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Original article

Impact of lung function and baseline clinical characteristics on patient-reported outcome measures in systemic sclerosis-associated interstitial lung disease

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Abstract

Objective. The SENSCIS® trial demonstrated a significant reduction of lung function decline in patients with SSc-associated interstitial lung disease (SSc-ILD) treated with nintedanib, but no significant effect on health-related quality of life (HRQoL). To assess whether SSc/SSc-ILD severity and large changes in lung function correlate with HRQoL, a post-hoc analysis of SENSCIS®, aggregating treatment arms, was undertaken.

Methods. Patient-reported outcome (PRO) measures [St. George's Respiratory Questionnaire (SGRQ), Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnoea, and HAQ–Disability Index (HAQ-DI), incorporating the Scleroderma HAQ visual analogue scale (SHAQ VAS)] at baseline and week 52 were assessed for associations to SSc-ILD severity.

Results. At baseline and at week 52, forced vital capacity (FVC) $<70\%$ predicted was associated with worse PRO measure scores compared with FVC $\geq 70\%$ predicted [week 52: SGRQ 45.1 *vs* 34.0 ($P < 0.0001$); FACIT-Dyspnoea 48.9 *vs* 44.5 ($P < 0.0001$); HAQ-DI 0.7 *vs* 0.6 ($P < 0.0228$); SHAQ VAS breathing problems 3.6 *vs* 2.6 ($P < 0.0001$)]. Patients with diffuse cutaneous SSc and other characteristics associated with SSc-ILD severity had worse PRO measure scores. Patients requiring oxygen or with $>30\%$ fibrosis on high-resolution computed tomography at baseline demonstrated worse PRO measure scores at week 52. After 1 year, patients with a major ($>10\%$) improvement/worsening in FVC demonstrated corresponding improvement/worsening in SGRQ and other PRO measures, significant for the SGRQ symptom domain ($P < 0.001$).

Conclusion. Severe SSc-ILD and major deteriorations in lung function have important impacts on HRQoL. Treatments that slow lung function decline and prevent severe SSc-ILD are important to preserve HRQoL.

Trial registration. clinicaltrials.gov, www.clinicaltrials.gov, NCT02597933

Key words: SSc-associated ILD, patient-reported outcome measures, treatment

CLINICAL SCIENCE

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Rheumatology key messages

- In the SENSCIS trial, worsening lung function and/or severe disease were associated with reduced HRQoL.
- Associations of HRQoL with lung function and SSc-ILD severity were independent of treatment arm.
- Treatments that slow lung function decline and prevent severe SSc-ILD are important to preserve HRQoL.

Introduction

SSc is a rare autoimmune disease, heterogeneous in presentation and characterized by fibrosis of the skin and internal organs, and vasculopathy [1, 2]. Interstitial lung disease (ILD) is a serious and relatively common manifestation of the disease [3–5], and is one of the leading causes of death in patients with SSc [4, 6]. An observational study performed in the EUSTAR database revealed that 35% of SSc-related deaths were caused by pulmonary fibrosis [6]. ILD usually develops early in the disease course [1]. The disease course of SSc-associated ILD (SSc-ILD) varies widely from minimal or no progression to a rapidly progressive phenotype [1, 7–10].

Patient-reported outcome (PRO) measures are important indicators of disease burden in fibrotic lung diseases, including SSc-ILD and idiopathic pulmonary fibrosis (IPF) [11, 12]. A range of PRO measures evaluating factors such as symptoms, fatigue and overall health-related quality of life (HRQoL) have been explored in both diseases [13–19]. PRO measures in IPF—a fibrotic, constantly progressive, non-inflammatory single-organ disease—may be more consistently associated with lung function than in SSc-ILD, a systemic, inflammatory, multi-organ disease with multiple disease components that potentially influence HRQoL. Nevertheless, in a study of 194 patients with SSc with a mean disease duration of 11.6 years, dyspnoea was a significant predictor of impaired lung function and reduced HRQoL, assessed by the HAQ, 36-Item Short Form Survey (SF-36) and World Health Organization Disability Assessment questionnaires [20]. In 138 patients with SSc-ILD with $\leq$7 years duration, SF-36 was able to discriminate between patients with greater and lesser degrees of breathlessness and correlated with pulmonary function tests [17]. In Scleroderma Lung Study (SLS) II, although PRO measures [St. George's Respiratory Questionnaire (SGRQ) and the Transitional Dyspnoea Index] were improved by treatment, these PRO measures correlated only weakly with lung function, suggesting they provide complementary information on therapeutic responsiveness not captured by changes in forced vital capacity (FVC) [21].

Nintedanib is a tyrosine kinase inhibitor with antifibrotic and anti-inflammatory properties, and is approved in Europe, the USA and several countries worldwide for the treatment of patients with IPF, SSc-ILD and chronic fibrosing ILDs with a progressive phenotype [22–24]. In the Phase III SENSCIS® trial, there was a significantly lower annual rate of decline in FVC in patients with SSc-ILD treated with nintedanib (–52.4 mL/year) compared with placebo (–93.3 mL/year; treatment difference 41 mL; $P = 0.04$), representing a relative reduction of 44% [25].

