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Original article

Changes on chest HRCT in systemic sclerosis-related interstitial lung disease after autologous haematopoietic stem cell transplantation

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Abstract

Objective. To evaluate extent of interstitial lung disease (ILD) and oesophageal involvement using high-resolution computed tomography (HRCT) in early diffuse SSc patients after autologous haematopoietic stem cell transplantation (aHSCT).

Methods. Overall chest HRCT, lung function and skin score changes were evaluated in 33 consecutive diffuse SSc patients before and after aHSCT during yearly routine follow-up visits between January 2000 and September 2016. Two independent radiologists blindly assessed the ILD extent using semi-quantitative Goh and Wells method, the widest oesophageal diameter (WOD) and the oesophageal volume (OV) on HRCT. Patients were retrospectively classified as radiological responders or non-responders, based on achieved stability or a decrease of 5% or more of HRCT-ILD at 24 months post-aHSCT.

Results. Using a linear mixed model, the regressions of the extent of ILD and of ground glass opacities were significant at 12 months (ILD $P = 0.001$; ground glass opacities $P = 0.0001$) and at 24 months (ILD $P = 0.007$; ground glass opacities $P = 0.0008$) after aHSCT, with 18 patients classified as radiological responders (probability of response 0.78 [95% CI 0.58, 0.90]). Meanwhile the WOD and the OV increased significantly at 12 months (WOD $P = 0.03$; OV $P = 0.34$) and at 24 months (WOD $P = 0.002$; OV $P = 0.007$). Kaplan–Meier analyses showed a trend towards better 5-year survival rates (100% *vs* 60%; hazard ratio 0.23 [95% CI 0.03, 1.62], $P = 0.11$) among radiological responders *vs* non-responders at 24 month follow-up after aHSCT.

Conclusion. Real-world data analysis confirmed significant improvement in extent of HRCT SSc-ILD 24 months after aHSCT, although oesophageal dilatation worsened requiring specific attention.

Key words: SSc, interstitial lung disease, high-resolution computed tomography, stem cell, autologous haematopoietic stem cell transplantation

CLINICAL SCIENCE

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Rheumatology key messages

- Systemic sclerosis-related interstitial lung disease overall extent improved after autologous haematopoietic stem cell transplantation.
- Seventy-eight percent of systemic sclerosis patients reached radiological response 24 months after autologous haematopoietic stem cell transplantation.
- Systemic sclerosis-related oesophagus dilatation and volume worsened consistently despite autologous haematopoietic stem cell transplantation.

Introduction

Early diffuse cutaneous SSc (dSSc) is a severe autoimmune connective-tissue disease characterized by vasculopathy, immune activation and subsequent fibrosis of skin, lungs, heart, kidney or gastrointestinal tract [1, 2]. Evidence of interstitial lung disease (ILD) on chest high-resolution computed tomography (HRCT) can be found in up to 80% of dSSc patients [3, 4]. Overall 30–40% of SSc patients will develop clinically significant ILD [5], with a 10-year mortality rate reaching 40% [6]. In SSc patients, chest HRCT has become the 'gold standard' examination for ILD diagnosis, surpassing the use of routine chest X-ray [7]. Detailed chest HRCT allows early detection and characterization of parenchymal involvement before emergence of clinical symptoms [8]. Parenchymal involvement can be present in different patterns, based on the presence of ground glass opacities, reticulation and/or honeycombing, which correlate with histological changes and SSc disease severity [8]. The most common HRCT imaging pattern is non-specific interstitial pneumonia, which is characterized by peripheral ground-glass opacities with an apical to basal gradient, and frequently associated with subpleural sparing. Fibrotic non-specific interstitial pneumonia is identified by the additional presence of reticulations, traction bronchiectasis and bronchiectasis in a similar distribution. The other pattern, usual interstitial pneumonia which is determined by the presence of honeycombing without ground-glass opacities, is observed in 10–20% of patients with SSc-ILD [4, 9]. Overall, the extent of ILD on HRCT is an independent predictor of mortality and ILD progression [10]. The presence of oesophageal dilatation related to disease involvement is another common finding on chest HRCT in SSc patients, and the link between oesophageal involvement and SSc-ILD has been clearly established [11–16].

Several immunosuppressive drugs (cyclophosphamide and mycophenolate mofetil) or biologics (including rituximab and tocilizumab) have been tested in SSc-ILD with varying degrees of efficacy on lung function tests and radiological imaging parameters [17–21] at 2-years follow-up. Recently, the SENSCIS trial in 576 patients with SSc-ILD showed that the annual rate of forced vital capacity (FVC) decline over a 1-year period was lower with nintedanib compared with placebo, allowing Food and Drug Administration and European Medicines Agency approval with no other clinical benefit yet reported in SSc patients [22]. In this context, autologous haematopoietic stem cell transplantation (aHSCT) in early rapidly progressive dSSc can improve patients' survival up to 5–7 years, with improved functional status, modified Rodnan skin score (mRSS), lung function and effective regression of skin and lung fibrosis [23–26]. The 2016 ACR-EULAR guidelines [25], the American Society for Transplantation and Cellular Therapy (ASBMT) [26] and the European Bone Marrow Transplant Association (EBMT) [27] recommend (with a grade I A level of evidence) the use of aHSCT for selected patients with early progressive severe dSSc patients [28, 29]. Limited data have been obtained concerning SSc-ILD on HRCT after aHSCT and no study has yet simultaneously assessed oesophageal involvement. We therefore aimed to analyse the evolution of HRCT lung involvement pattern and oesophageal diameter and volume in early rapidly progressive dSSc patients before and up to 5 years post-aHSCT.

