Factors Prognostic of Greater Decline in Forced Vital Capacity in Patients with Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD): Data from the Placebo Group of the SENSCIS® Trial

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Introduction

- The progression of SSc-ILD is variable and unpredictable. However, observational studies have identified certain patient characteristics that may be prognostic of a greater rate of decline in forced vital capacity (FVC) in patients with SSc-ILD.[1–3]
- The SENSCIS trial enrolled 576 patients with SSc-ILD, who were randomised to receive nintedanib (n=288) or placebo (n=288).[4]

Aim

- To investigate whether baseline variables were prognostic of a greater rate of decline in FVC (mL/year) over 52 weeks in patients with SSc-ILD who received placebo in the SENSCIS trial.

Methods

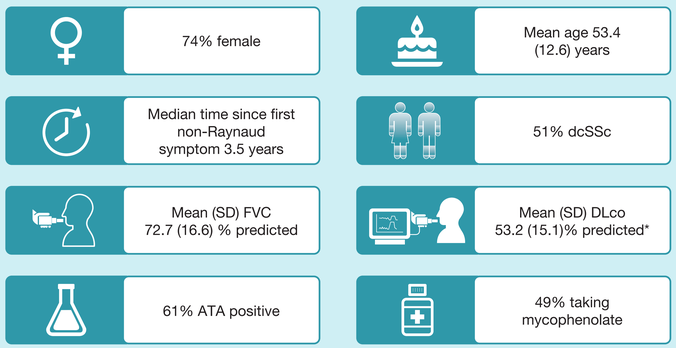
- Subjects in the SENSCIS trial had SSc with onset of first non-Raynaud symptom ≤7 years before screening, extent of fibrotic ILD ≥10% on an HRCT scan, FVC ≥40% predicted and diffusion capacity of the lung for carbon monoxide (DLco) 30–89% predicted.
- Patients taking prednisone ≤10 mg/day and/or stable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

Analyses

- Using data from the placebo group, we investigated baseline characteristics as prognostic factors for a greater rate of decline in FVC (mL/year) over 52 weeks, based on a random coefficient regression model with effects of anti-topoisomerase I antibody (ATA) status, sex, time, baseline FVC (mL), age and height, and subgroup-by-time and baseline-by-time interactions.
- We investigated the association of baseline characteristics with time to absolute decline from baseline in FVC >5% predicted over 100 weeks based on Cox's regression models using:
  - univariate models considering prognostic factors as categorical terms
  - univariate models considering certain prognostic factors as continuous terms
  - multivariable models with variables selected via stepwise multivariable regression including all pre-selected variables with backward selection, using an alpha-to-stay criterion of 0.2.

Results

Baseline characteristics of patients who received placebo in the SENSCIS trial (n=288)

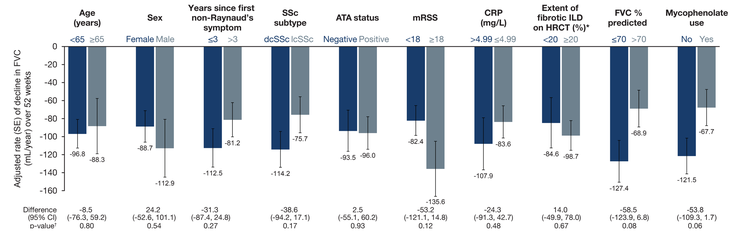


*Data not available for 4 patients.

Baseline characteristics as prognostic factors for a greater rate of decline in FVC (mL/year) over 52 weeks

- In the primary analysis, the adjusted rate (SE) of decline in FVC in the placebo group was -93.3 (13.5) mL/year.[4]
- Using a random coefficient regression model, none of the baseline factors investigated was prognostic ($p<0.05$) of a greater rate of decline in FVC (mL/year) over 52 weeks, but baseline FVC ≤70% predicted and not taking mycophenolate at baseline showed trends toward being prognostic factors (Figure 1).

Figure 1. *Baseline characteristics as prognostic factors for a greater rate of decline in FVC (mL/year) over 52 weeks*



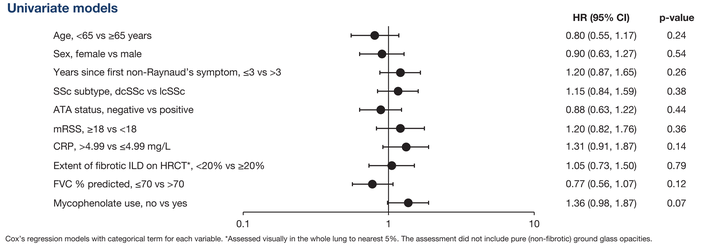
Random coefficient regression model with effects of ATA status, sex, time, baseline FVC (mL), age and height, and subgroup-by-time and baseline-by-time interactions. *Assessed visually in the whole lung to nearest 5%. The assessment did not include pure (non-fibrotic) ground glass opacities. †p-value for subgroup-by-time interaction.