In SENSCIS®, despite significant differences in rate of lung function decline between arms, no meaningful change in HRQoL was observed in either arm over 52 weeks [25]. To assess the possibility that distinct baseline characteristics associated with greater lung function impairment and the occurrence of large changes in lung function over 52 weeks might correlate with more pronounced changes in HRQoL, a post-hoc analysis of SENSCIS® was undertaken, aggregating treatment arms from baseline to week 52.

Methods

Study design

SENSCIS® was a randomized, double-blind, Phase III trial in which patients were randomized to receive either nintedanib 150 mg administered orally twice daily or placebo (previously described in [25]). Patients were aged at least 18 years and had a diagnosis of SSc according to classification criteria of the American College of Rheumatology and European League Against Rheumatism [26], with onset of first non-Raynaud's symptom within the previous 7 years. ILD was defined by a high-resolution CT (HRCT) scan performed in the previous 12 months showing fibrosis affecting at least 10% of the lungs, FVC $\geq$40% predicted and diffusing capacity of the lung for carbon monoxide (DL_{CO}) 30–89% predicted. Background therapy of MMF or MTX was permitted providing it was a stable dose for $\geq$6 months before entry. The trial was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethical Committee/Institutional Review Board of each participating centre (see Supplementary Data S1, available at *Rheumatology* online). Written informed consent was obtained from all patients.

PRO measures

The primary end point of the SENSCIS® trial was the annual rate of decline in FVC (mL/year) over a 52-week period. HRQoL was assessed over 52 weeks with PRO measure questionnaires at baseline and at weeks 24 and 52. The questionnaires used included: (1) the SGRQ (key secondary end point), a 2-part questionnaire covering three domains (symptoms, activities and impacts) and measuring the impact of respiratory conditions on patients' lives within the previous 4 weeks, with higher

scores indicating a more severe impact on health status; (2) the Functional Assessment of Chronic Illness Therapy (FACIT)-Dyspnoea questionnaire (secondary end point), a 20-item questionnaire comprised of 10 items assessing breathlessness in daily living and 10 items assessing functional limitations using a recall period of the previous 7 days, with higher scores representing worse dyspnoea or increased functional limitation; and (3) the HAQ–Disability Index (HAQ-DI) (secondary end point), a questionnaire with eight sections querying the ability to complete daily activities, together with six additional visual analogue scales (VAS) comprising the 26-item Scleroderma HAQ (SHAQ), with VASs querying 'breathing problems/lung involvement' and five other SSc symptoms using a recall period of 1 week, with higher scores indicating more severe limitation/disability. For more information on these, please see the Supplementary Material, available at *Rheumatology* online. Questionnaires were self-completed by patients in a quiet area prior to any other trial-related examination, in the following order: SGRQ, FACIT-Dyspnoea and SHAQ.

Assessment of PRO measures according to characteristics at baseline and week 52

For this post-hoc analysis, the two treatment arms were pooled. Baseline PRO measure scores were analysed in subgroups by both baseline lung function and SSc-specific characteristics potentially associated with poor prognosis and ILD progression. These included cutaneous SSc subset, modified Rodnan skin score (mRSS), age, gender, anti-topoisomerase I antibody (ATA) status, MMF use, functional gender-age-physiology ILD (ILD-GAP) score [27], FVC (categorized by ≥70% predicted or <70% predicted, considered to be a threshold of ILD severity), and extent of fibrosis on HRCT (10–<30% *vs* ≥30%; inclusion criteria specified ≥10% fibrosis).

PRO measures at week 52 were assessed according to FVC at week 52 (≥70% predicted or <70% predicted) and by supplemental oxygen use and by extent of fibrosis at baseline. Changes in PRO measures from baseline to week 52 were analysed according to categories of absolute change in FVC% predicted over 52 weeks (minor: 2–<5%; moderate: 5–10%; major: >10%), as well as similar categories of relative change in FVC (mL). These cut-offs are associated with meaningful differences in patients with IPF [28] and have been adapted for SSc-ILD [29]. Further analyses were conducted based on occurrence of cough, hospitalization, respiratory infection and gastrointestinal symptoms at baseline and/or during the 52-week trial period.

Statistical analyses

Baseline demographics and patient characteristics were analysed descriptively [mean (S.D.), frequencies]. Besides descriptive statistics [mean (S.D.), mean difference (S.D.)], exploratory *P*-values for the mean differences between subgroup categories were calculated using two-sided t-tests. Unadjusted baseline mean and S.D. of PRO measure scores were calculated considering all patients included in the mixed model for repeated measures (MMRM). Changes from baseline PRO measure scores were analysed using an MMRM with fixed categorical effects of ATA status, visit and subgroup-by-visit interaction, and fixed continuous effect of baseline PRO measure score by visit. Adjusted means were based on all analysed patients in the model (not only patients with a baseline and measurement at week 52).

Results

Baseline characteristics

A total of 576 patients were randomized in the SENSCIS® trial. Baseline characteristics are shown in Supplementary Table S1, available at *Rheumatology* online. Mean age was 54.0 years and median time since first non-Raynaud's symptom was 3.5 years. Mean FVC% predicted was 72.5%, and mean DL_{CO}% predicted was 53.0%. The mean extent of fibrosis on HRCT was 36.0%. Mean (S.D.) baseline SGRQ total score was 40.1 (20.6), baseline FACIT-Dyspnoea score was 46.3 (9.8), FACIT-Dyspnoea functional limitation score was 46.3 (9.7), and SHAQ VAS breathing problems score was 3.0 (2.8).

