Interstitial lung disease in patients with systemic sclerosis: what can we learn from the SENSCIS trial?

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ABSTRACT

The SENSCIS trial of nintedanib versus placebo is the largest trial conducted to date in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD). This trial enrolled 576 patients with an extent of fibrotic ILD on high-resolution computed tomography of >10%. Median time since first non-Raynaud symptom was 3.4 years. Almost half of the patients were receiving a stable dose of mycophenolate at baseline. Key findings of the trial included that at baseline, despite having significant lung fibrosis on HRCT and impairment in lung function, 20% of the patients did not have cough and 30% did not have dyspnoea. Over 52 weeks, a marked decline in forced vital capacity (FVC) was observed (-112.0 mL/year in patients with diffuse cutaneous SSc [dcSSc] and -74.5 mL/year in patients with limited cutaneous SSc [lcSSc] in the placebo group). Loss of FVC was associated with an increased risk of SSc-related hospitalisation or death. Although certain subgroups of patients were at higher risk of progression, it was not possible to make a robust prediction of FVC decline based on baseline characteristics. The relative effect of nintedanib versus placebo on reducing the rate of FVC decline was consistent across subgroups based on factors including anti-topoisomerase I antibody (ATA) status, dcSSc vs lcSSc, and use of mycophenolate at baseline. The side-effects of nintedanib were mainly gastrointestinal events, particularly diarrhoea. Nintedanib did not have a significant effect on skin fibrosis or health-related quality of life. Overall, the results of the SENSCIS trial support the importance of prompt identification and treatment of SSc-ILD and the consideration of nintedanib as a treatment option.

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease characterised by immune dysregulation and fibrosis of the skin and internal organs (1). Interstitial lung disease (ILD) is a common manifestation of systemic sclerosis (SSc) that may lead to pulmonary fibrosis and is associated with poor outcomes (2, 3). SSc-ILD is the leading cause of death related to SSc (4).

The pathogenesis of SSc-ILD involves an interplay of inflammation and fibrosis, which may coexist from an early stage of disease (5). A trigger, such as microvascular injury, induces inflammation and an autoimmune response that results in infiltration of monocytes and macrophages within the lung parenchyma and accumulation of inflammatory cells in the alveolar space. Cytokines including chemokines and growth factors such as endothelins, platelet-derived growth factor, and vascular endothelial growth factor stimulate the recruitment and proliferation of leukocytes, mesenchymal progenitor cells and fibroblasts. Activated T and B cells secrete profibrotic mediators, stimulating the differentiation of fibroblasts into myofibroblasts and leading to excess deposition of extracellular matrix (ECM) in the lungs (5).

Nintedanib is an intracellular inhibitor of tyrosine kinases that has both anti-inflammatory and anti-fibrotic effects (6, 7). Pre-clinical studies, including studies in models of SSc, have shown that nintedanib inhibits processes fundamental to the development and progression of pulmonary fibrosis (Fig. 1) including myofibroblast accumulation, ECM deposition, and vascular remodelling (6-11).

The SENSCIS trial was a placebo-controlled trial designed to assess the efficacy and safety of nintedanib in

