Original article

Dyspnoea and cough in patients with systemic sclerosis–associated interstitial lung disease in the SENSCIS trial

Elizabeth R. Volkmann [ID] [1],*, Michael Kreuter[2],*, Anna M. Hoffmann-Vold [ID] [3], Marlies Wijsenbeek[4], Vanessa Smith [ID] [5], Dinesh Khanna[6], Christopher P. Denton [ID] [7], Wim A. Wuyts[8], Corinna Miede[9], Margarida Alves[10], Steven Sambevski[10] and Yannick Allanore[11], on behalf of the SENSCIS trial investigators

Abstract

Objective. The aim of these analyses was to investigate the rate of decline in forced vital capacity (FVC) in patients with SSc-associated interstitial lung disease (SSc-ILD) with and without cough or dyspnoea in the SENSCIS trial.

Methods. Patients in the SENSCIS trial were randomized to receive nintedanib or placebo. Subgroups with and without cough or dyspnoea at baseline were defined by responses to the St George's Respiratory Questionnaire.

Results. At baseline, 114/575 patients (19.8%) did not have cough and 172/574 patients (30.0%) did not have dyspnoea. In the placebo group, the rate of FVC decline over 52 weeks was similar in patients with and without cough (-95.6 and -83.4 mL/year, respectively) or dyspnoea (-95.8 and -87.7 mL/year, respectively). The effect of nintedanib vs placebo on reducing the rate of FVC decline was numerically more pronounced in patients without than with cough [difference: 74.4 (95% CI -11.1, 159.8) vs 31.5 (-11.1, 74.1)] and without than with dyspnoea [79.8 (9.8, 149.7) vs 25.7 (-19.9, 71.3)], but interaction P-values did not indicate heterogeneity in the treatment effect between these subgroups ($P = 0.38$ and $P = 0.20$, respectively).

Conclusion. In the placebo group of the SENSCIS trial, the rate of FVC decline was similar irrespective of the presence of cough or dyspnoea at baseline. The effect of nintedanib on reducing the rate of FVC decline was numerically more pronounced in patients without than with cough or dyspnoea at baseline, but no statistically significant heterogeneity was observed between the subgroups.

Trial registration. ClinicalTrials.gov, https://clinicaltrials.gov, NCT02597933.

Key words: nintedanib, connective tissue diseases, vital capacity, systemic scleroderma

[1]Department of Medicine, Division of Rheumatology, University of California, David Geffen School of Medicine, Los Angeles, CA, USA, [2]Center for Interstitial and Rare Lung Diseases, Pneumology and Respiratory Care Medicine, Thoraxklinik, University of Heidelberg, Member of the German Center for Lung Research, Heidelberg, Germany, [3]Department of Rheumatology, Oslo University Hospital, Oslo, Norway, [4]Department of Respiratory Medicine, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands, [5]Department of Rheumatology and Internal Medicine, Ghent University Hospital, Ghent, Belgium, [6]Department of Medicine, University of Michigan, Ann Arbor, MI, USA, [7]University College London Division of Medicine, Centre for Rheumatology and Connective Tissue Diseases, London, UK, [8]Unit for Interstitial Lung Diseases, Department of Pulmonary Medicine, University Hospitals Leuven, Leuven, Belgium, [9]mainanalytics GmbH, Sulzbach (Taunus), [10]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany and [11]Department of Rheumatology A, Descartes University, APHP, Cochin Hospital, Paris, France

Correspondence to: Elizabeth R. Volkmann, David Geffen School of Medicine, University of California, 1000 Veteran Avenue, Ste 32-59, Los Angeles, CA 90095, USA. E-mail: EVolkmann@mednet.ucla.edu

*Elizabeth R. Volkmann and Michael Kreuter contributed equally to this study.

Rheumatology key messages

- The SENSCIS trial enrolled patients with systemic sclerosis–associated interstitial lung disease regardless of respiratory symptoms.
- The rate of forced vital capacity (FVC) decline was similar irrespective of cough or dyspnoea.
- The effect of nintedanib on FVC decline was similar irrespective of cough or dyspnoea.

Introduction

SSc is a rare and heterogeneous autoimmune disease characterized by immune dysregulation, microvascular damage and progressive fibrosis of the skin and internal organs [1]. Interstitial lung disease (ILD) is the leading cause of death in patients with SSc [2]. Dyspnoea and cough are common in patients with SSc-ILD [3–7] and have a negative impact on patients' quality of life [4, 8–10]. Cough in patients with SSc-ILD may be due to the SSc-ILD itself [4–6], to gastroesophageal reflux disease (GERD) [11, 12], to other comorbidities [13], or to medication use [14]. Similarly, dyspnoea is a common manifestation of ILD, but may also occur due to comorbidities such as pulmonary hypertension or cardiac involvement [15, 16].

The severity and timing of onset of cough and dyspnoea in patients with SSc-ILD are variable. Many patients do not report symptoms even when ILD is evident on high-resolution CT (HRCT) and their lung function is impaired [7, 17–19]. This may be due in part to patients with SSc-ILD reducing activities that require exertion, or to limitations in the questionnaires used to assess respiratory symptoms.