Cross-sectional relationship between HRQoL and patient characteristics at baseline and week 52

Across the pooled treatment arms, baseline PRO measure scores were generally worse in patients with diffuse cutaneous SSc, with more advanced lung function impairment (FVC <70% predicted), greater extent of fibrosis on HRCT (≥30%), worse skin disease (mRSS ≥18), higher ILD-GAP stage [27], presence of gastroesophageal reflux disease (GERD), and presence of upper gastrointestinal symptoms in those who were receiving MMF (Table 1).

At week 52, patients with less lung function impairment (FVC ≥70% predicted) reported favourable mean scores of PRO measures compared with those with greater impairment (FVC <70% predicted): SGRQ 34.0 *vs* 45.0 ($P < 0.0001$); FACIT-Dyspnoea 44.5 *vs* 48.9 ($P < 0.0001$); HAQ-DI 0.6 *vs* 0.7 ($P < 0.0228$); and SHAQ VAS breathing problems 2.6 *vs* 3.6 ($P < 0.0001$), respectively, with similar findings across subdomains (Table 2A and Fig. 1).

Patients using supplemental oxygen at baseline reported worse mean scores in most PRO measures at week 52 than those not on oxygen, again reflecting worse HRQoL in patients with more severe disease: SGRQ 55.3 *vs* 38.4 ($P < 0.0001$); FACIT-Dyspnoea 52.7 *vs* 46.3 ($P = 0.0007$); and SHAQ VAS breathing problems 4.5 *vs* 3.0 ($P = 0.0029$), respectively, with similar findings within subdomains (Table 2B and Fig. 2A). Similarly, patients with ≥30% fibrosis on HRCT at baseline reported worse mean scores in most PRO measures at week 52 than those with 10–<30% fibrosis: SGRQ 42.5

Table 1 Baseline HRQoL scores by baseline characteristics

Baseline characteristic	Baseline mean (s.d.) PRO measure score				
	SGRQ total score	FACIT-Dyspnoea	FACIT-Dyspnoea functional limitation	HAQ-DI	SHAQ VAS breathing problems
Gender					
Female ($n = 403$–430)	39.6 (21.3)	46.7 (9.9)	46.9 (10.0)	0.7 (0.7)	2.97 (2.83)
Male ($n = 129$–142)	41.5 (18.1)	45.3 (9.4)	44.7 (8.4)	0.4 (0.5)	3.12 (2.81)
Age					
<65 years ($n = 420$–451)	39.9 (20.3)	45.7 (9.5)	45.9 (9.6)	0.6 (0.6)	3.02 (2.82)
≥65 years ($n = 112$–121)	40.7 (21.4)	48.7 (10.5)	47.9 (9.7)	0.7 (0.7)	2.96 (2.84)
SSc subtype					
dcSSc ($n = 276$–296)	42.5 (21.0)	47.4 (10.2)	47.9 (9.9)	0.8 (0.7)	3.50 (2.89)
lcSSc ($n = 256$–276)	37.4 (19.7)	45.2 (9.3)	44.7 (9.1)	0.4 (0.5)	2.48 (2.66)
Time since onset of first non-Raynaud's symptom					
≤3 years ($n = 229$–245)	39.7 (21.3)	45.7 (10.1)	45.8 (9.7)	0.6 (0.6)	2.92 (2.92)
>3 years ($n = 303$–327)	40.3 (20.0)	46.8 (9.5)	46.8 (9.6)	0.6 (0.7)	3.07 (2.75)
FVC % predicted					
<70% ($n = 236$–252)	45.8 (19.7)	48.6 (9.4)	48.6 (9.2)	0.7 (0.7)	3.58 (2.95)
≥70% ($n = 296$–320)	35.5 (20.1)	44.6 (9.8)	44.5 (9.6)	0.6 (0.6)	2.55 (2.64)
Extent of fibrosis by HRCT					
10–<30% ($n = 226$–246)	35.5 (21.2)	44.4 (10.1)	44.9 (9.8)	0.6 (0.7)	2.47 (2.59)
≥30% ($n = 306$–326)	43.5 (19.4)	47.8 (9.3)	47.4 (9.4)	0.6 (0.6)	3.40 (2.93)
mRSS					
<18 ($n = 410$–444)	38.6 (19.9)	45.8 (9.5)	45.4 (9.4)	0.5 (0.6)	2.78 (2.73)
≥18 ($n = 120$–127)	45.0 (21.9)	48.3 (10.3)	49.6 (9.9)	1.0 (0.8)	3.75 (3.01)
ILD-GAP stage					
0–1 ($n = 359$–388)	37.4 (20.3)	45.1 (9.3)	45.3 (9.5)	0.6 (0.7)	2.73 (2.78)
2–3 ($n = 139$–146)	44.1 (20.4)	48.2 (10.4)	48.2 (9.9)	0.6 (0.7)	3.59 (2.81)
4–5 ($n = 25$–30)	50.1 (17.2)	51.0 (8.9)	50.2 (8.6)	0.6 (0.6)	3.50 (3.18)
GERD					
Yes ($n = 393$–425)	42.9 (20.4)	47.6 (9.8)	47.6 (9.7)	0.7 (0.7)	3.37 (2.91)
No ($n = 139$–147)	31.8 (18.8)	42.7 (8.8)	42.6 (8.6)	0.4 (0.6)	1.99 (2.30)
Upper GI symptoms					
Yes ($n = 399$–432)	42.8 (20.4)	47.5 (9.8)	47.5 (9.7)	0.7 (0.7)	3.35 (2.91)
No ($n = 133$–140)	31.9 (18.7)	42.7 (8.7)	42.6 (8.5)	0.4 (0.6)	1.97 (2.28)
MMF at baseline					
Yes ($n = 258$–277)	42.4 (20.1)	47.7 (9.7)	47.7 (9.6)	0.7 (0.7)	3.45 (2.92)
No ($n = 274$–295)	37.9 (20.8)	45.1 (9.7)	45.0 (9.5)	0.5 (0.6)	2.59 (2.67)