Methods

Study design and patients

Adult patients (aged above 18 years) with an early dSSc diagnosis according to the 1980 American Rheumatism Association criteria [30] or the 2013 ACR/EULAR classification criteria [31] who were treated with aHSCT between January 2000 and September 2016 at either the Saint-Louis or Saint-Antoine hospitals (Assistance Publique—Hôpitaux de Paris) or at the Toulouse University Hospital (France) were eligible for this study. Patients were consecutively selected for this retrospective study if they had at least (i) chest HRCT performed within 3 months before aHSCT and (ii) 1-year follow-up after aHSCT or longer; (iii) pulmonary function tests (PFTs) performed within 2 weeks of each chest HRCT examination. All patients gave written informed consent for clinical data collection and were prospectively followed in an expert MATHEC French centre according to the French Society for Bone Marrow Transplant and Stem Cell Therapy (Société Francophone de Greffe de Moelle et Thérapie Cellulaire) [32] and the EBMT guidelines [28, 29].

Transplant procedure

The transplant procedure has been previously described [32]. Briefly, mobilization and collection of peripheral

blood haematopoietic stem cells were performed using cyclophosphamide at 2 g/m^2/day on two consecutive days followed 4 days later by human G-CSF (rHu G-CSF) at 5 μg/kg/day subcutaneously until the last apheresis. Peripheral blood haematopoietic stem cell were collected when CD34$^+$ cells were above 20/μl in peripheral venous blood. Conditioning was performed at least 4 weeks later, using cyclophosphamide at 50 mg/kg/day from day 5 to day 2 prior to HSC reinjection with or without CD34$^+$ selection and without or with rabbit antithymocyte globulin.

Clinical follow-up before and after aHSCT

SSc patient' demographics, clinical features and biological characteristics were collected at baseline (within 3 months before aHSCT) and after aHSCT during routine clinical follow-up at yearly intervals plus or minus 6 months, as previously described [32]. Data collection included the following.

i. Age, gender, disease duration (since onset of first non-Raynaud phenomenon symptom), BMI and smoking status.
ii. Extent of skin fibrosis as measured by the mRSS [33].
iii. Cardiac and pulmonary evaluation, including: New York Heart Association functional classification at rest, total 6-min walking distance (in meters), results from PFTs including FVC (% of predicted value), total lung capacity (% of predicted value), carbon monoxide diffusing lung capacity (% of predicted value), according to the American Thoracic Society and European Respiratory Society (ATS/ERS) consensus standards [34], and from echocardiography, including the presence of pericardial effusion, left ventricular ejection fraction (%) and pulmonary arterial systolic pressure (mmHg).
iv. Laboratory parameters including haemoglobin level, serum creatinine, creatinine phospho-kinases plus antinuclear, anticentromere and anti-topoisomerase-I autoantibodies status.
v. Previous immunosuppressive drugs exposure.

For each patient, clinical response during follow-up after aHSCT was assessed at each time points and defined by at least 25% improvement in mRSS and/or ≥10% improvement in FVC or carbon monoxide diffusing lung capacity as compared with baseline, and without need for additional immunosuppression [23, 35, 36].

Image acquisition protocol

Chest HRCT was performed with a periodically calibrated multidetector CT scanner. HRCT images were obtained from the lung apices to the bases during suspended end-inspiration in the prone position. Intravenous contrast medium was not used. Data were reconstructed with filtered back projection, a slice thickness of 1 mm, an increment of 0.8 mm, and using a sharp (B60f) or very sharp convolution kernel (B70f).

HRCT image analyses and quantitative HRCT scoring

Two experienced chest radiologists, unaware of the patient's baseline and evolutive characteristics, worked independently. Each HRCT was evaluated separately and not as compared with the other ones. In cases of disagreement, the radiologists re-examined the scans in question to reach a consensus. The readout was performed on a dedicated PACS-Viewer and licensed reading screens. All images were displayed first on mediastinal (level, 35 HU; width, 450 HU), then on lung windows (level, −700 HU; width, 1500 HU). All chest HRCTs were first analysed for the presence of pleural effusions, oedema, haemorrhages or infections, in which case these had to be excluded from the final analysis. The extent of SSc-ILD was evaluated according to the semi-quantitative method proposed by Goh and Wells *et al.* [9, 37, 38] at the following five levels: (i) origin of great vessels; (ii) carina; (iii) pulmonary venous confluence; (iv) between levels 3 and 5; and (v) 1 cm above the right hemidiaphragm. The following features were quantified at each level. First, the overall extent of SSc-related ILD, including both reticular pattern and ground-glass opacities, was estimated to the nearest 5%. Second, the relative proportions of ILD (up to a total of 100%) made up of a reticular pattern and ground-glass opacities were quantified. Third, the extent of emphysema, which was defined as areas of decreased attenuation, usually without discrete walls, and of non-uniform distribution causing permeative destruction of lung parenchyma, was quantified to the nearest 5%. For each patient, the overall extent of ILD, ground-glass opacities, reticular pattern and emphysema was derived by averaging the respective scores at each level and mean values were used in the analysis. Limited *vs* extensive SSc-ILD was defined using the Goh staging system [39] with a threshold of 20% for the overall ILD extent on chest HRCT.

According to the observed radiological response 24 months after aHSCT, SSc patients were retrospectively classified as radiological responders, if the overall ILD extent was stable or decreased by 5% or more [37, 40, 41]. Otherwise, patients were classified as non-responders.