The SENSCIS trial enrolled patients with and without respiratory symptoms, in contrast to Scleroderma Lung Studies I and II, which only enrolled patients with respiratory symptoms. In the SENSCIS trial, the rate of decline in forced vital capacity (FVC) (mL/year) over 52 weeks was reduced by 44% in patients randomized to nintedanib compared with placebo [20]. Furthermore, nintedanib reduced the risk of an absolute decline in FVC of ≥10% predicted or death over 52 weeks [21].

While there is some evidence that the presence of cough or dyspnoea may be associated with the progression of ILDs [22–25], the relationships between cough and dyspnoea and the course of SSc-ILD have not been established. The purpose of the present analyses was to assess the rate of FVC decline, and the effect of nintedanib on the rate of FVC decline, in patients with and without cough and dyspnoea at baseline in the SENSCIS trial.

Material and methods

Trial design

The design of the SENSCIS trial (NCT02597933) has been published, together with the trial protocol [20].

Briefly, eligible patients had SSc with onset of first non-RP symptom ≤7 years before screening, extent of fibrotic ILD ≥10% on HRCT (based on assessment of the whole lung), FVC ≥40% predicted, and diffusion capacity of the lung for carbon monoxide (DL_{CO}) 30–89% predicted. Patients on prednisone ≤10 mg/day or equivalent and/or stable therapy with mycophenolate or MTX for ≥6 months were allowed to participate. Patients were randomized 1:1 to receive nintedanib or placebo stratified by the presence of anti-topo I antibody (ATA). Patients remained on blinded treatment until the last patient had reached week 52 but for ≤100 weeks. The trial was carried out in compliance with the principles of the Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice of the International Conference on Harmonization. The trial was performed at 194 sites in 32 countries and was approved by an independent ethics committee or institutional review board at every site. The sites are listed in the primary manuscript on the trial results [20]. Patients provided written informed consent before trial entry.

Analyses

In *post hoc* analyses, we analysed the efficacy and safety of nintedanib in subgroups of patients with and without cough at baseline and with and without dyspnoea at baseline based on patients' answers to the questions in the St George's Respiratory Questionnaire (SGRQ) [26]. Patients who ticked boxes for 'most days a week', 'several days a week' or 'a few days a month' (rather than 'only with chest infection' or 'not at all') in response to the question 'Over the last month, I have coughed …' were considered to have cough. Patients who ticked these boxes in response to the question 'Over the last month, I have had shortness of breath ….' were considered to have dyspnoea.

We assessed the following outcomes in the nintedanib and placebo groups in subgroups with and without cough and with and without dyspnoea: rate of decline in FVC (mL/year) over 52 weeks; proportion of patients with absolute decline in FVC >5% predicted and >10% predicted at week 52; proportion of patients with relative decline in FVC >5% predicted and >10% predicted at week 52; time to absolute decline in FVC ≥10% predicted or death over 52 weeks; absolute change from baseline in SGRQ total score at week 52; proportion of patients with an absolute increase (worsening) in SGRQ total score of ≥4 points at week 52. An increase in SGRQ total score of ≥4 points has been suggested to

represent a meaningful change in patients with idiopathic pulmonary fibrosis [27]. We also assessed the rate of decline in FVC over 52 weeks in subgroups with both cough and dyspnoea, either cough only or dyspnoea only, and neither cough nor dyspnoea at baseline.

The rate of decline in FVC (mL/year) over 52 weeks was analysed using a random coefficient regression model (with random slopes and intercepts) with fixed categorical effects of ATA status and sex, fixed continuous effects of baseline FVC (mL), age, and height and including baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time interaction terms. The analysis was based on all measurements taken over 52 weeks, including those from patients who discontinued trial medication, in patients who had a baseline and $\geq$1 post-baseline FVC measurement. The proportions of patients with absolute/relative declines in FVC >5% or >10% predicted and with an increase in SGRQ total score of $\geq$4 points at week 52 were compared between subgroups using a logistic regression model including terms for treatment, ATA status, subgroup and treatment-by-subgroup interaction. Odds ratios were estimated for the effect of treatment within each subgroup. Missing values were imputed using a worst-value-carried-forward approach.

The time to absolute decline in FVC $\geq$10% predicted or death over 52 weeks was analysed using a Cox proportional hazards model stratified by ATA status with terms for treatment, subgroup and treatment-by-subgroup interaction. Absolute change from baseline in SGRQ total score at week 52 was based on a mixed model for repeated measures (MMRM), with fixed categorical effects of ATA status, treatment-by-subgroup-by-visit interaction and a fixed continuous covariate of baseline SGRQ total score-by-visit interaction. For all analyses, an interaction test was applied to assess potential heterogeneity in the effect of nintedanib between the subgroups, with no adjustment for multiple testing. Adverse events were coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) and are presented descriptively.

Results

Patients

Of 575 patients with information on cough and 574 patients with information on dyspnoea, 114 patients (19.8%) did not have cough and 172 patients (30.0%) did not have dyspnoea at baseline. Of 574 patients with information on both symptoms, 353 patients (61.5%) had both cough and dyspnoea, 156 patients (27.2%) had cough only or dyspnoea only, and 65 patients (11.3%) had neither cough nor dyspnoea. Of the patients with cough, 353 (76.6%) reported cough most or several days a week and 108 (23.4%) reported cough a few days a month. Of the patients who reported dyspnoea, 283 (70.4%) reported dyspnoea most or several

days a week and 119 (29.6%) reported dyspnoea a few days a month.