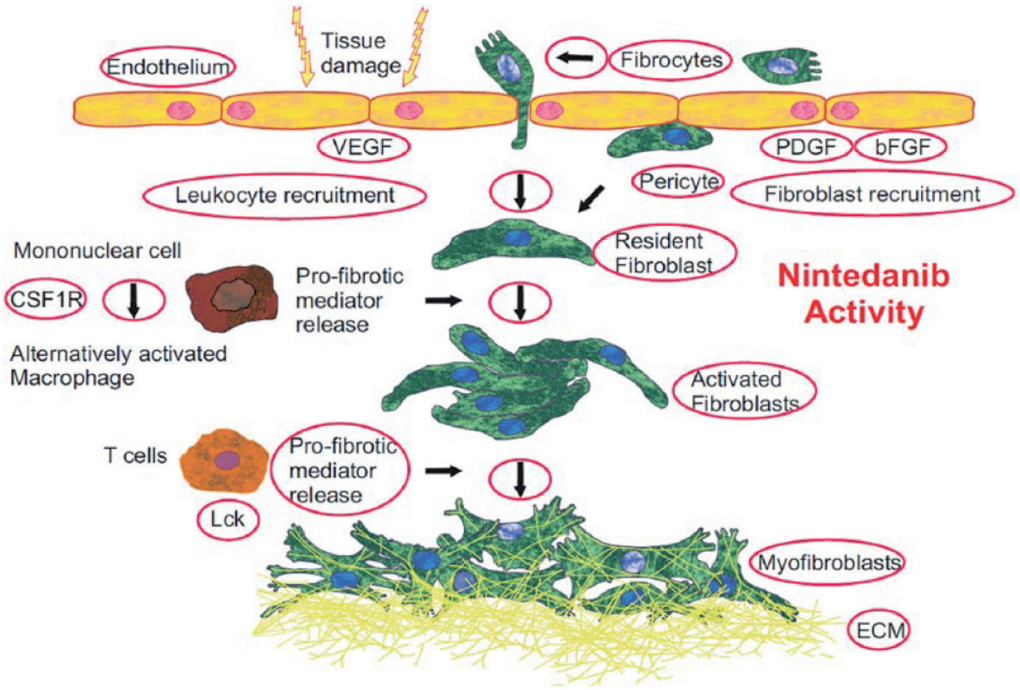

Fig. 1. Effects of nintedanib on pathogenic mechanisms with relevance to SSc-ILD based on experiments on human cells or animal models (7).
FGFR: fibroblast growth factor receptor; PDGFR: platelet-derived growth factor receptor; VEGF: vascular endothelial growth factor; Lck: lymphocyte-specific tyrosine-protein kinase; CSF1R: colony stimulating factor 1 receptor.
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patients with SSc-ILD. It is the largest trial in patients with SSc-ILD to have been conducted to date. In this article, we review the key learnings from the SENSCIS trial for clinicians who manage patients with SSc-ILD in clinical practice.

The SENSCIS trial

Patients in the SENSCIS trial had SSc with onset of first non-Raynaud symptom in the prior ≤7 years, an extent of fibrotic ILD on high-resolution computed tomography (HRCT) ≥10% (based on assessment of the whole lung) and a forced vital capacity (FVC) ≥40% predicted (12). Recent progression of ILD was not an inclusion criterion. Patients taking prednisone ≤10 mg/day and/or stable therapy with mycophenolate or methotrexate for ≥6 months were allowed to participate. Patients were randomised 1:1 to receive nintedanib 150 mg twice daily or placebo (stratified by anti-topoisomerase I antibody [ATA] status) until the last patient had reached week 52 but for ≤100 weeks. Dose reductions and treatment interruptions were allowed to manage adverse events (13).

The baseline characteristics of the 576 patients with SSc-ILD who participated in the SENSCIS trial are summarised in Figure 2. Approximately half of the patients had diffuse cutaneous SSc (dcSSc), 75% were female and 61% were ATA positive. The median time since first non-Raynaud symptom was 3.4 years. At baseline, mean FVC was 72.5% predicted and mean DLco was 53.0% predicted. Almost half of the patients (48%) were receiving a stable dose of mycophenolate at baseline.