Two additional experienced radiologists in abdominal imaging independently evaluated the oesophagus on HRCT images. The widest oesophagus diameter (WOD) was measured above and below the aortic arch. A diagnosis of oesophageal dilatation was defined as a luminal coronal supra-aortic diameter exceeding 4 mm and an infra-aortic diameter exceeding 9 mm, whatever the content (air, liquid or solid) [38]. The entire oesophagus volume (OV) was automatically generated. The radiologists manually traced the oesophagus contour on each axial CT slice using a commercial interactive volumetry-assist software (Terarecon, Inc, North Carolina), which allowed summing of the areas of the manually traced regions in each slice by the reconstruction interval. The final painted oesophageal volume determined using the interactive software was shown to represent an accurate volume of the entire oesophagus [42].

Statistical analysis

Continuous variables were summarized as medians (interquartile range [IQR]) and categorical variables were presented as numbers (percentage). Intraclass correlation coefficients (ICCs) were used to evaluate agreement between the two radiologists, to assess the inter-rater reliability for the respective evaluations of the overall extent of ILD, the ground-glass opacities extent, the reticular pattern extent, and for measures of the WOD. Based on the 95% confidence interval of the ICC estimate, values <0.5, between 0.5 and 0.75, between 0.75 and 0.9, and >0.90 are indicative of poor, moderate, good and excellent agreement, respectively [43].

We fitted linear mixed-effect models to assess the change over time to take into account both fixed and random effects, correlations within the data, irregularly timed measurements and missing data [44]. We expressed it in least square mean (S.D.).

Significant differences ($P \leq 0.05$) between patient groups (radiological responder *vs* non-responder at 24 months follow-up after aHSCT) were assessed with two-way ANOVA.

Association between baseline characteristics and radiological response at 24 month follow-up were assessed using logistic regressions. Cumulative survival rates after aHSCT were computed by the Kaplan–Meier method and significance was tested with the log-rank test. The effect of radiological response status on mortality at 24 month follow-up after aHSCT was entered into the Cox proportional hazards model, adjusted on age and gender. Mortality was expressed by hazard ratio (HR) with a 95% CI. All tests were two-sided at 0.05 α-risk. Statistical analyses were performed with SAS v 9.4 (SAS Institute, Cary, NC, USA) and GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA) software.

Ethics consideration

The data were documented in the MATHEC database (www.mathec.com) as part of routine clinical care in accordance to Good Clinical Practice and complied with the requirements of the Commission Nationale Informatique et Liberté (CNIL; registration no. 1986127). In compliance with French regulation relating to clinical non-interventional research, this study does not require ethics committee approval.

Results

Patient characteristics at baseline and during post-transplant follow-up

Out of the 45 eligible patients during the study period, 12 were excluded since either baseline ($n = 10$ patients) or 1 year follow-up ($n = 2$ patients, including one dead) chest HRCT was not available for review. Thirty-three early rapidly progressive dSSc patients (60.6% female; mean age: 45.5 (13.5) years), who had undergone a first aHSCT were included in this study. Table 1 summarizes

Table 1 Patients clinical and functional characteristics and SSc organ involvement before treatment by aHSCTAQ19

Characteristic	Value	*n*
Age at aHSCT, mean (S.D.), years	45.5 (13.5)	33
Sex, female, *n* (%)	20 (60.6)	33
Disease duration since SSc diagnosis, mean (S.D.), months	28.0 (17.7)	33
Body mass index, mean (S.D.), kg/m^2	24.0 (3.7)	33
Smoking status (ever *vs* never), *n* (%)	9 (27.3)	33
Skin involvement		
Modified Rodnan Skin Score (0–51), mean (S.D.)	24.0 (10.9)	32
Lung involvement		33
NYHA class of dyspnoea, *n* (%)		
1	17 (51.5)	
2	13 (39.4)	
3	3 (9.1)	
6 min walking test, distance, mean (S.D.), m	470 (109)	21
Pulmonary function test		
FVC, mean (S.D.), % predicted	77.9 (19.2)	31
TLC, mean (S.D.), % predicted	82.4 (18.5)	31
DL_{CO}, mean (S.D.), % predicted, corrected for Hb	51.5 (15.5)	33
Interstitial lung disease on HRCT, *n* (%)	29 (87.9)	33
Pulmonary hypertension, *n* (%)	3 (9.1)	33
Cardiac involvement (echocardiography)		
Pericardial effusion, *n* (%)	1 (3.0)	33
LVEF, mean (S.D.), %	69.8 (8.5)	33
PASP, mean (S.D.), mm	33.1 (5.7)	33
Gastrointestinal involvement		
Clinical symptoms, *n* (%)	16 (48.5)	33
Immunological status and biological values		
Antinuclear antibodies positive, *n* (%)	33 (100)	33
Anticentromere antibodies positive, *n* (%)	1 (3.0)	33
Antitopoisomerase-1 antibody positive, *n* (%)	23 (69.7)	33
Haemoglobin, mean (S.D.), g/dl	12.2 (1.4)	32
Serum creatinine, mean (S.D.), µmol/l	62.2 (18.2)	32
Serum creatine kinase, mean (S.D.), UI/l	117.4 (71.9)	32
Overall chest HRCT patterns		
ILD extent, mean (S.D.), %	15.4 (14.3)	33
Ground-glass opacities extent, mean (S.D.), %	10.3 (10.3)	33
Reticular pattern extent, mean (S.D.), %	5.1 (6.8)	33
Presence of emphysema, *n* (%)	4 (12.1)	33
HRCT extensive disease extent >20%[a], *n* (%)	13 (39.4)	33
Oesophageal dilatation, *n* (%)	33 (100)	33
Widest oesophageal diameter, mean (S.D.), mm	24.4 (7.7)	33
Oesophageal volume, mean (S.D.), mm^3	26 (20.6)	33
Previous immunosuppressive drugs exposure, *n* (%)		

