Decline in forced vital capacity (FVC) in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) with and without dyspnoea: data from the SENSCIS trial

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INTRODUCTION

- Dyspnoea is common in patients with SSc-ILD,[1] but its severity and timing of onset are variable.
- Little evidence is available on the association between dyspnoea and progression of SSc-ILD.
- The SENSCIS trial enrolled patients with SSc-ILD irrespective of symptoms. In the overall population, nintedanib reduced the rate of decline in forced vital capacity (FVC) (mL/year) over 52 weeks by 44% compared with placebo, with adverse events characterised mainly by gastrointestinal events.[2]

AIM

- To assess the characteristics at baseline, rate of decline in FVC, and the effect of nintedanib on the rate of decline in FVC, in patients with and without dyspnoea at baseline in the SENSCIS trial.

METHODS

Trial design

- Patients in the SENSCIS trial had SSc with first non-Raynaud symptom within ≤7 years before screening, extent of fibrotic ILD ≥10% on high-resolution computed tomography (HRCT) (based on assessment of the whole lung), FVC ≥40% predicted, and DLco 30–89% predicted.
- Patients taking prednisone ≤10 mg/day and/or stable therapy with mycophenolate or methotrexate for ≥6 months prior to randomisation were allowed to participate.
- Patients were randomised to receive nintedanib or placebo until the last patient had reached week 52 but for ≤100 weeks.

Analyses

- In post-hoc analyses, we analysed outcomes in subgroups with and without dyspnoea at baseline based on responses to the St. George's Respiratory Questionnaire (SGRQ).[3]
  - Patients who reported having shortness of breath "most days a week", "several days a week" or "a few days a month" (rather than "only with chest infection" or "not at all") over the last month were considered to have dyspnoea.
- We analysed the following outcomes:
  - Rate of decline in FVC (mL/year) over 52 weeks.
  - Proportions of patients with absolute and relative declines in FVC >5% predicted and FVC >10% predicted at week 52. Missing values were imputed using a worst value carried forward approach.
  - Time to absolute decline in FVC ≥10% predicted or death.
- Interaction p-values were calculated to assess potential heterogeneity in the treatment effect of nintedanib between the subgroups.

CONCLUSIONS

- In the SENSCIS trial, patients with SSc-ILD who had dyspnoea at baseline had a numerically greater extent of fibrotic ILD and numerically lower FVC % predicted than patients without dyspnoea. However, both patients with and without dyspnoea had a considerable extent of fibrotic ILD on HRCT and impairment in FVC.
- The rate of decline in FVC in the placebo group was similar irrespective of the presence of dyspnoea at baseline.
- The effect of nintedanib on reducing the rate of FVC decline was numerically more pronounced in patients without than with dyspnoea at baseline, but no statistically significant heterogeneity was observed between these subgroups. The adverse event profile of nintedanib was consistent between the subgroups.
- These data suggest that the presence of dyspnoea alone should not be used to determine when to initiate nintedanib in patients with SSc-ILD.

RESULTS

Patients

Baseline characteristics

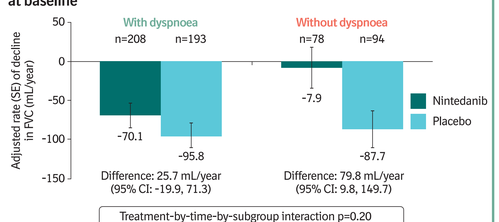
With dyspnoea (n=402)		Without dyspnoea (n=172)
54.2	Mean age (years)	53.4
73.6	Female, %	79.1
51.7	Diffuse cutaneous SSc, %	51.7
3.5	Mean time since onset of non-Raynaud symptom (years)	3.5
71.0	Mean FVC % predicted	76.5
50.9	Mean DLco % predicted*	58.3
37.7	Mean extent of fibrotic ILD on HRCT (%)†	31.6
53.5	Corticosteroids, %	41.9
50.0	Mycophenolate, %	44.8

*Corrected for haemoglobin. Seven patients had a missing DLco value.
†Assessed in whole lung to nearest 5% by central review. Pure (non-fibrotic) ground glass opacity was not included.