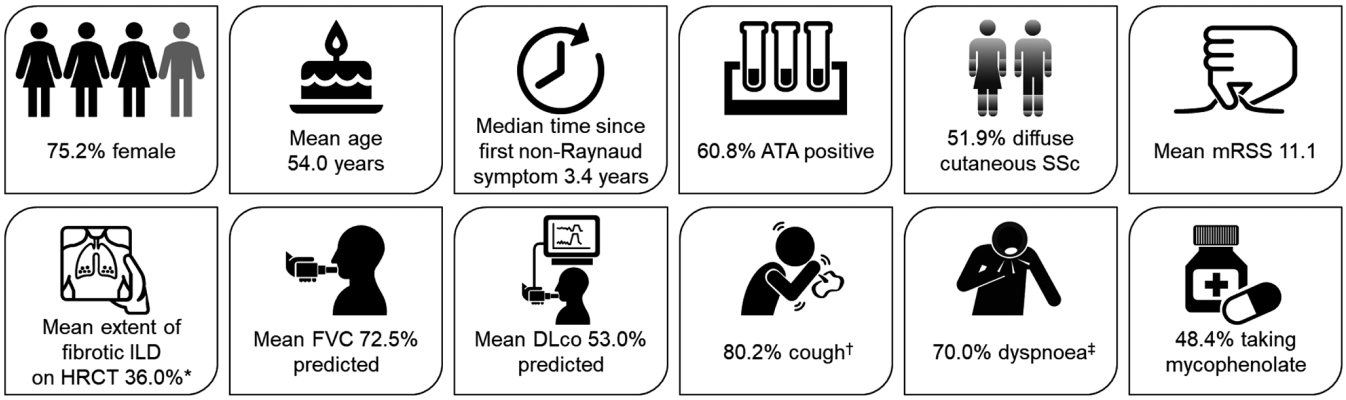
Learning 1: It is important to screen patients with SSc for ILD

All patients with SSc are at risk of developing ILD. ILD often develops early in the course of SSc (14). Experts recommend that all patients diagnosed with SSc undergo an HRCT scan to screen for ILD (15, 16). Restricting screening to patients with respiratory symptoms would result in patients with SSc-ILD being missed. Although all the patients enrolled in the SENSCIS trial had ≥10% extent of fibrotic ILD on HRCT, based on responses to the St. George's Respiratory Questionnaire (SGRQ), 20% did not have cough and 30% did not have dyspnoea at baseline (17). Patients without dyspnoea had a sizeable extent of fibrosis on HRCT (mean of 32%) and marked impairment in FVC (mean of 77% of the predicted value) (17).

A novel analysis compared FVC in patients with SSc-ILD in the SENSCIS trial with the FVC that would be estimated in a hypothetical reference population of healthy individuals matched for age, sex, ethnicity and height (18). At baseline, the patients in the SENSCIS trial had a much lower mean FVC than the healthy reference population (2460 mL in the nintedanib group *vs*. 3403 mL in the hypothetical healthy reference group) (18). The effective lung age of the patients in the SENSCIS trial (*i.e*. the age of a healthy individual with the same FVC) was approximately 29 years higher than their real age (18). These analyses show that substantial loss of lung function can occur in the few years following the onset of SSc-ILD and highlight the importance of early identification and treatment of SSc-ILD to preserve lung function.

Learning 2: Fibrosing SSc-ILD can be progressive, even in "lower risk" patients

Decline in FVC in patients with SSc-ILD indicates progression and has been associated with mortality (2, 19, 20). A marked decline in FVC was observed during the SENSCIS trial. In the placebo group, the rate of decline in FVC was -93.3 mL/year over 52 weeks (12) and -88.8 mL/year over 100 weeks (21). Different thresholds have been pro-



N=576. Not all patients provided data for all variables. *Assessed visually in whole lung to nearest 5%. Pure (non-fibrotic) ground glass opacities were not included. †Patients who reported having coughed "most days a week", "several days a week" or "a few days a month" over the last month in response to a question in the SGRQ. ‡Patients who reported having shortness of breath "most days a week", "several days a week" or "a few days a month" over the last month in response to a question in the SGRQ. ATA, anti-topoisomerase I antibody; DLco; diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; mRSS, modified Rodnan skin score; SGRQ, St. George's Respiratory Questionnaire; SSc, systemic sclerosis.

Fig. 2. Baseline characteristics of patients with SSc-ILD in the SENSCIS trial (12, 17).