dcSSc: diffuse cutaneous SSc; FACIT: Functional Assessment of Chronic Illness Therapy; FVC: forced vital capacity; GERD: gastroesophageal reflux disease; GI: gastrointestinal; HAQ-DI: HAQ–Disability Index; HRCT: high-resolution CT; HRQoL: health-related quality of life; ILD-GAP: interstitial lung disease gender-age-physiology; lcSSc: limited cutaneous SSc; mRSS: modified Rodnan skin score; PRO: patient-reported outcome; SGRQ: St. George's Respiratory Questionnaire; SHAQ VAS: Scleroderma HAQ visual analogue scale.

vs 35.2 ($P < 0.0001$); FACIT-Dyspnoea 47.8 *vs* 45.1 ($P = 0.0029$); and SHAQ VAS breathing problems 3.4 *vs* 2.6 ($P = 0.0014$), respectively, with similar findings within subdomains (Table 2C and Fig. 2A).

Longitudinal relationship between changes in FVC and changes in HRQoL from baseline

At week 52, there was little or no change in mean SGRQ total score or in any of the subdomains among patients with no change in FVC% predicted from baseline (Fig. 3). Considering patients with major FVC decline (>10%, $n = 37$), moderate FVC decline (5–10%, $n = 81$–83) or minor FVC decline (2–<5%, $n = 92$–97), there was a trend towards worsening in SGRQ with greater decline: change in total SGRQ score was +5.5, +1.4 and –0.6 in the major, moderate and minor decline groups, respectively. In patients with major (>10%, $n = 9$), moderate (5–10%, $n = 33$–34) or minor (2–<5%, $n = 66$–67) improvements in FVC, a trend towards improvement in SGRQ was seen: total SGRQ score was –3.8, –3.4 and –1.8 in the major, moderate and minor decline groups, respectively. The number of patients in each group is expressed as a range due to missing values in some domains. Changes in SGRQ appeared to be largely driven by the symptom

TABLE 2 Week 52 PRO measure scores stratified by A: FVC% predicted at week 52, B: supplemental oxygen use at baseline and C: extent of fibrosis at baseline

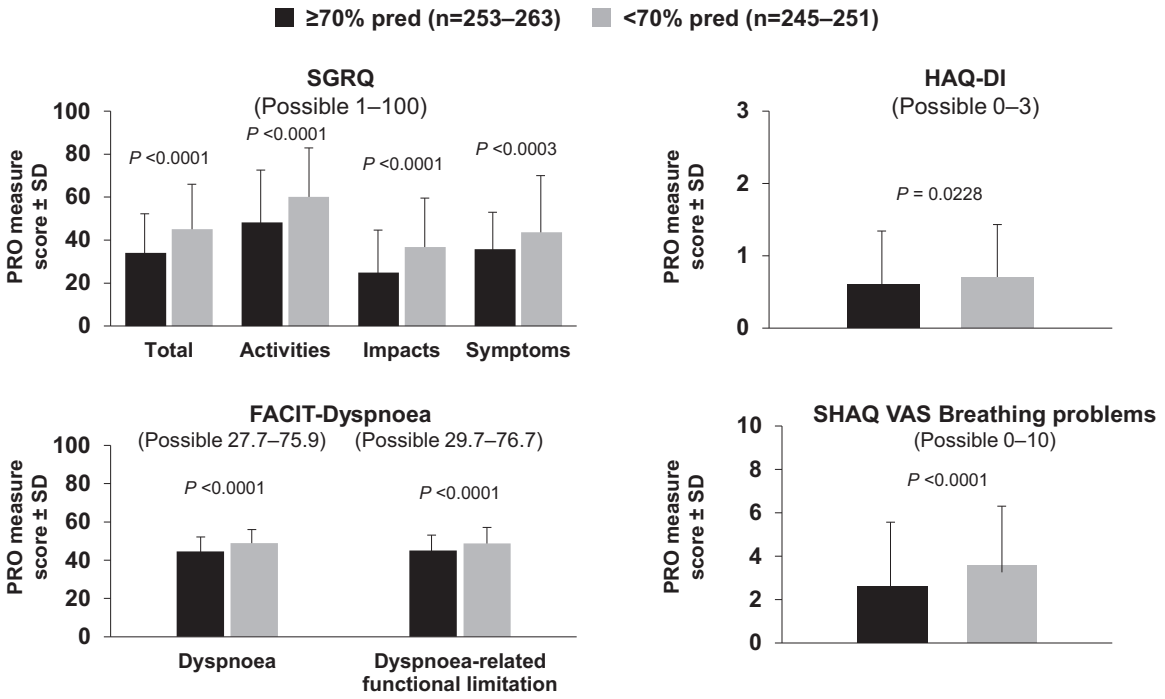
	A: FVC% predicted groups				Mean difference (S.D.)	*P*-value
	FVC ≥70% predicted		FVC <70% predicted			
	n	Mean (S.D.)	*n*	Mean (S.D.)		
SGRQ						
Total	260	34.0 (20.6)	248	45.1 (20.3)	−11.1 (20.5)	<0.0001
Activities	260	48.2 (26.6)	249	60.1 (23.5)	−11.9 (25.1)	<0.0001
Impacts	261	24.9 (20.2)	251	36.7 (21.4)	−11.8 (20.8)	<0.0001
Symptoms	263	35.7 (25.0)	251	43.6 (24.9)	−7.9 (24.9)	0.0003
FACIT-Dyspnoea						
Dyspnoea	258	44.5 (10.3)	249	48.9 (9.7)	−4.4 (10.0)	<0.0001
Dyspnoea-related functional limitation	260	45.0 (10.2)	251	48.8 (9.8)	−3.7 (10.0)	<0.0001
HAQ-DI	259	0.6 (0.7)	250	0.7 (0.7)	−0.1 (0.7)	0.0228
SHAQ VAS breathing problems	253	2.6 (2.7)	245	3.6 (2.7)	−1.0 (2.7)	<0.0001