Association of baseline factors with time to absolute decline from baseline in FVC >5% predicted over 100 weeks

- In univariate models with categorical terms, none of the baseline factors investigated was associated with an increased risk of an absolute decline from baseline in FVC >5% predicted over 100 weeks, although not taking mycophenolate showed a trend toward being a prognostic factor (Figure 2).
- When backward selection was performed using a model with all categorical variables, the final model included the terms CRP and FVC % predicted (Figure 2).

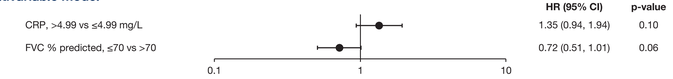
Figure 2. *Time to absolute decline from baseline in FVC >5% predicted over 100 weeks with categorical terms in the model*

Univariate models



Cox's regression models with categorical term for each variable. *Assessed visually in the whole lung to nearest 5%. The assessment did not include pure (non-fibrotic) ground glass opacities.

Multivariable model

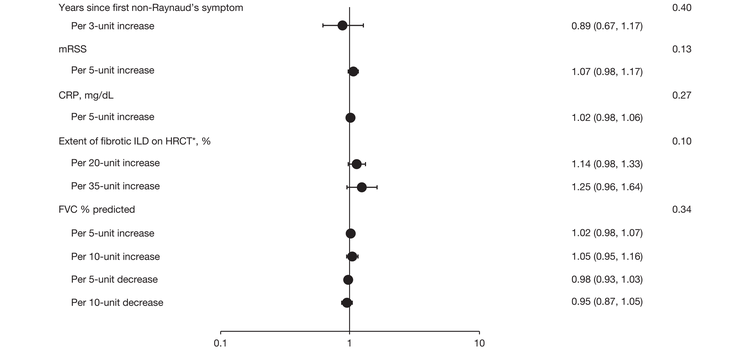


Cox's regression model. Variables were selected by backward selection using an alpha-to-stay criterion of 0.2. Initial model included categorical terms for ATA status, gender, age, mycophenolate use, SSc subtype, FVC % predicted, mRSS, CRP, time since first onset of non–Raynaud symptom, and extent of fibrotic ILD on HRCT.

- In univariate models with continuous terms, none of the baseline factors investigated was associated with an absolute decline from baseline in FVC >5% predicted over 100 weeks (Figure 3).
- When backward selection was performed using a model including categorical and continuous terms, the final model included only the categorical term for mycophenolate use (Figure 3).

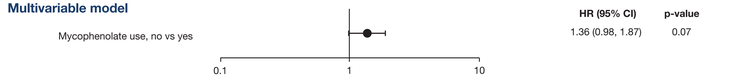
Figure 3. *Time to absolute decline from baseline in FVC >5% predicted over 100 weeks with categorical and continuous terms in the model*

Univariate models



Cox's regression models with continuous term for each variable. *Assessed visually in the whole lung to nearest 5%. The assessment did not include pure (non-fibrotic) ground glass opacities.

Multivariable model



Cox's regression model. Variables were selected by backward selection using an alpha-to-stay criterion of 0.2. Initial model included categorical terms for ATA status, gender, age, mycophenolate use, SSc subtype, and continuous terms for FVC % predicted, mRSS, CRP, time since first onset of non–Raynaud symptom, and extent of fibrotic ILD on HRCT.

Conclusions

- **In these analyses of data from the placebo group of the SENSCIS trial, no baseline characteristic was prognostic of a greater rate of decline in FVC across models, although our findings suggest that baseline FVC ≤70% predicted and not taking mycophenolate at baseline may be associated with a greater rate of decline in FVC.**
- **These findings suggest that the course of SSc-ILD is difficult to predict, that prognostic factors identified in certain populations of patients with SSc-ILD may not apply to all populations, and that new parameters or combinations of factors might be needed to predict the course of SSc-ILD.**
- **Ongoing analyses of data from the placebo group of the SENSCIS trial include multivariable analyses of factors that may be prognostic of the rate of FVC decline or of categorical declines in FVC.**

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