At baseline, in patients with and without cough, respectively, the mean (S.D.) extent of fibrotic ILD on HRCT was 37.2 (21.3)% and 30.7 (20.3)%, the mean (S.D.) FVC was 71.5 (16.1) and 76.7 (18.3)% predicted, the mean (S.D.) high-sensitivity CRP was 5.6 (9.7) and 9.6 (29.2) mg/l, 66.6% and 46.5% had GERD, 80.3% and 77.2% were taking drugs for gastric acid–related disorders, 50.1% and 49.1% were taking CSs, 48.4% and 49.1% were taking mycophenolate, and 8.7% and 6.1% were taking angiotensin-converting enzyme (ACE) inhibitors (Table 1). Among the patients who reported cough on their baseline SGRQ, 10.0% in the nintedanib group and 9.1% in the placebo group had cough noted as a 'baseline medical condition' by the investigator in the case report form completed at screening; among patients who did not report cough on their baseline SGRQ, these proportions were 5.2% and 1.8%, respectively.

At baseline, in patients with and without dyspnoea, respectively, the mean (S.D.) extent of fibrotic ILD on HRCT was 37.7 (21.7)% and 31.6 (19.4)%, the mean (S.D.) FVC was 71.0 (16.3)% and 76.5 (16.8)% predicted, the mean (S.D.) high-sensitivity CRP was 5.8 (10.3) and 7.8 (24.3) mg/l, 68.9% and 47.7% had GERD, 82.8% and 72.1% were taking drugs for gastric acid–related disorders, 53.5% and 41.9% were taking CSs, and 50.0% and 44.8% of patients were taking mycophenolate (Table 2). Among the patients who reported dyspnoea on their baseline SGRQ, 13.4% in the nintedanib group and 7.3% in the placebo group had dyspnoea noted as a 'baseline medical condition' by the investigator in the case report form completed at screening; among those who did not report dyspnoea on their baseline SGRQ, these proportions were 5.1% and 3.2%, respectively.

Outcomes in subgroups by cough at baseline

In the placebo group, the rate of decline in FVC (mL/year) over 52 weeks was similar in patients with and without cough at baseline (Fig. 1A). The effect of nintedanib *vs* placebo on reducing the rate of decline in FVC (mL/year) was numerically more pronounced in patients without than with cough, but the exploratory interaction *P*-value did not indicate heterogeneity in the treatment effect between these subgroups ($P = 0.38$) (Fig. 1A). The proportions of patients with absolute/relative declines in FVC >5% or >10% predicted were similar or lower in patients treated with nintedanib than placebo in patients with and without cough at baseline, with no heterogeneity detected between the subgroups (Table 3). Similarly, no heterogeneity was detected between these subgroups in the time to an absolute decline in FVC $\geq$10% predicted or death ($P = 0.33$) (Table 3).

Changes in SGRQ total score at week 52 were small in both the nintedanib and placebo groups in both subgroups by cough at baseline. No heterogeneity was detected in the effect of nintedanib on the absolute change in SGRQ total score between the subgroups by cough (Table 3).

TABLE 1 Baseline characteristics in subgroups by cough at baseline

	Patients with cough[a]		Patients without cough[a]	
	Nintedanib (*n* = 229)	Placebo (*n* = 232)	Nintedanib (*n* = 58)	Placebo (*n* = 56)
Age (years)	54.8 (11.8)	53.5 (12.8)	53.8 (11.9)	52.6 (11.8)
Female	172 (75.1)	166 (71.6)	49 (84.5)	46 (82.1)
Years since onset of first non-RP symptom	3.5 (1.6)	3.5 (1.8)	3.5 (1.6)	3.5 (1.8)
dcSSc	120 (52.4)	122 (52.6)	32 (55.2)	24 (42.9)
ATA positive	138 (60.3)	142 (61.2)	35 (60.3)	35 (62.5)
High-sensitivity CRP[b]	5.3 (8.9)	5.9 (10.6)	8.4 (19.5)	10.9 (36.9)
Extent of fibrotic ILD on HRCT[c]	38.5 (21.8)	36.0 (20.7)	29.7 (20.1)	31.9 (20.7)
FVC (mL)	2443 (701)	2535 (839)	2511 (867)	2565 (714)
FVC % predicted	71.3 (15.8)	71.8 (16.4)	77.0 (19.6)	76.4 (17.1)
DL_{CO} % predicted[d,e]	51.8 (14.7)	53.1 (15.2)	57.5 (15.6)	53.5 (14.9)
SpO_2 (%)[f]	97.6 (1.8)	97.5 (2.6)	97.7 (2.2)	97.6 (2.4)
mRSS[g]	11.6 (9.4)	10.7 (8.7)	10.1 (8.3)	11.6 (9.3)
SGRQ total score[f]	43.9 (18.8)	42.3 (20.3)	28.0 (20.7)	27.1 (19.4)
Phlegm[h]	154 (67.2)	152 (65.5)	7 (12.1)	13 (23.2)
Asthma[i]	12 (5.2)	8 (3.4)	2 (3.4)	0
Gastroesophageal reflux disease[j]	158 (69.0)	149 (64.2)	27 (46.6)	26 (46.4)
Drugs for gastric acid–related disorders[k]	183 (79.9)	187 (80.6)	45 (77.6)	43 (76.8)
Immunosuppressants[k]	198 (86.5)	195 (84.1)	54 (93.1)	47 (83.9)
CSs[k]	124 (54.1)	107 (46.1)	28 (48.3)	28 (50.0)
Inhaled CSs[l]	34 (14.8)	30 (12.9)	5 (8.6)	4 (7.1)
Mycophenolate (mofetil or sodium)	109 (47.6)	114 (49.1)	30 (51.7)	26 (46.4)
ACE inhibitors[m]	22 (9.6)	18 (7.8)	3 (5.2)	4 (7.1)
Cough reported by investigator at screening[n]	23 (10.0)	21 (9.1)	3 (5.2)	1 (1.8)

