, Burt et al (15) demonstrated how diseased-lung volume assessed through volumetric chest CT was significantly decreased 1 year after HSCT in SSc patients. A pilot study by Launay et al (20) reported a rapid improvement of SSc-ILD 6 months after HSCT that was mainly driven by the reversion of GGO, but, in some patients, was transient over time when longer-term follow-up HRCTs were analyzed. Nonetheless, also the stabilization of ILD extent that was observed in patients treated with CYC is in line with the available literature evidence. Post hoc analyses of the SLS-I and SLS-II trials (18,19) described the effect of CYC in preventing progression of ILD extent. Moreover, both after HSCT and after CYC, an improvement of PFTs can be expected (16,28). Our findings of a potential efficacy of HSCT and also of a role of CYC in modifying the evolution of SSc-ILD are thus consistent with prior studies.

Combining data from the 2 treatment groups, we observed a significant correlation between modifications in HRCT scores and changes of FVC and DLco at follow-up. Although we could only analyze a limited number of patients, and the correlations that we found are weak, our results suggest that a relationship

between HRCT findings and functional impairments can be identified in SSc patients (29). The role of PFTs in screening, diagnosis, and severity assessment of SSc-ILD is well established (4). Additionally, our data are in line with the recent evidence-based guidance for the identification and management of SSc-ILD (4), delineating the relevance of using PFTs alongside HRCT to monitor progression of the disease.

As a secondary aim of our study, we analyzed which pretreatment disease-related or patient-related characteristics predicted better response to immunosuppressive therapy. Due to the limited number of patients included, our results cannot be considered conclusive but, in univariate analysis, patients with higher GGO score, higher total ILD score, and lower DLco at baseline were more likely to experience an improvement of HRCT-ILD 1 year after treatment, while no correlation with RET scores was shown. Interestingly, a retrospective analysis of the SLS-I trial (30) identified more severe reticular changes at baseline as a predictor of better response to CYC in terms of FVC improvement. However, it should be noted that this study (30) used a different HRCT scoring method and severity of GGO was apparently not considered in the regression model. In the current study, we included patients treated with HSCT, which were not present in the SLS-I trial. As a consequence, it is difficult to compare our results and the SLS-I trial with regard to the contribution of GGO and reticulation on ILD evolution. Moreover, we could not build a multivariable model and the independency of the predictors could not be investigated.

Our study is not without limitations. First, it has a retrospective observational design. The majority of patients were not allocated randomly to HSCT or CYC, and, within the CYC group, not all patients received the same number of pulses. However, this method was consistent with the purpose of our study. Literature on the role of HSCT in SSc-ILD is mostly derived from RCTs, with a few contributions from observational cohorts (20,31). We aimed to investigate the evolution of ILD in a real-world scenario, where SSc patients are treated on the basis of clinical decisions. As a result, patients in the HSCT group had more severe skin involvement but, despite this, our study was focused exclusively on lung disease and specifically in patients treated with HSCT, with the CYC group included as frame of reference. Moreover, all posttreatment investigations were performed according to standard procedures, independently of patients' symptoms. Secondly, we could only include 51 patients, and the limited population size eventually prevented the possibility to conduct in-depth analyses. Furthermore, the application of visual semiquantitative scoring methods might be questionable, but it is important to emphasize that all HRCT images were centrally acquired using the same protocol and were scored by 2 experienced investigators with consensus reached when needed. Hence, we believe that the evaluation of HRCTs was accurate. Finally, we decided to limit the study to the first year of follow-up, thus preventing the possibility to make considerations about longer-term effects of HSCT and CYC.

In conclusion, this study shows that, after 1 year, 90% of patients treated with HSCT or CYC present stable or reduced ILD extent, but the improvement in HRCT-ILD observed after HSCT was indicative of a favorable effect that did not emerge in the CYC group. Our study contributes real-world data from a considerable number of patients treated with HSCT, and screening optimization and further research might help to redefine the role of HSCT (which is currently considered a rescue therapy) as an effective option to prevent the progression of, and even potentially reverse, SSc-ILD.

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 submitted for publication. Dr. Ciaffi 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. Ciaffi, van Leeuwen, Boonstra, Kroft, Schouffoer, Ninaber, Huizinga, de Vries-Bouwstra.

Acquisition of data. Ciaffi, van Leeuwen, Boonstra, Kroft, Schouffoer, Ninaber, Huizinga, de Vries-Bouwstra.

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