	B: Supplemental oxygen use				Mean difference (S.D.)	*P*-value
	No		Yes			
	N	Mean (S.D.)	*n*	Mean (S.D.)		
SGRQ						
Total	478	38.4 (20.9)	30	55.3 (18.6)	−16.9 (20.8)	<0.0001
Activities	479	52.8 (25.6)	30	73.3 (21.7)	−20.5 (25.4)	<0.0001
Impacts	481	29.7 (21.2)	31	46.9 (21.6)	−17.2 (21.2)	<0.0001
Symptoms	483	39.0 (25.3)	31	49.2 (22.7)	−10.2 (25.1)	0.0284
FACIT-Dyspnoea						
Dyspnoea	476	46.3 (10.1)	31	52.7 (11.4)	−6.4 (10.1)	0.0007
Dyspnoea-related functional limitation	480	46.6 (10.0)	31	51.9 (10.7)	−5.3 (10.1)	0.0045
HAQ-DI	478	0.6 (0.7)	31	0.9 (0.7)	−0.3 (0.7)	0.0227
SHAQ VAS breathing problems	467	3.0 (2.7)	31	4.5 (3.1)	−1.5 (2.7)	0.0029

	C: Extent of fibrosis at baseline				Mean difference (S.D.)	*P*-value
	<30%		≥30%			
	N	Mean (S.D.)	*n*	Mean (S.D.)		
SGRQ						
Total	216	35.2 (20.9)	292	42.5 (20.9)	−7.2 (20.9)	0.0001
Activities	217	49.5 (26.9)	292	57.4 (24.5)	−7.8 (25.5)	0.0007
Impacts	219	26.8 (20.3)	293	33.7 (22.1)	−6.9 (21.4)	0.0003
Symptoms	218	35.4 (25.3)	296	42.7 (24.8)	−7.3 (25.0)	0.0012
FACIT-Dyspnoea						
Dyspnoea	214	45.1 (10.3)	293	47.8 (10.0)	−2.7 (10.2)	0.0029
Dyspnoea-related functional limitation	216	45.8 (10.4)	295	47.7 (9.9)	−2.0 (10.1)	0.0312
HAQ-DI	215	0.6 (0.7)	294	0.6 (0.6)	−0.02 (0.7)	0.7680
SHAQ VAS breathing problems	209	2.6 (2.6)	289	3.4 (2.8)	−0.8 (2.7)	0.0014

FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: HAQ–Disability Index; HRCT: high-resolution CT; PRO: patient-reported outcome; SGRQ: St. George's Respiratory Questionnaire; SHAQ VAS: Scleroderma HAQ visual analogue scale.

Fig. 1 PRO measures at week 52 in subgroups by FVC% predicted at week 52



The number of patients with data for PRO measures was variable, so a range is shown. FACIT: Functional Assessment of Chronic Illness Therapy; FVC: forced vital capacity; HAQ-DI: HAQ–Disability Index; PRO: patient-reported outcome; SGRQ: St. George's Respiratory Questionnaire; SHAQ VAS: Scleroderma HAQ visual analogue scale.

domain, which was the only domain demonstrating a statistically significant association between HRQoL and FVC change: the change in the symptom domain score was +11.1 in patients with major decline and −28.0 in patients with major improvement in FVC (exploratory *P*-value <0.0001) (Fig. 3). Mean changes in HAQ-DI, FACIT-Dyspnoea and SHAQ VAS breathing problems were small, with large variability and no clear differences between treatment arms or subgroups (data not shown).

Patients with a relative decline in FVC of ≥10% demonstrated a worsening of SGRQ mean total score by 5.0 from baseline to week 52, and a small worsening in FACIT-Dyspnoea and functional limitation scores (Table 3). In patients with a relative increase in FVC of >5%, there was an improvement in the SGRQ mean total score by 4.2, without marked improvement in any other PRO measure.