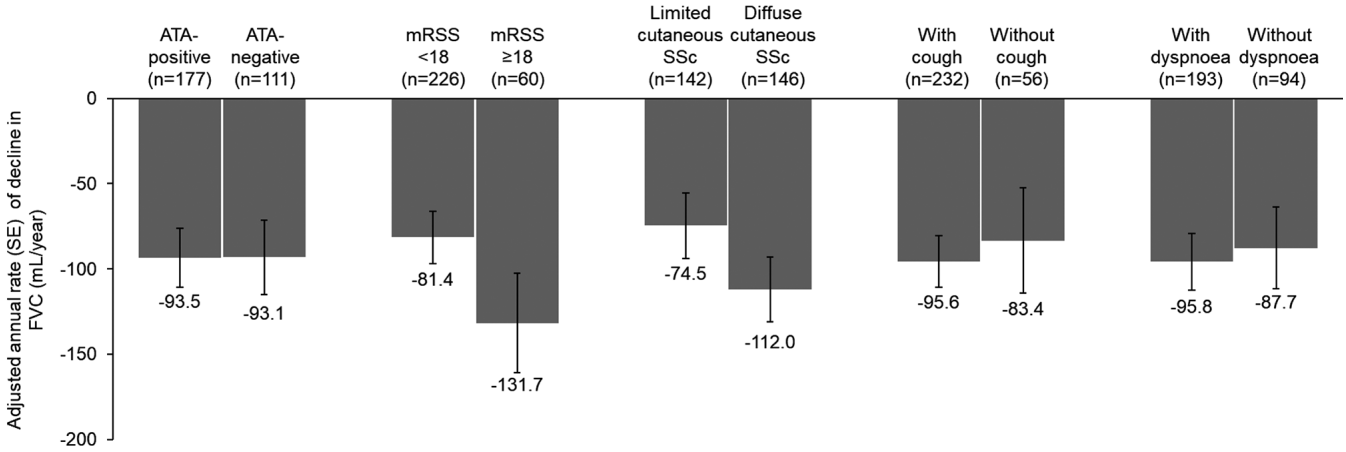


Fig. 3. Rate of decline in FVC (mL/year) over 52 weeks in the placebo group of the SENSCIS trial in subgroups by baseline characteristics (17, 31).

posed for the decline in FVC that represents clinically meaningful progression of SSc-ILD. The most commonly used threshold is a decline in FVC % predicted of >10% (2, 20, 22). This degree of FVC decline was seen in 23.3% of patients in the placebo group of the SENSCIS trial over 100 weeks (21). In May 2022, a clinical practice guideline issued by international pulmonology societies included an absolute decline in FVC % predicted >5% within 1 year in the criteria for definition of progressive pulmonary fibrosis (PPF) in patients with ILDs other than idiopathic pulmonary fibrosis. Such a decline in FVC was observed in 28.5% of patients in the placebo group of the SENSCIS trial (12). An absolute decrease in FVC % predicted ≥3.3% was proposed as the threshold for worsening of FVC based on data from Scleroderma Lung Studies I and II, anchored to the health transition question from the Medical Outcomes Short Form-36 (23). Over 52 weeks, 43.8% of patients in the placebo group of the SENSCIS trial reached this threshold (24).

Decline in FVC in patients with ILDs is known to increase the risk of hospitalisation (25, 26). Over 52 weeks of the SENSCIS trial, 13.7% of patients were hospitalised or died. Using a joint modelling approach, which allows for the combined analysis of longitudinal and time-to-event endpoints, a significant association was observed between FVC decline and the risk of SSc-related hospitalisation or death (27). A 3-unit decrease in FVC % predicted corresponded to an almost 1.5-fold increase in the risk of subsequent SSc-related hospitalisation or death over 52 weeks. Although there is not a close relationship between FVC and HRQL in patients with ILDs (28, 29), in the SENSCIS trial, meaningful changes in patient-reported outcomes were detected in patients who had a change in FVC % predicted >10% over 52 weeks (30). This suggests that decline in lung function is ultimately associated with deterioration in HRQL in patients with SSc-ILD.