Data are *n* (%) or mean (S.D.). [a]Information on cough at baseline was missing for 1 patient in the nintedanib group. [b]Normal range: ≤4.99 mg/L; data missing for 45 patients. [c]Assessed in whole lung to nearest 5% by central review. Pure (non-fibrotic) ground-glass opacity was not included. [d]Corrected for haemoglobin. [e]Data missing for 7 patients. [f]Data missing for 10 patients. [g]Data missing for 2 patients. [h]Patients who ticked boxes for 'most days a week', 'several days a week' or 'a few days a month' (rather than 'only with chest infection' or 'not at all') to the question 'Over the last month, I have brought up phlegm …' were considered to have phlegm at baseline. [i]Based on preferred term in the Medical Dictionary for Regulatory Activities (MedDRA). [j]Oesophageal involvement (dysphagia, reflux) reported at screening. [k]Customized drug grouping. [l]WHO Anatomical Therapeutic Chemical (ATC) codes for 'adrenergics, inhalants' and 'other drugs for obstructive airway diseases, inhalants' within the customized drug grouping 'corticosteroids'. [m]WHO ATC codes for 'ACE inhibitors, plain' and 'ACE inhibitors, combinations' within the customized drug grouping 'antihypertensives'. [n]Based on MedDRA preferred terms 'cough', 'productive cough' and 'upper−airway cough syndrome'. ACE, angiotensin-converting enzyme; ATA, anti-topo 1 antibody; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution CT; ILD, interstitial lung disease; mRSS, modified Rodnan skin score; SGRQ, St George's Respiratory questionnaire; SpO_2, oxygen saturation.

The proportion of patients with an increase (worsening) in SGRQ total score of ≥4 points at week 52 was similar in patients treated with nintedanib and placebo both in patients with and without cough, with no heterogeneity detected between the subgroups (Table 3).

The adverse event profile of nintedanib was similar in the subgroups by cough (Supplementary Table S1, available at *Rheumatology* online). The proportions of patients with adverse events that led to discontinuation of trial medication in the nintedanib and placebo groups, respectively, were 15.7% and 6.5% in patients with cough at baseline and 17.2% and 17.9% in those without cough at baseline.

Outcomes in subgroups by dyspnoea at baseline

In the placebo group, the rate of decline in FVC (mL/year) was similar in patients with and without dyspnoea at baseline (Fig. 1B). The effect of nintedanib *vs* placebo on reducing the rate of decline in FVC was numerically more pronounced in patients without than with dyspnoea, but the exploratory interaction *P*-value did not

TABLE 2 Baseline characteristics in subgroups by dyspnoea at baseline

	Patients with dyspnoea[a]		Patients without dyspnoea[a]	
	Nintedanib (*n* = 209)	Placebo (*n* = 193)	Nintedanib (*n* = 78)	Placebo (*n* = 94)
Age (years)	54.8 (12.0)	53.6 (12.7)	53.9 (11.2)	53.0 (12.5)
Female	159 (76.1)	137 (71.0)	62 (79.5)	74 (78.7)
Years since onset of first non-RP symptom	3.4 (1.6)	3.5 (1.7)	3.6 (1.7)	3.4 (1.9)
dcSSc	113 (54.1)	95 (49.2)	39 (50.0)	50 (53.2)
ATA positive	132 (63.2)	113 (58.5)	41 (52.6)	63 (67.0)
High-sensitivity CRP[b]	5.5 (9.4)	6.0 (11.2)	6.8 (16.8)	8.6 (29.4)
Extent of fibrotic ILD on HRCT[c]	38.7 (21.8)	36.6 (21.6)	31.3 (20.8)	31.9 (18.3)
FVC (mL)	2395 (672)	2531 (829)	2623 (871)	2570 (790)
FVC % predicted	70.6 (16.1)	71.4 (16.6)	77.4 (17.5)	75.6 (16.1)
DL$_{CO}$ % predicted[d,e]	50.9 (14.7)	50.9 (14.2)	58.4 (14.8)	58.2 (15.7)
SpO$_2$ (%)[f]	97.6 (1.8)	97.6 (2.4)	97.6 (2.1)	97.3 (2.7)
mRSS[g]	11.3 (9.3)	10.5 (9.0)	11.4 (8.9)	11.7 (8.6)
SGRQ total score[f]	47.8 (16.9)	45.8 (18.7)	21.6 (15.4)	25.9 (18.8)
Asthma[h]	12 (5.7)	7 (3.6)	2 (2.6)	1 (1.1)
Gastroesophageal reflux disease[i]	147 (70.3)	130 (67.4)	38 (48.7)	44 (46.8)
Drugs for gastric acid–related disorders[j]	174 (83.3)	159 (82.4)	54 (69.2)	70 (74.5)
Immunosuppressants[j]	185 (88.5)	167 (86.5)	67 (85.9)	74 (78.7)
CSs[j]	121 (57.9)	94 (48.7)	31 (39.7)	41 (43.6)
Inhaled CSs[k]	36 (17.2)	28 (14.5)	3 (3.8)	6 (6.4)
Mycophenolate (mofetil or sodium)	102 (48.8)	99 (51.3)	37 (47.4)	40 (42.6)
ACE inhibitors[l]	17 (8.1)	11 (5.7)	8 (10.3)	11 (11.7)
Dyspnoea reported by investigator at screening[m]	28 (13.4)	14 (7.3)	4 (5.1)	3 (3.2)