(continued)

Table 1 Continued

Characteristic	Value	*n*
Prednisone or equivalent	20 (60.6)	33
Methotrexate	4 (12.1)	33
Mycophenolate mofetil	5 (15.2)	33
Cyclophosphamide	6 (18.2)	33

[a]Abnormal computed tomography scan includes fibrosis, honeycombing or ground-glass pattern. aHSCT: autologous haematopoietic stem cell transplantation; DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; HRCT: high-resolution computed tomography of the chest; ILD: interstitial lung disease; LVEF: left ventricle ejection fraction as measured by cardiac echography; NYHA: New York heart association; PASP: pulmonary arterial systolic hypertension; TLC: total lung capacity.

baseline characteristics. At baseline, mean disease duration since SSc diagnosis was 28.0 (17.7) months, with a mean mRSS of 24.0 (10.9) and mean FVC of 77.9 (19.2)% of the predicted value and a diffusion capacity of 51.5 (15.5)% of the predicted value. The mean follow-up after aHSCT was 67.0 (33.7) months with four deaths reported during the study period.

After aHSCT, significant improvement in skin fibrosis with sustained fall in mRSS values was observed up to 60 months follow-up in all patients (Fig. 1A and Table 2). At 24 months, an increase in the FVC values (% of predicted) ($P = 0.47$) (Fig. 1B and Table 2) and a significant decrease in mRSS scores ($P = 0.0001$) were observed as compared with before aHSCT. The overall probability of a clinical response was 0.68 (95% CI 0.49, 0.82).

Chest HRCT lung and oesophagus changes after aHSCT

Out of 170 chest HRCT analysed from 33 patients, seven were excluded from the final analysis due to presence of cardiac oedema and three were examined twice to reach consensus between radiologists. Good or excellent agreement was observed between the two expert radiologists when analysing the overall extent of ILD (ICC = 0.92 [95% CI 0.89, 0.94]), ground-glass opacities extent (ICC = 0.97 [95% CI 0.96, 0.98]), reticular pattern extent (ICC = 0.92 [95% CI 0.90, 0.95]) and the widest oesophagus diameter (ICC = 0.94 [95% CI 0.92, 0.96]). Before aHSCT, the mean extent of ILD was 15.4 (14.3)%. Ground-glass opacities were the dominant pattern, with a mean extent of 10.3 (10.3)%. The mean extent of observed reticular pattern was 5.1 (6.8)%, with an increase of alterations from apex to base. The presence of emphysema was found in four patients. Thirteen (39.4%) patients had extensive ILD with an extent >20% of the whole lung volume. Oesophageal dilatation was present in all 33 patients, with a mean WOD of 24.4 (7.7) mm and a mean OV of 26 (20.6) mm^3 (Table 2).

The long term post-aHSCT evolution of ILD extent, including ground-glass opacities and reticular pattern of the whole lung volume are illustrated in Figs 1C and 2. Improvements in extent of ILD and ground glass-opacities were observed. Absolute respective changes from baseline in quantitative scores until 12 and 24 months after aHSCT showed a decrease in the overall extent of ILD (−5.2 points and −3.8 points) and ground-glass opacities (−6.3 points and −5.2 points), while the reticular pattern extent (+0.2 point and +1.4 points), the WOD (+3.3 points and +4.1 points) and the OV (+8.3 points and +12.9 points) increased (Table 2). Using a linear mixed model, the regressions of the extent of ILD and of ground glass opacities were significant at 12 months (ILD $P = 0.001$; ground glass opacities $P = 0.0001$) and at 24 months (ILD $P = 0.007$; ground glass opacities $P = 0.0008$) after aHSCT, while the WOD and the OV increased significantly at 12 months (WOD $P = 0.03$; OV $P = 0.34$) and at 24 months (WOD $P = 0.002$; OV $P = 0.007$) (Figs 1D and 2). Among the 13 patients with extensive SSc-ILD extent at baseline, 50% improved to a limited disease status (SSc-ILD extent <20%) at 12 months ($P = 0.002$) and 54.5% at 24 months ($P = 0.006$). None of the four patients with no lung involvement on chest HRCT at baseline developed ILD during follow-up.

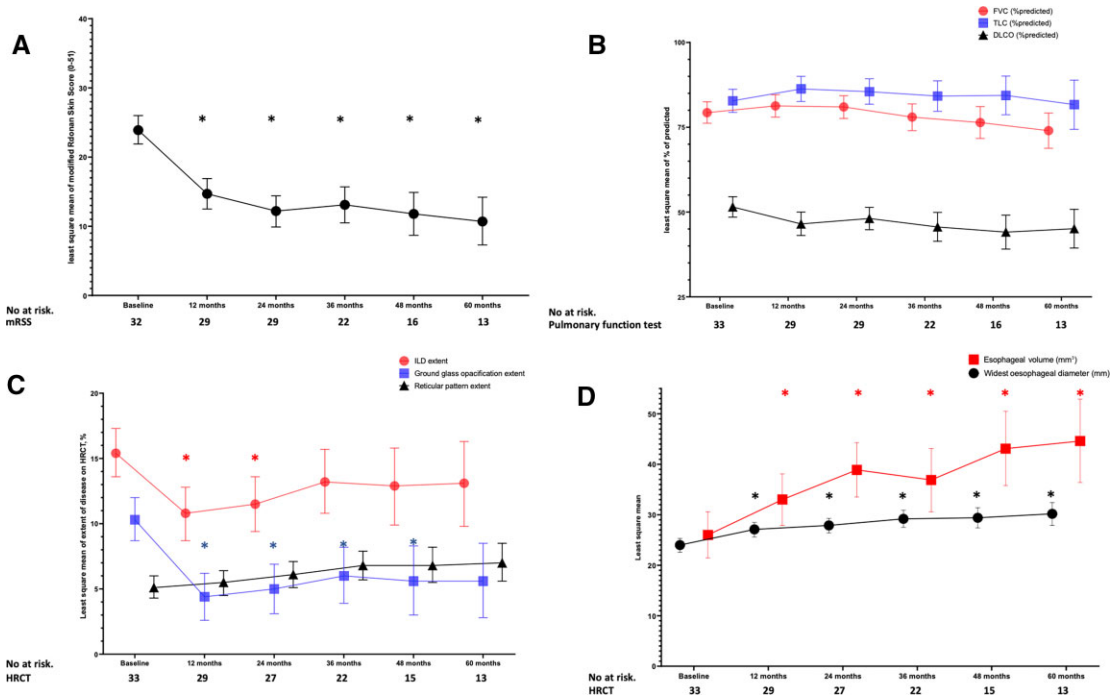
Radiological response at 24 months after aHCST