Longitudinal relationship between changes in HRQoL and the occurrence of cough, hospitalization, infection and gastrointestinal symptoms over 52 weeks

Patients with cough reported as an adverse event during the trial generally had worse SGRQ mean total scores at baseline compared with those without cough (43.6 *vs* 39.5) and greater worsening from baseline to week 52 (2.9 *vs* −0.6) (Supplementary Table S2, available at *Rheumatology* online), driven by the SGRQ symptom domain. There were only small changes in the other PRO measures in both subgroups.

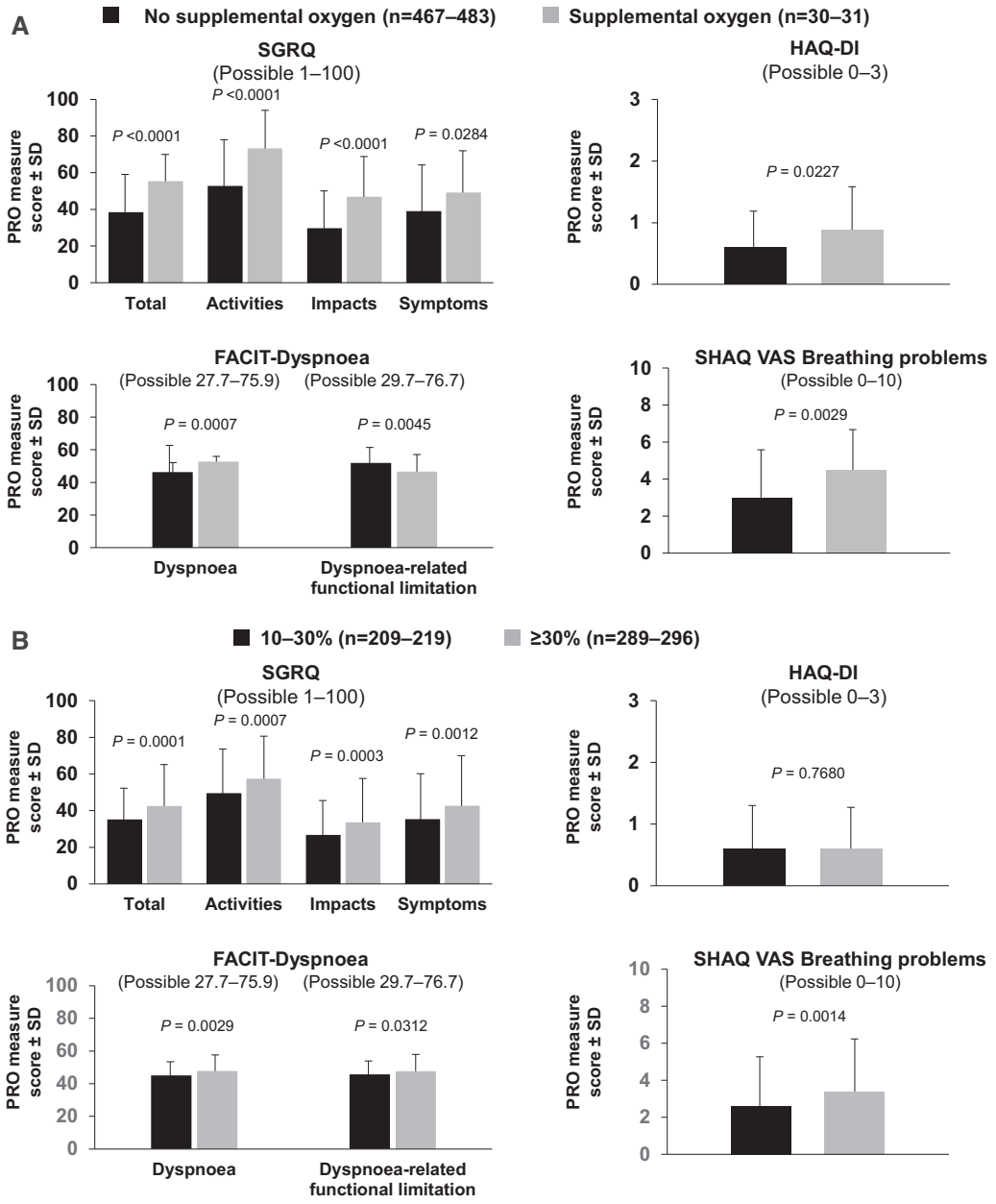
Patients who were hospitalized at any time during the 52-week period also demonstrated worse SGRQ scores at baseline (43.6 *vs* 39.5) and greater worsening over the 52-week period compared with those not hospitalized (3.0 *vs* −0.6) (Supplementary Table S3, available at *Rheumatology* online), again driven by the symptom domain. Only small changes in other PRO measures were seen.

There were no differences observed in SGRQ or other PRO measures in relation to patients who reported respiratory infections during the trial ($n = 238$) or those who reported new onset of gastrointestinal symptoms during the trial ($n = 374$) (data not shown).