Data are *n* (%) or mean (S.D.). [a]Information on dyspnoea at baseline was missing for 1 patient each in the nintedanib and placebo groups. [b]Normal range: ≤4.99 mg/L; data missing for 45 patients. [c]Assessed in whole lung to nearest 5% by central review. Pure (non-fibrotic) ground-glass opacity was not included. [d]Corrected for haemoglobin. [e]Data missing for 7 patients. [f]Data missing for 10 patients. [g]Data missing for 2 patients. [h]Based on preferred term in the Medical Dictionary for Regulatory Activities (MedDRA). [i]Oesophageal involvement (dysphagia, reflux) reported at screening. [j]Customized drug grouping. [k]WHO Anatomical Therapeutic Chemical (ATC) codes for 'adrenergics, inhalants' and 'other drugs for obstructive airway diseases, inhalants' within the customized drug grouping 'corticosteroids'. [l]WHO ATC codes for 'ACE inhibitors, plain' and 'ACE inhibitors, combinations' within the customized drug grouping 'antihypertensives'. [m]Based on MedDRA preferred terms 'dyspnoea' and 'dyspnoea exertional'. ACE, angiotensin-converting enzyme; ATA, anti-topo 1 antibody; DL$_{CO}$, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution CT; ILD, interstitial lung disease; mRSS, modified Rodnan skin score; SGRQ, St George's Respiratory questionnaire; SpO$_2$, oxygen saturation.
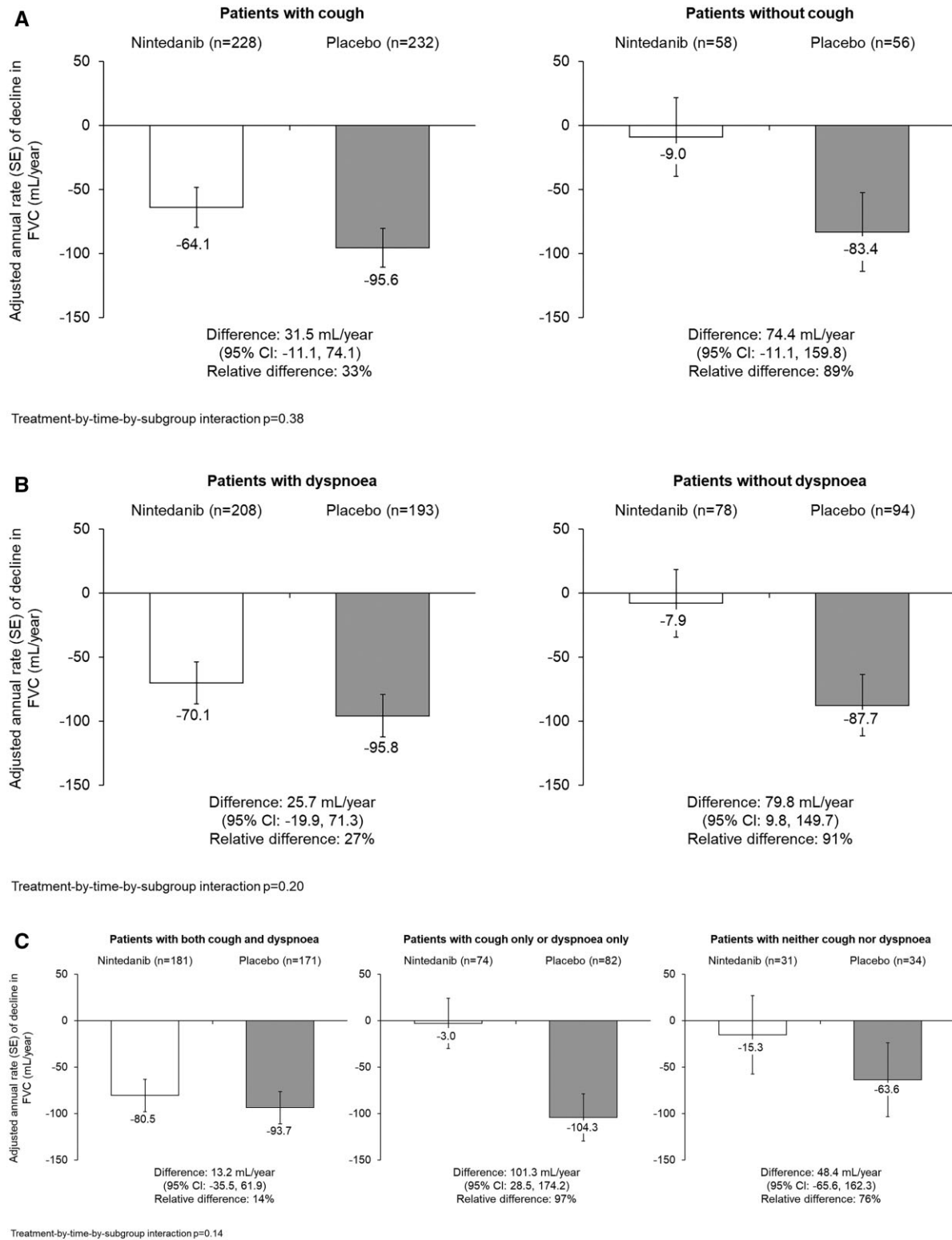
indicate heterogeneity in the treatment effect between these subgroups (*P* = 0.20) (Fig. 1B). The proportions of patients with absolute/relative declines in FVC >5% or >10% predicted were similar or lower in patients treated with nintedanib than placebo in patients with and without dyspnoea at baseline, with no heterogeneity detected between the subgroups (Table 4). Similarly, no heterogeneity was detected between these subgroups in the time to an absolute decline in FVC ≥10% predicted or death (*P* = 0.81) (Table 4).