At 24 months after aHSCT, 18 patients were classified as radiological responders and five were classified as non-responders (probability of response 0.78 [95% CI 0.58, 0.90]), of whom 10 (58.8%) had a decrease of 5% or more in overall extent of ILD. Five patients received mycophenolate mofetil after aHSCT within the first 24 months after transplant (three in the radiological responder group and two in the radiological non-responder group). No significant correlations were found between radiological response at 24 months after aHSCT and baseline demographic characteristics, PFTs, 6-min walking distance, mRSS, heart or renal function parameters, WOD, or OV.

At 60 months after aHSCT, classification of patients as radiological responders and non-responders identified a significant difference between these groups when analysing their relative changes in predicted values of FVC ($P = 0.009$) and carbon monoxide diffusing lung capacity ($P = 0.020$) as compared with pre-aHSCT baseline values (Fig. 3A and B). Overall, clinical disease response at 60 months after aHSCT was significantly associated with radiological response at 24 months ($P = 0.01$, Fig. 3C). There was a trend towards overall better survival (HR 0.24 [95% CI 0.03, 1.73], $P = 0.16$) in radiological responders at 24 months as compared with non-responders, with respective survival rates at 60 months of 100% *vs* 60%.

The relative changes in WOD during patient follow-up at 60 months compared with pre-aHSCT baseline values were significantly different between radiological responders and non-responders at 24 months ($P = 0.05$), whereas the relative changes of OV were not significant ($P = 0.14$) (Fig. 4A and B). WOD and OV at study entry had no

FIG. 1 Evolution of mRSS, pulmonary function, ILD extent and oesophageal dilatation after aHSCT



(**A and B**) Evolution of modified Rodnan skin score (mRSS) (**A**) and pulmonary function (**B**) values in all patients from pre-transplant period (baseline) until long-term follow-up (5 years) after autologous haematopoietic stem cell transplantation (aHSCT) in 33 SSc patients. (**C and D**) Evolution of interstitial lung disease (ILD), ground-glass opacities, reticular pattern extent and oesophageal volume on high-resolution computed tomography (HRCT) based on assessment of the whole lung before and until long-term follow-up (5 years) after aHSCT in 33 SSc patients. *$P < 0.01$ by least square mean generated by linear mixed-model regression. DLCO: carbon monoxide diffusing lung capacity; FVC: forced vital capacity; TLC: total lung capacity.

impact on survival (WOD, HR 1.0 [95% CI 0.93, 1.09], $P = 0.88$; OV, HR 1.0 [95% CI 0.99, 1.05], $P = 0.13$).

Discussion

The present study examined the largest patient cohort to-date for long-term changes of chest HRCT SSc-ILD involvement after aHSCT [35, 41, 45, 46]. A significant improvement in the overall extent of ILD on chest HRCT was observed at 24 months follow-up after aHSCT in 33 patients with early rapidly progressive dSSc. In the Scleroderma Lung Studies [17, 18, 40], both cyclophosphamide and mycophenolate mofetil failed to show an association with a change in computer-aided quantitative diagnostic scores of lung fibrosis on HRCT in either the lobe of most involvement or the whole lung. However, there was a modest statistically significant reduction in quantitative ILD scores in the whole lung in the mycophenolate mofetil and cyclophosphamide groups at 24 months (mean [S.E.] of 2.52 [60.76]%, $P = 0.001$). Two other randomized controlled trials using tocilizumab (IL-6 receptor antagonist) as compared with placebo in early dSSc patients [21, 47] reported significant improvement in lung function. Although the phase 3 focuSSced trial [4], with 210 early dSSc patients included overall, did not meet its primary end point and found no statistical difference in the mRSS from baseline to week 48 between tocilizumab and placebo group (adjusted difference –1.73 [95% CI –3.78, 0.32], $P = 0.10$) [21], the FVC (% of predicted) results suggested stabilization of lung function (adjusted difference + 4.2 [95% CI +2.0, +6.4], $P = 0.0002$) in the treatment arm compared with placebo (secondary end point). In a *post hoc* analysis of this trial, Roofeh *et al.* reported a significant reduction in the quantitative ILD score and in the quantitative lung fibrosis scores, as calculated by fully automated software for quantification of chest HRCT analysis in 55 early dSSc patients in the tocilizumab arm compared with 49 early dSSc in the placebo arm from baseline to 48 weeks (mean [S.E.] quantitative ILD: −1.8 [95% CI −3.8, 0.09] *vs* 1.5 [95% CI −0.3, 3.3], $P = 0.02$; mean quantitative lung fibrosis: −0.5 [95% CI −1.3, 0.3] *vs* 0.7 [95% CI 0.3, 1.2], $P = 0.001$ respectively) [48].