Discussion

In the SENSCIS® trial, no significant change was observed in the secondary outcome—SGRQ—with no difference between treatment arms, despite a significant and clinically meaningful reduction in FVC decline over 1 year. This post-hoc analysis of pooled data from the SENSCIS® trial suggests that, in this population, meaningful changes in PRO measures could be detected in patients with large incremental changes in FVC.

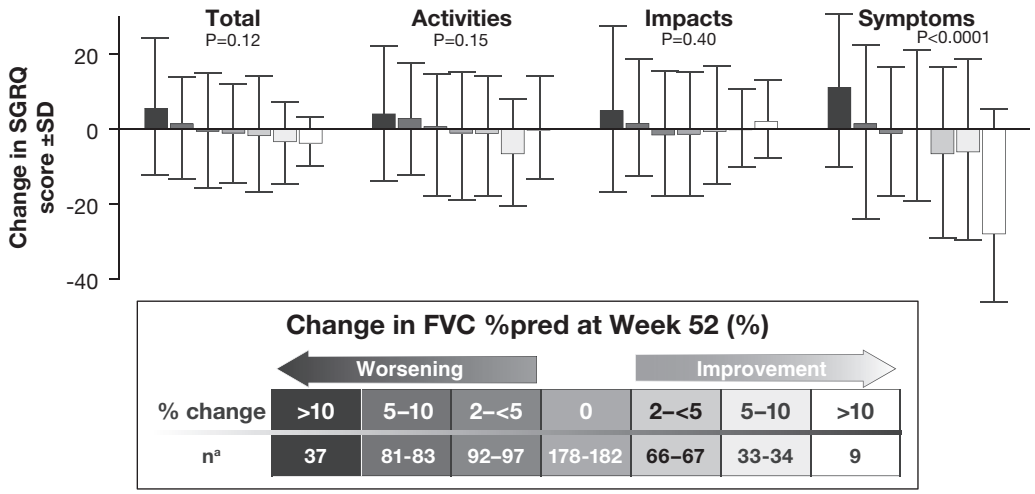
FIG. 2 PRO measures at week 52 in subgroups by (**A**) supplemental oxygen use at baseline and (**B**) extent of fibrosis by HRCT at baseline



The number of patients with data for PRO measures was variable, so a range is shown. FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: HAQ–Disability Index; HRCT: high-resolution CT; PRO: patient-reported outcome; SGRQ: St. George's Respiratory Questionnaire; SHAQ VAS: Scleroderma HAQ visual analogue scale.

Furthermore, higher degrees of impairment and more advanced disease at baseline were associated with both significantly poorer baseline PRO measure scores and significant changes in HRQoL. These data show that severe and progressive ILD has a major impact on HRQoL. As this may first become apparent by cumulative, sometimes even minor decline over several years in some patients, it is important to prevent disease progression and development of severe ILD to maintain quality of life. The ability of PRO measures to detect change may depend on the extent of impairment at baseline as well as the magnitude of change over time. The recently published consensus recommendations for the management of SSc-ILD [30] also include quality of life measures. Therefore, it is important to identify specific PRO measures which should be included in the assessment of

FIG. 3 Change in SGRQ scores at week 52 in patients with major, moderate or minor changes in FVC% predicted at week 52



Increasing SGRQ score represents deterioration in HRQoL. [a]The number of patients with data within each change category was variable, depending on the measure, so a range is shown. FVC: forced vital capacity; HRQoL: health-related quality of life; SGRQ: St. George's Respiratory Questionnaire.

TABLE 3 Change from baseline in PRO measures in patients with a relative decline in FVC of 10% or a relative increase in FVC >5% at week 52

	Relative decline >10% FVC	Relative increase >5% FVC
Mean SGRQ total score	*n* = 98	*n* = 78
Baseline (S.D.)	43.6 (20.6)	42.3 (21.2)
week 52 (S.D.)	46.5 (22.1)	37.2 (21.2)
Change from baseline (S.E.)[a]	5.0 (1.5)	–4.2 (1.6)
FACIT-Dyspnoea	*n* = 98	*n* = 79
Baseline (S.D.)	47.9 (10.2)	47.9 (9.2)
week 52 (S.D.)	49.3 (11.5)	46.9 (10.4)
Change from baseline (S.E.)[a]	2.6 (0.7)	–0.5 (0.8)
FACIT-Dyspnoea functional limitation	*n* = 99	*n* = 79
Baseline (S.D.)	48.3 (10.2)	47.6 (9.3)
week 52 (S.D.)	49.0 (10.8)	46.6 (9.9)
Change from baseline (S.E.)[a]	2.2 (0.7)	–0.5 (0.7)
HAQ-DI	***n* = 97**	***n* = 78**
Baseline (S.D.)	0.7 (0.8)	0.6 (0.6)
week 52 (S.D.)	0.7 (0.7)	0.6 (0.6)
Change from baseline (S.E.)[a]	0.1 (0.0)	0.0 (0.0)
SHAQ VAS breathing problems	***n* = 91**	***n* = 73**
Baseline (S.D.)	3.20 (2.83)	3.28 (2.82)
week 52 (S.D.)	3.50 (2.88)	3.11 (2.81)
Change from baseline (S.E.)[a]	0.63 (0.24)	–0.01 (0.26)