Changes in SGRQ total score at week 52 were small in both the nintedanib and placebo groups in both subgroups by dyspnoea at baseline. No heterogeneity was detected in the effect of nintedanib *vs* placebo on the absolute change in SGRQ total score between the subgroups (Table 4). The proportion of patients with an increase (worsening) in SGRQ total score of ≥4 points at week 52 was similar in patients treated with nintedanib and placebo both in patients with and without dyspnoea at baseline, with no heterogeneity detected between the subgroups (Table 4).

The adverse event profile of nintedanib was similar in the subgroups by dyspnoea (Supplementary Table S2, available at *Rheumatology* online). The proportions of

FIG. 1 Rate of decline in FVC (mL/year) over 52 weeks in subgroups by respiratory symptoms at baseline in the SENSCIS trial

Rate of decline in FVC (mL/year) over 52 weeks in subgroups by (A) cough at baseline, (B) dyspnoea at baseline, and (C) both cough and dyspnoea, cough only or dyspnoea only, or neither cough nor dyspnoea. FVC, forced vital capacity.

TABLE 3 Outcomes in subgroups by cough at baseline

	Patients with cough		Patients without cough	
	Nintedanib (n = 228)	Placebo (n = 232)	Nintedanib (n = 58)	Placebo (n = 56)
Rate of decline in FVC (mL/year) over 52 weeks, adjusted rate (s.e.)	−64.1 (15.6)	−95.6 (15.1)	−9.0 (30.7)	−83.4 (30.8)
Difference (95% CI)	31.5 (−11.1, 74.1)		74.4 (−11.1, 159.8)	
Treatment-by-time-by-subgroup interaction	P = 0.38			
Relative decline in FVC (mL) >5% at week 52, n (%)	80 (35.1)	100 (43.1)	15 (25.9)	25 (44.6)
Odds ratio (95% CI)	0.71 (0.49, 1.04)		0.43 (0.20, 0.95)	
Treatment-by-subgroup interaction	P = 0.26			
Relative decline in FVC (mL) >10% at week 52, n (%)	41 (18.0)	42 (18.1)	7 (12.1)	10 (17.9)
Odds ratio (95% CI)	0.99 (0.62, 1.60)		0.63 (0.22, 1.81)	
Treatment-by-subgroup interaction	P = 0.44			
Absolute decline in FVC >5% predicted at week 52, n (%)	49 (21.5)	65 (28.0)	10 (17.2)	17 (30.4)
Odds ratio (95% CI)	0.70 (0.46, 1.08)		0.48 (0.20, 1.17)	
Treatment-by-subgroup interaction	P = 0.45			
Absolute decline in FVC >10% predicted at week 52, n (%)	17 (7.5)	19 (8.2)	3 (5.2)	5 (8.9)
Odds ratio (95% CI)	0.90 (0.46, 1.78)		0.55 (0.13, 2.44)	
Treatment-by-subgroup interaction	P = 0.56			
Absolute decline in FVC ≥10% predicted or death at week 52, n (%)	34 (14.8)[a]	49 (21.1)	6 (10.3)	13 (23.2)
Hazard ratio (95% CI)[b]	0.71 (0.46, 1.10)		0.41 (0.16, 1.09)	
Treatment-by-subgroup interaction	P = 0.33			
Absolute change from baseline in SGRQ total score at week 52, adjusted mean (s.e.)[c]	0.2 (1.0)	−1.2 (1.0)	3.1 (2.0)	0.5 (2.1)
Difference (95% CI)	1.4 (−1.3, 4.1)		2.6 (−3.0, 8.1)	
Treatment-by-time-by-subgroup interaction	P = 0.72			
Absolute increase from baseline in SGRQ total score of ≥4 points at week 52, n (%)[d]	87 (39.9)	72 (31.9)	24 (44.4)	21 (40.4)
Odds ratio (95% CI)	1.42 (0.96, 2.09)		1.18 (0.54, 2.55)	
Treatment-by-subgroup interaction	0.68			