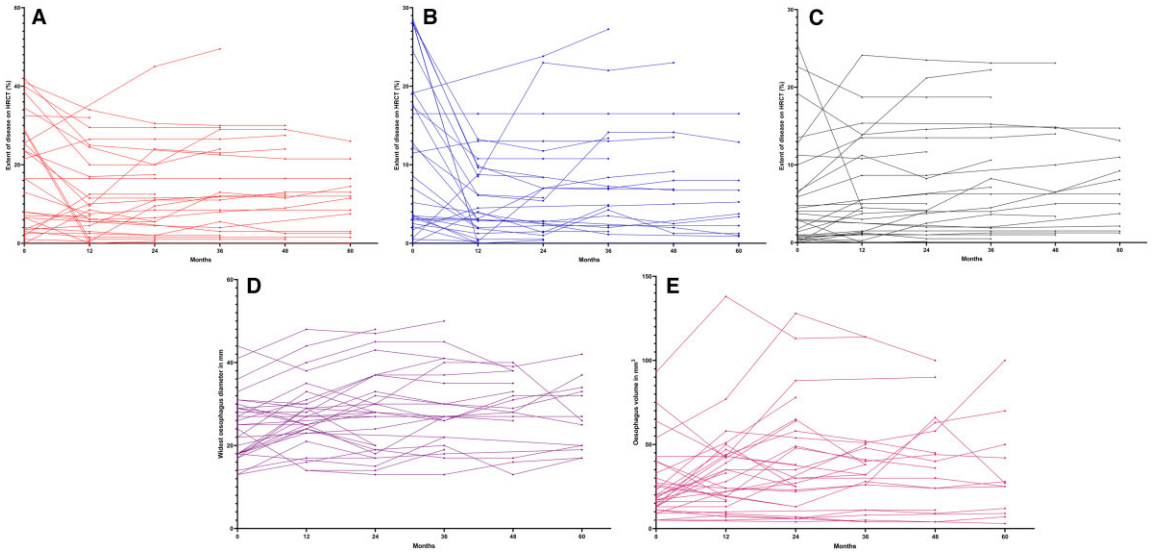
Our group previously reported [45] an overall improvement at 6 months after aHSCT in 5 out of 6 patients with SSc-related ILD compared with baseline, using the semi-

Table 2 Changes in chest HRCT patterns, in lung function and in mRSS values after aHSCT

Parameter	Baseline value	Absolute difference changes compared to baseline values				
		12 months	24 months	36 months	48 months	60 months
Number of patients	33	29	27	22	15	13
Overall chest HRCT patterns						
ILD extent of the whole lung, mean (S.D.), %	15.4 (14.3)	−5.2 (9.6)	−3.8 (10.7)	−2 (11.3)	−3.6 (11.4)	−2.9 (9)
Ground-glass opacities extent of the whole lung, mean (S.D.), %	10.3 (10.3)	−6.3 (9.2)	−5.2 (9.5)	−4.3 (9.6)	−5.9 (11.1)	−4.5 (7.8)
Reticular pattern extent of the whole lung, mean (S.D.), %	5.1 (6.8)	+0.2 (5)	+1.4 (3.9)	+2.3 (4.6)	+2.3 (3.4)	+1.7 (3.7)
HRCT extensive disease extent >20% of the whole lung, *n* (%)	13 (39.4)	6 (20.7)	5 (18.5)	8 (36.4)	5 (33.3)	2 (15.4)
Widest oesophageal diameter, mean (S.D.), mm	24.4 (7.7)	+3.3 (5.6)	+4.1 (7.2)	+5.5 (5.8)	+6.9 (5.9)	+7.3 (6.2)
Oesophageal volume, mean (S.D.), mm^3	26 (20.6)	+8.3 (19.3)	+12.9 (22.3)	+8.8 (18.5)	+18.3 (17.4)	+16.4 (26.4)
6 min walking test, distance, mean (S.D.), m	470 (109)	+38 (66)	+59 (79)	+22 (92)	+63 (57)	+96 (59)
Pulmonary function test						
FVC, mean (S.D.), % predicted	77.9 (19.2)	+1.8 (10.4)	+1.4 (12.6)	−2.8 (13.4)	−4.8 (16.5)	−5 (15)
TLC, mean (S.D.), % predicted	82.4 (18.5)	+3.3 (18.6)	+3.1 (16.4)	−1.7 (10.5)	−0.8 (13.2)	−3.4 (7.3)
DLCO, mean (S.D.), % predicted corrected for hb	51.5 (15.5)	−5.4 (15.1)	−3.2 (13.4)	−7.2 (15.1)	−8 (18.9)	−5 (20.5)
mRSS (0–51), mean (S.D.)	24.0 (10.9)	−9.5 (7.3)	−11.5 (8.1)	−10.3 (11.5)	−9.9 (9.3)	−11.1 (9.3)

Results are described as absolute differences. DLCO: diffusing capacity for carbon monoxide; FVC: forced vital capacity; HRCT: high resolution computed tomography of the chest; ILD: interstitial lung disease; mRSS: modified Rodnan skin score; TLC: total lung capacity.