[a]Based on mixed model for repeated measures with fixed categorical effects of ATA status, visit and subgroup-by-visit interaction, and fixed continuous effect of baseline PRO measure score by visit. Visit is the repeated measure. Adjusted mean is based on all analysed patients in the model (not only patients with a baseline and measurement at week 52). ATA: anti-topoisomerase I antibody; FACIT: Functional Assessment of Chronic Illness Therapy; FVC: forced vital capacity; HAQ-DI: HAQ–Disability Index; PRO: patient-reported outcome; SGRQ: St. George's Respiratory Questionnaire; SHAQ VAS: Scleroderma HAQ visual analogue scale.

disease severity and for the monitoring of patients with SSc-ILD. A recent review of treatment approaches for SSc-ILD highlights the need for a holistic approach, incorporating HRQoL as well as lung function assessments [31]. An analysis of the SLS-II study in patients with SSc-ILD with baseline FVC 66.5% predicted

who had an average absolute improvement in FVC of 3.0–3.3% after 2 years demonstrated corresponding improvements in PRO measures [21]. In the focuSSed Phase III trial of tocilizumab *vs* placebo in patients with early, diffuse and inflammatory SSc, fewer patients in the tocilizumab arm had FVC decline >10%, but there were no significant differences between arms in changes in PRO measures [32]. In 24 patients with SSc (including 16 with SSc-ILD) treated with imatinib in a Phase IIa study, improvements in PRO measures were seen, but it is not clear if these were related to changes in pulmonary function [33]. In the INPULSIS® study in patients with IPF, there was no difference in HRQoL between treatment arms, but changes in lung function correlated with changes in HRQoL [13–16, 34]. Despite baseline HRQoL being comparable between IPF patients in the INPULSIS® studies and those with SSc-ILD in SENSCIS®, the markedly different rate of FVC decline observed between the two diseases and the small numbers of patients with 'major' changes in FVC over the course of the SENSCIS® study may be a possible explanation for the differences in performance of PRO measures between these studies.

In the current study, worse baseline PRO measure scores correlated with risk factors for progressive ILD and death in SSc, including diffuse skin involvement, higher ILD-GAP stage, presence of GERD [35] and upper gastrointestinal symptoms, and MMF use at baseline, which may be a marker of more advanced or more rapidly progressive disease (although finding in relation to MMF may be complicated by the fact that MMF use has also been shown to be associated with improvements in HRQoL). Worse baseline PRO measure scores also correlated with hospitalization during the study, further suggesting an association between HRQoL and disease progression.

Presence of cough was associated with worse HRQoL at baseline and decline in HRQoL over time. However, cough, a major symptom driving PRO measures, is a multi-factorial phenomenon in SSc, potentially resulting from other factors beyond ILD (e.g. asymptomatic GERD), reinforcing the need for tight control of GERD. Although the new onset of gastrointestinal symptoms was not associated with impaired HRQoL, SSc management demands tight control of GERD in management of SSc to prevent both oesophageal damage and ILD-inciting micro-aspiration [35]. Treatments slowing disease progression and potentially ameliorating debilitating symptoms such as cough and dyspnoea may protect long-term HRQoL, with slower decline in health status, as demonstrated in IPF [34].

While the PRO measures utilized here are designed for use in respiratory diseases, they are not ILD- or SSc-specific. The SGRQ was initially developed for chronic obstructive pulmonary disease [36], which is characterized by a very different pathophysiology to fibrotic lung disease, with a distinct symptom profile. Furthermore, SSc is a systemic disease in which inflammation can impact humoral, haematological and musculoskeletal function, leading to fatigue, poor cognition and diffuse pain; as such, HRQoL metrics may capture the impact of non-respiratory complications of SSc [37]. In future, the use of an SSc-ILD-specific HRQoL metric may potentially be more sensitive to smaller increments of FVC change, whilst the systematic control for GERD-related cough and stratification of contribution from confounding SSc comorbidities may improve the assessment of HRQoL in patients with SSc-ILD in the context of pharmacological and non-pharmacological treatments.

Further study limitations in SENSCIS® include that although lung function and PRO measures were primary and secondary endpoints, respectively, the study was not specifically designed to examine associations between lung function, clinical characteristics and PRO measures. Therefore, the analysis is unlikely to be reflective of real-world experience. Furthermore, participation in a clinical trial can, in itself, variably influence HRQoL and patient-reported symptoms [38].

In conclusion, the findings from this study indicate that changes in lung function parameters are associated with changes in patients' HRQoL. In particular, patients whose FVC falls below 70% predicted, who require supplemental oxygen and/or who have high extent of lung fibrosis on HRCT may experience reduction in HRQoL shown by the PRO measures employed in this study, although this may only be apparent following cumulative decline over several years. Treatments that slow or prevent decline in lung function can therefore have a major impact on HRQoL in the long term.

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Data availability statement

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to relevant material, including participant-level clinical study data, as needed by them to fulfil their role and obligations as authors under the ICMJE criteria.

Clinical study documents and participant clinical study data are available to be shared on request after publication of the primary manuscript in a peer-reviewed journal, and if regulatory activities are complete and other criteria met as per the BI Policy on Transparency and Publication of Clinical Study Data (see https://www.mystudywindow.com/msw/datasharing). Bona fide, qualified scientific and medical researchers are eligible to request access to the clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Legal Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request. Prior to providing access, clinical study documents and data will be examined, and, if necessary, redacted and de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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