[a]Analysed in 229 patients in the nintedanib group with cough at baseline. [b]Time-to-event analysis. [c]Analysed in 226 patients in the nintedanib group and 230 patients in the placebo group with cough at baseline, and 56 patients in the nintedanib group and 53 patients in the placebo group without cough at baseline. [d]Analysed in 218 patients in the nintedanib group and 226 patients in the placebo group with cough at baseline, and 54 patients in the nintedanib group and 52 patients in the placebo group without cough at baseline. FVC, forced vital capacity; SGRQ, St George's Respiratory Questionnaire.

patients with adverse events that led to discontinuation of trial medication in the nintedanib and placebo groups, respectively, were 17.7% and 7.8% in patients with dyspnoea at baseline and 11.5% and 10.6% in those without dyspnoea at baseline.

Outcomes in subgroups by cough and dyspnoea at baseline

In the placebo group, the rate of decline in FVC was similar in patients who had both cough and dyspnoea, cough only or dyspnoea only, or neither cough nor

dyspnoea (Fig. 1C). The effect of nintedanib *vs* placebo on reducing the rate of decline in FVC was numerically more pronounced in patients with fewer or no symptoms, but the exploratory interaction *P*-value did not indicate heterogeneity in the treatment effect across subgroups ($P = 0.14$).

Discussion

Our analyses demonstrated that patients with SSc-ILD enrolled in the SENSCIS trial who had cough or dyspnoea at baseline had a numerically greater extent of fibrotic ILD and a numerically lower FVC % predicted and DL_{CO} % predicted at baseline than patients without these symptoms. Data from Scleroderma Lung Studies I and II, which enrolled patients with SSc-ILD and exertional dyspnoea based on Mahler's Dyspnoea Index, indicated that the presence of cough at baseline (based on cough severity index or on responses to the questions about cough and phlegm in the SGRQ) was associated with lower DL_{CO}, worse dyspnoea and a greater extent of fibrosis on HRCT, but not with lower FVC [5, 10]. It should be noted that in the SENSCIS trial, both the patients who did not have cough and the patients who did not have dyspnoea had a mean extent of fibrotic ILD (based on assessment of the whole lung) of over 30%. These findings highlight that respiratory symptoms may be a late presentation of SSc-ILD, at least in a subgroup of patients, and support the screening of all patients with SSc for ILD, irrespective of symptoms, as recommended by experts [28–30].

Among patients in the SENSCIS trial who reported cough or dyspnoea in response to the question in the SGRQ, only around 10% had that symptom recorded by the investigator. The reasons for this difference are unknown, but it is possible that the investigators did not ask the patients explicit questions about these symptoms at screening. This observation suggests that patient-reported-outcomes measures such as the SGRQ may support physicians in identifying patients with these symptoms in routine clinical practice.

In our analyses, no difference in the rate of loss of lung function over the following year was detected between subgroups based on the presence of cough or dyspnoea at baseline. This is consistent with an analysis of data from 535 patients with SSc-ILD in the EUSTAR database, which found no significant difference in the 5-year decline in FVC between patients with or without dyspnoea at baseline [31]. These findings highlight the importance of regular monitoring of *all* patients with SSc-ILD for progression, not just those with severe or symptomatic disease [28].

Compared with patients who received placebo, patients treated with nintedanib had a lower rate of decline in FVC across the subgroups. Interestingly, we observed numerically greater effects of nintedanib in the subgroups without dyspnoea and without cough,

despite these subgroups having less severe disease at baseline based on the extent of fibrotic ILD on HRCT. These results suggest that the presence of cough or dyspnoea alone should not be used as an indicator of when SSc-ILD is 'severe' enough to warrant treatment. Experts in the field have proposed that the initiation of treatment for SSc-ILD should be based on more than one measure of disease severity (e.g. extent of fibrosis on HRCT, pulmonary function tests, symptoms) as well as on other factors, including risk factors for progression and patient preferences [28, 30, 32]. Prompt treatment of SSc-ILD may help to preserve lung function and ultimately improve outcomes.

Consistent with previous studies [5, 7], there was a high prevalence of cough (80%) and dyspnoea (70%) in the SENSCIS trial. Managing symptoms and maintaining patients' quality of life should be part of a holistic approach to the care of patients with SSc-ILD [33]. However, alleviation of cough and dyspnoea in patients with ILD is challenging given the lack of treatments with robust evidence of efficacy [6, 34]. In Scleroderma Lung Study II, patients with SSc-ILD and exertional dyspnoea who were treated with CYC or mycophenolate for 24 months experienced significant improvements in dyspnoea (based on the Transitional Dyspnoea Index) and in SGRQ total score, but there was no placebo control [35]. In the SENSCIS trial, there was no statistically significant effect of nintedanib on change in SGRQ total score [20], and no heterogeneous effect of nintedanib on change in SGRQ total score between patients with or without cough or dyspnoea at baseline was detected.