The SENSCIS trial is rare among clinical trials in patients with SSc in that it included a sizeable number of patients (277; 48% of the trial population) with limited cutaneous SSc (lcSSc), who are at lower risk of organ complications than patients with dcSSc. The rate of decline in FVC was higher in the patients with dcSSc-ILD than lcSSc-ILD (-112.0 mL/year *vs*. -74.5 mL/year over 52 weeks in the placebo group) (31) (Fig. 3). However, it should be noted

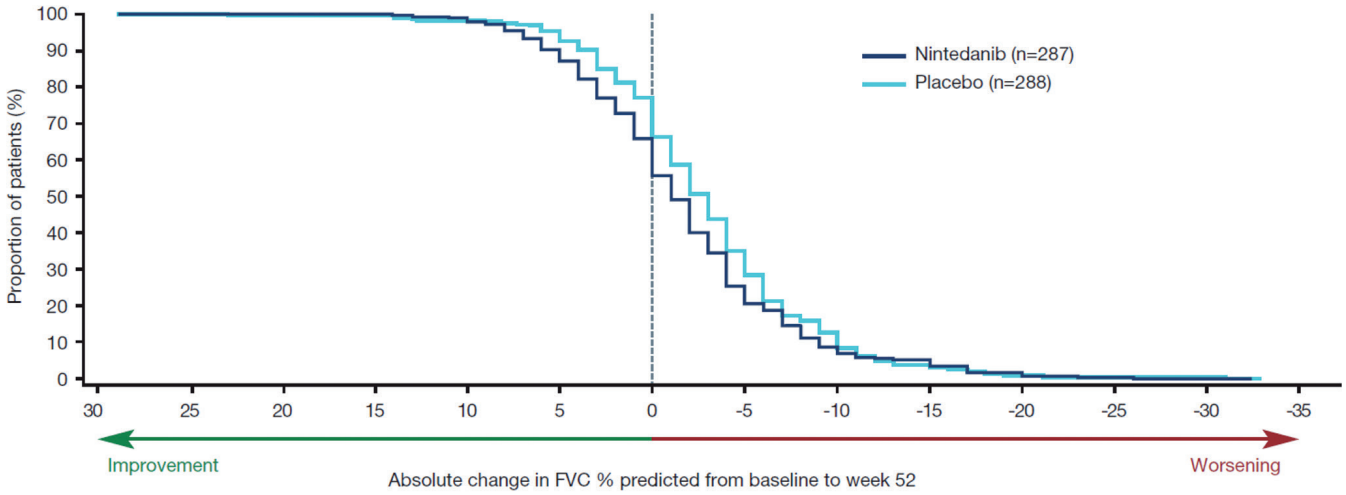


Fig. 4. Cumulative distribution of patients by change in FVC % predicted over 52 weeks in the SENSCIS trial (45).

that the decline in FVC observed over 52 weeks in patients with lcSSc-ILD was still clinically relevant, highlighting that patients with lcSSc should be viewed as at risk of development and progression of SSc-ILD.

Learning 3: The course of SSc-ILD is variable and unpredictable

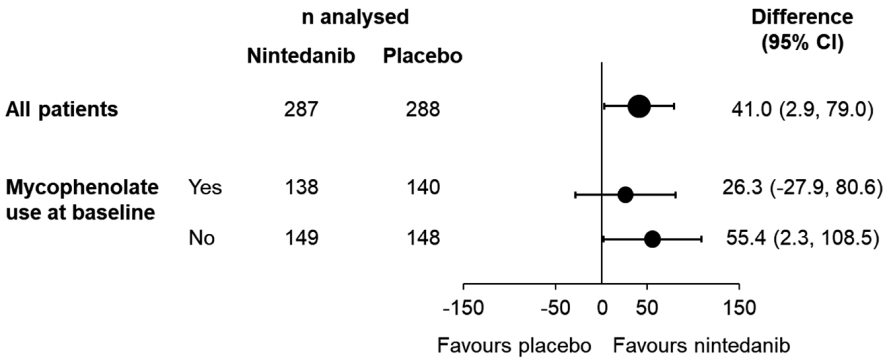
Previous studies have shown that the course of SSc-ILD is variable, with some patients experiencing periods of relative stability and others progressive decline (3, 32). This variability was also evident in the SENSCIS trial. Not all patients experienced progression of SSc-ILD during the trial. In the placebo group, about a third (33.7%) of patients did not have any decline in FVC % predicted over 52 weeks (24). The proposed threshold for improvement of FVC based on data from Scleroderma Lung Studies I and II (anchored to the health transition question from the Medical Outcomes Short Form-36) is a 3-unit increase in FVC % predicted. Over 52 weeks of the SENSCIS trial, 14.9% of patients in the placebo group had an increase in FVC meeting this threshold (24).