Rate of decline in FVC (mL/year) over 52 weeks

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

Rate of decline in FVC (mL/year) over 52 weeks in subgroups by dyspnoea at baseline

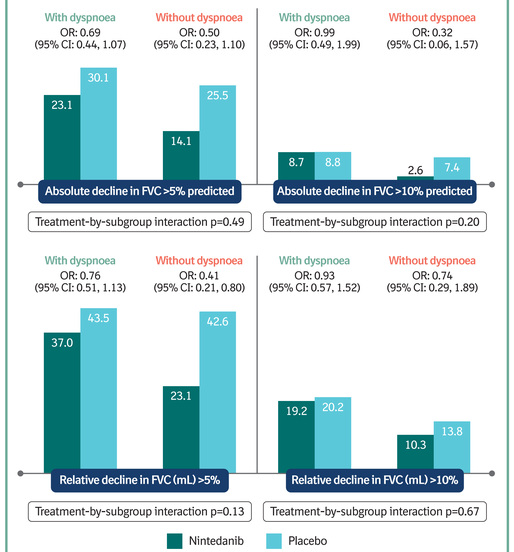


Based on random coefficient regression model with fixed effects of anti-topoisomerase I antibody (ATA) status, sex, baseline FVC, age and height and including baseline-by-time, treatment-by-subgroup and treatment-by-subgroup-by-time interaction terms.

Categorical declines in FVC

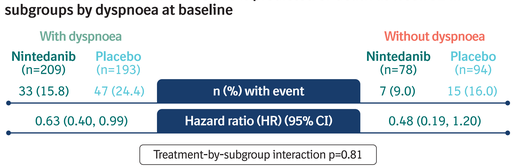
- No statistically significant heterogeneity was detected between subgroups by dyspnoea in the effect of nintedanib versus placebo on categorical declines in FVC, or on time to absolute decline in FVC ≥10% predicted or death.

Proportions of patients with absolute and relative declines in FVC at week 52 in subgroups by dyspnoea at baseline



The interaction p-values were based on a logistic regression model including treatment, ATA status, subgroup and treatment-by-subgroup interaction. OR, odds ratio.

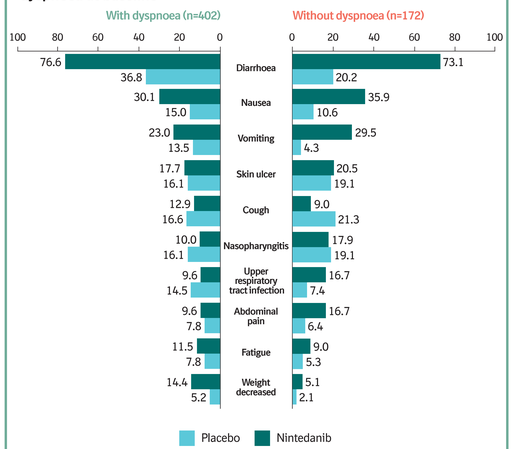
Time to absolute decline in FVC ≥10% predicted or death at week 52 in subgroups by dyspnoea at baseline



The HR and confidence interval (CI) were based on a Cox regression model with term for treatment and stratified by ATA status. The interaction p-value was based on a Cox regression model stratified by ATA status with terms for treatment, subgroup and treatment-by-subgroup interaction.

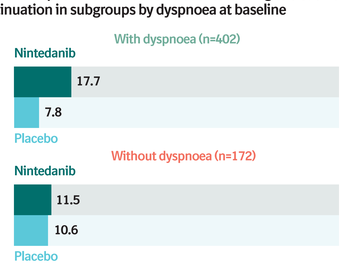
Adverse events

Adverse events (reported irrespective of causality) in subgroups by dyspnoea at baseline



Adverse events were coded using preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Data are % of patients with ≥1 such adverse event, reported over 52 weeks (or until 28 days after last trial drug intake in patients who discontinued trial drug before week 52). Adverse events reported in >10% of patients in either treatment group in the overall trial population are shown.

Proportions of patients with adverse events leading to treatment discontinuation in subgroups by dyspnoea at baseline



Data are % of patients with ≥1 such adverse event reported over 52 weeks.

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