Limitations of our analyses include that they were not powered for formal statistical testing of the individual subgroups, and the interaction *P*-values should be regarded as exploratory. Our analyses were not adjusted for the presence of comorbidities (such as GERD, pulmonary hypertension, or cardiac involvement) that may have an impact on respiratory symptoms or the course of FVC decline, nor for the use of comedications. The presence of cough and dyspnoea at baseline were based solely on responses to two questions in the SGRQ, which have not been validated as a means of determining the presence of cough or dyspnoea in patients with ILDs. We only investigated subgroups based on the presence of cough or dyspnoea at baseline and did not consider whether development or resolution of cough during the trial was associated with a different course of SSc-ILD.

In conclusion, in patients with SSc-ILD in the SENSCIS trial, patients with cough or dyspnoea at baseline had a numerically greater extent of fibrotic ILD and numerically lower FVC % predicted than patients without dyspnoea or cough, but patients without cough or dyspnoea also showed considerable fibrosis on HRCT and impairment in FVC. The rate of decline in FVC in the placebo group was numerically similar irrespective of the presence of cough or dyspnoea at baseline. The effect of nintedanib on reducing the rate of FVC decline

TABLE 4 Outcomes in subgroups by dyspnoea at baseline

	Patients with dyspnoea		Patients without dyspnoea	
	Nintedanib (*n* = 208)	Placebo (*n* = 193)	Nintedanib (*n* = 78)	Placebo (*n* = 94)
Rate of decline in FVC (mL/year) over 52 weeks, adjusted mean (S.E.)	−70.1 (16.3)	−95.8 (16.5)	−7.9 (26.4)	−87.7 (23.9)
Difference (95% CI)	25.7 (−19.9, 71.3)		79.8 (9.8, 149.7)	
Treatment-by-time-by-subgroup interaction	*P* = 0.20			
Relative decline in FVC (mL) >5% at week 52, *n* (%)	77 (37.0)	84 (43.5)	18 (23.1)	40 (42.6)
Odds ratio (95% CI)	0.76 (0.51, 1.13)		0.41 (0.21, 0.80)	
Treatment-by-subgroup interaction	*P* = 0.13			
Relative decline in FVC (mL) >10% at week 52, *n* (%)	40 (19.2)	39 (20.2)	8 (10.3)	13 (13.8)
Odds ratio (95% CI)	0.93 (0.57, 1.52)		0.74 (0.29, 1.89)	
Treatment-by-subgroup interaction	*P* = 0.67			
Absolute decline in FVC >5% predicted at week 52, *n* (%)	48 (23.1)	58 (30.1)	11 (14.1)	24 (25.5)
Odds ratio (95% CI)	0.69 (0.44, 1.07)		0.50 (0.23, 1.10)	
Treatment-by-subgroup interaction	*P* = 0.49			
Absolute decline in FVC >10% predicted at week 52, *n* (%)	18 (8.7)	17 (8.8)	2 (2.6)	7 (7.4)
Odds ratio (95% CI)	0.99 (0.49, 1.99)		0.32 (0.06, 1.57)	
Treatment-by-subgroup interaction	*P* = 0.20			
Absolute decline in FVC ≥10% predicted or death at week 52, *n* (%)	33 (15.8)[a]	47 (24.4)	7 (9.0)	15 (16.0)
Hazard ratio (95% CI)[b]	0.63 (0.40, 0.99)		0.48 (0.19, 1.20)	
Treatment-by-subgroup interaction	*P* = 0.81			
Absolute change from baseline in SGRQ total score at week 52, adjusted mean (S.E.)[c]	0.0 (1.1)	−0.7 (1.1)	2.9 (1.8)	−1.3 (1.6)
Difference (95% CI)	0.7 (−2.2, 3.6)		4.3 (−0.2, 8.8)	
Treatment-by-time-by-subgroup interaction	*P* = 0.19			
Absolute increase from baseline in SGRQ total score of ≥4 points at week 52, *n* (%)[d]	77 (39.1)	63 (33.7)	34 (45.3)	30 (33.3)
Odds ratio (95% CI)	1.27 (0.84, 1.93)		1.63 (0.86, 3.07)	
Treatment-by-subgroup interaction	*P* = 0.52			

[a]Analysed in 209 patients in the nintedanib group with dyspnoea at baseline. [b]Time-to-event analysis. [c]Analysed in 206 patients in the nintedanib group and 190 patients in the placebo group with dyspnoea at baseline, and 76 patients in the nintedanib group and 92 patients in the placebo group without dyspnoea at baseline. [d]Analysed in 197 patients in the nintedanib group and 187 patients in the placebo group with dyspnoea at baseline, and 75 patients in the nintedanib group and 90 patients in the placebo group without dyspnoea at baseline. FVC, forced vital capacity; SGRQ, St George's Respiratory Questionnaire.

was numerically more pronounced in patients without than with cough or dyspnoea at baseline, but no statistically significant heterogeneity was observed between these subgroups. These data suggest that the presence of cough or dyspnoea alone should not be used to inform when to initiate nintedanib in patients with SSc-ILD. More research is needed to understand the underlying mechanisms and potential prognostic value of cough and dyspnoea in patients with SSc-ILD.

Acknowledgement

Data availability statement

See online supplementary material, available at *Rheumatology* online.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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