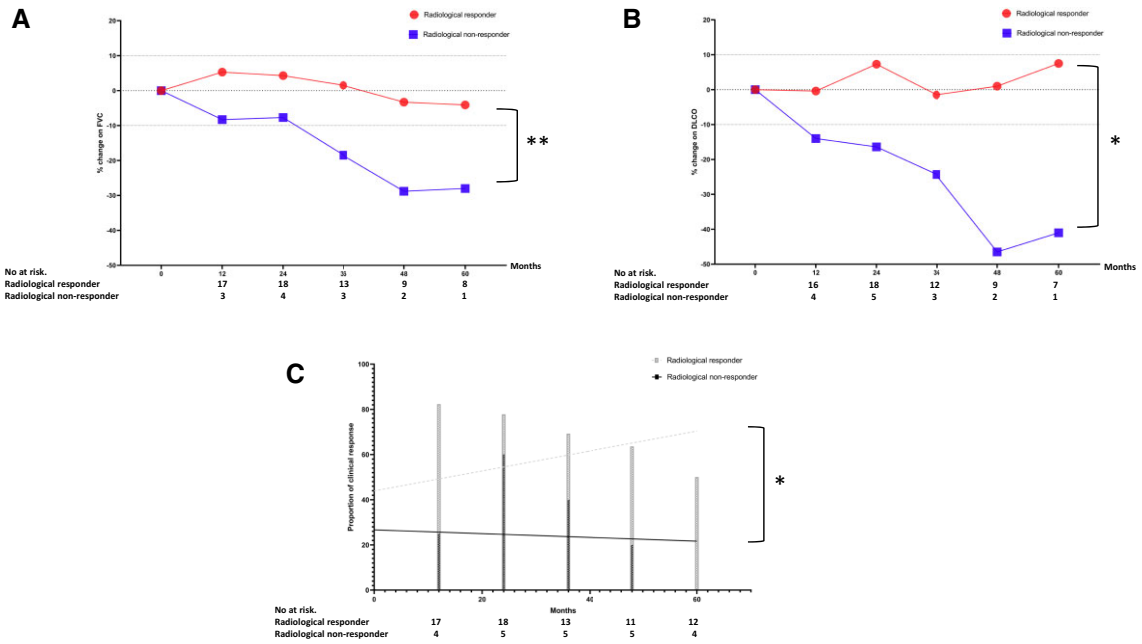
Fig. 2 Individual changes over time after aHSCT ILD of ground-glass opacities, reticular pattern and oesophageal dilatation



Spaghetti plots of individual changes over time after autologous haematopoietic stem cell transplantation (aHSCT) of interstitial lung disease (ILD) extent (**A**), ground-glass opacity extent (**B**), reticular pattern extent (**C**), widest oesophageal diameter (**D**) and oesophageal volume (**E**) in 33 SSc patients

quantitative Goh and Wells method. In the ASSIST trial [35], a decrease in chest HRCT volumetric automated measurement of lung disease was reported at 1-year follow-up in 10 aHSCT recipients, while measurements increased in the nine controls receiving monthly i.v. cyclophosphamide. Patients in the control group whose disease progressed and were at least one year after start of treatment were allowed to switch to transplantation.

FIG. 3 Relative change in FVC, DLCO, and clinical response in radiological responder and non-responder patients



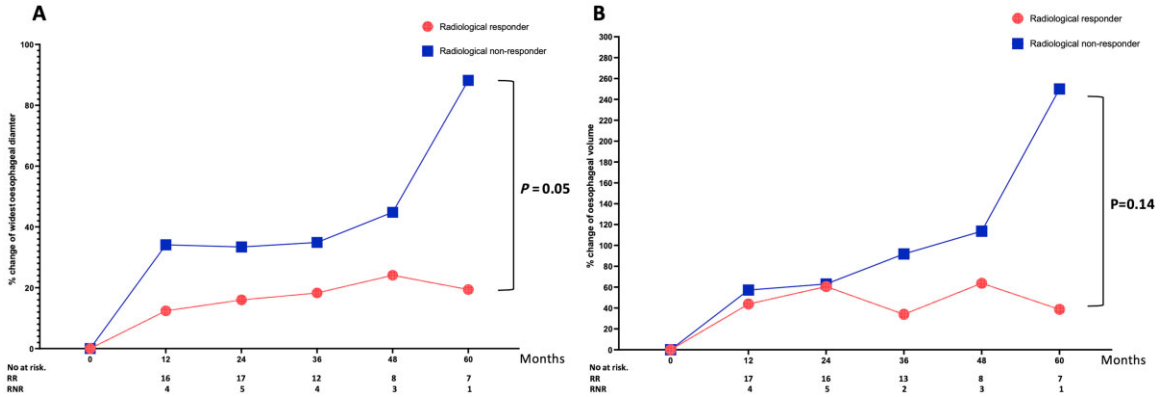
(**A and B**) Relative change in percentage of predicted forced vital capacity (FVC) and carbon monoxide diffusing lung capacity (DLCO) in the 2-year radiological responder and non-responder patients from pre-transplant period (baseline) until long-term follow-up (5 years) after autologous haematopoietic stem cell transplantation (aHSCT) in 33 SSc-patients. (**C**) Dashed lines represent improvement (+10%) or worsening (−10%) on FVC or DLCO. Percentage of clinical response in the 2-year radiological responder and non-responder patients from pre-transplant period (baseline) until long-term follow-up (5 years) after aHSCT in 33 SSc-patients. Radiological response was defined as stability or decreases of 5% or more in overall ILD extent in the whole lung volume at 2 years after aHSCT. Clinical disease response to treatment was defined as a >25% improvement in mRSS and/or ≥10% improvement in FVC or DLCO as compared with baseline and without need of further immunosuppression. *$P < 0.05$, **$P < 0.01$ at long-term time point.

At 24 months after transplantation, there was significant improvement in chest HRCT volumetric automated measurement of involved lung in 11 dSSc patients. Consistent with these findings, Kloth *et al.* showed a statistically significant improvement in total lung volume ($P = 0.018$) and high attenuation value ($P = 0.020$), as calculated by fully automated software, in 26 early rapidly progressive dSSc at 24 months after aHSCT [46]. Recently, using quantitative automated HRCT analysis, Wada *et al.* reported [41] a significant reduction in pulmonary densities but no change in lung volume in 15 early rapidly progressive dSSc with improved pulmonary function 18 months after AHSCT, compared with baseline values. Ciaffi *et al.* used the visual semi-quantitative scoring method proposed by Goh and Wells *et al.* [39] to retrospectively describe the evolution of SSc-ILD, in 51 patients at 1 year follow-up after treatment by either haematopoietic stem cell transplantation or CYC, according to the latest EULAR recommendations [25, 37]. This retrospective HRCT analysis found a mean change in total ILD score of –5.1% (95% CI –10.2, 0.0) in the 20 SSc patients of the aHSCT treatment group ($P = 0.050$), and –1.0% (95% CI –4.3, 2.3) in the 31 SSc patients of the CYC treatment group ($P = 0.535$), one year after treatment. Our study, using the semi-quantitative Goh and Wells methodology [39, 49], confirmed these results with a significant improvement in ILD and ground-glass opacity extent quantitative scores after transplant, which peaked at 24 months post-transplant.

At 24-months follow-up, 18 patients were classified radiological responders and five non-responders, 10 of whom had a decrease of 5% or more in overall ILD extent in the whole lung volume. Validated clinical responder definitions after aHSCT [23, 35, 36, 50] are mainly supported by PFTs and mRSS. This definition could be amended to take into account radiological response criteria. This would allow identification of immune reconstitution profiles that may reflect the persistence of underlying disease in non-radiological responders and call for personalized therapeutic strategies after transplant using maintenance immunosuppression (mycophenolate mofetil, rituximab) or mesenchymal stromal cell infusion, in order to damper the autoimmune and inflammatory response [51].

Our study is the first to document WOD and oesophageal volume over a 5-year post-aHSCT follow-up. This is of major clinical importance, because oesophageal dilatation is associated with SSc severity and mortality in SSc

FIG. 4 Relative change in widest oesophageal diameter and oesophageal volume in radiological responder and non-responder patients



Relative change in percentage of widest oesophageal diameter (**A**) and oesophageal volume (**B**) in the 2-year radiological responder and non-responder patients from pre-transplant period (baseline) until long-term follow-up (5 years) after autologous haematopoietic stem cell transplantation (aHSCT) in 33 SSc-patients. Radiological response was defined as stability or decreases of 5% or more in overall ILD extent in the whole lung volume at 2 years after aHSCT. RNR: radiological non-responder; RR: radiological responder.

[13, 52] as well as SSc-related ILD severity and progression. The Canadian Scleroderma Research Group confirmed the link between oesophageal involvement and SSc-associated ILD. Zhang *et al.* [11] identified that symptoms of oesophageal dysmotility and gastroesophageal reflux disease (GERD) were associated with worsening FVC. Burt *et al.* reported patulous oesophagus [35, 53] in 60–90% of SSc patients prior to transplant. In our study, all patients had oesophagus dilatation before transplant, which participated in disease severity. One main finding of our study was the consistent and systematic significant worsening of SSc-related oesophagus dilatation measured by WOD and oesophageal volume relative to pre-transplant levels, despite treatment with aHSCT. These results contrasted with a persistently improved skin score and improved SSc-related ILD after transplant, with uncoupling response to aHSCT between the skin and lung on the one hand and the oesophagus on the other. Such findings raise the possibility that different mechanisms underlie oesophageal involvement in SSc and underscore the need for specific attention to oesophagus management after aHSCT.

Reproducibility and low variability of the chest HRCT review analysis was evidenced by the good or excellent inter-rater agreements between the two expert radiologists. These findings reinforced the strength of our method to capture changes on chest HRCT in SSc-related ILD after aHSCT.

Our study has several limitations. The design was retrospective. Although recommended by EBMT and national guidelines, physical follow-up, functional evaluations and HRCT scans were not mandatory, and were not obtained at all time points. There was also significant variation in HRCT data acquisition, due to the study design, but we overcame this bias by implementing a centralized review of all HRCT scans. The two expert radiologists were blinded to patient baseline and evolutive characteristics and treatment outcomes (i.e. clinical, PFTs or echocardiography). For technical reasons, the HRCT dates were not blurred on the computer screen and one may argue about potential improvement bias when the radiologists were reviewing the HRCTs if the order was known. However, both radiologists evaluated each HRCT separately and not as compared with the other ones to mitigate improvement bias. Our results show that changes in extent of ILD on HRCT followed the same trends as those of established PFTs post-transplant. This suggest that quantitative chest HRCT can be used as a monitoring tool in patients with SSc undergoing aHSCT. Radiological response was not correlated to disease severity or clinical phenotype before aHSCT. This may be due to improved patient selection before transplant, as a result of growing knowledge in the field and adhering to updated guidelines [29]. Unfortunately, this does not allow us to identify *a priori* potential non-responder patients for whom it will be necessary to develop other therapeutic approaches.

In conclusion, this study reported real-world data showing stability or improvement of ILD related to SSc, as evaluated on chest HRCT 24 months after aHSCT according to the semi-quantitative method proposed by Goh and Wells. As opposed to the effects on lung involvement, aHSCT was not associated with therapeutic outcomes on oesophageal volume, which constantly worsened over the course of the study. Attention is warranted towards SSc oesophagus involvement after aHSCT.

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Data availability statement

The data underlying this article cannot be shared publicly to ensure the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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