Risk factors identified for progression of SSc-ILD include early disease (33), elevated inflammatory markers (34, 35) and progression of skin fibrosis (36). In the placebo group of the SENSCIS trial, the rate of decline in FVC was greater in patients with <18 months since first non-Raynaud symptom (-167.8 mL/year), elevated inflammatory markers, defined as C-reactive protein ≥6 mg/L and/or platelets ≥330 x 10^9/L (-100.7 mL/year), or significant skin fibrosis (mRSS ≥18) (-131.7 mL/year) than in the overall trial population (-93.3 mL/year) (37). However, although certain subgroups of patients in the SENSCIS trial were at higher risk of progression, it was not possible to make a robust prediction of the decline in FVC based on baseline characteristics. In an analysis performed using a flexible modelling approach, which considered the extent of fibrotic ILD and FVC as continuous variables, there was only weak evidence of an association between a greater extent of fibrotic ILD on HRCT at baseline and a greater decline in FVC over 52 weeks (38). The rate of decline in FVC was also similar between patients with and without cough or dyspnoea at baseline (17) and between patients who were ATA positive and ATA negative (31) (Fig. 3). These data support the monitoring of all patients with SSc-ILD for progression, even those with no established risk factors. Experts recommend that monitoring should include pulmonary function tests, assessment of symptoms and quality of life (15, 16, 39, 40). In cases of worsening of lung function or symptoms, repeat HRCT may be indicated (15, 39, 40). Potential causes of deterioration in lung function or symptoms other than ILD, such as development or worsening of pulmonary hypertension (41), should be considered.

Learning 4: Treatment with nintedanib slows the progression of SSc-ILD

In the SENSCIS trial, the rate of decline in FVC over 52 weeks was -52.4 mL/year in the nintedanib group *versus* -93.3 mL/year in the placebo group (difference: 41.0 mL/year [95% CI: 2.9, 79.0]; p=0.04) (12). This corresponded to a relative reduction in the rate of FVC decline of 44%, which was similar to that observed in trials in patients with IPF (49%) and in patients with other types of progressive pulmonary fibrosis (57%) (42-44). For nearly all thresholds of decline in FVC % predicted, the proportion of patients with that decline was smaller in the nintedanib group than in the placebo group (Fig. 4) (45). Over 52 weeks, 20.6% of patients in the nintedanib group and 28.5% of patients in the placebo group had an absolute decline in FVC % predicted >5% (45).

Almost half of the patients in the SENSCIS trial (48%) were taking a stable dose of mycophenolate at baseline (median dose: 2000 mg/day). The absolute effect of nintedanib versus placebo on reducing the rate of decline in FVC over 52 weeks was lower in patients taking than not taking mycophenolate (difference 26.3 *vs.* 55.4 mL/year), but the relative effect of nintedanib was similar between these subgroups (reductions of 40% and 46%, respectively) (Fig. 5) (46). Of note, patients taking both mycophenolate and nintedanib lost 43.3 mL of FVC over 52 weeks, which is close to the loss of



Patients taking mycophenolate were required to have been on a stable dose for ≥6 months before randomization.
Treatment-by-time-by-subgroup interaction: p=0.45.

Fig. 5. Rate of decline in FVC (mL/yr) over 52 weeks in the SENSCIS trial in patients randomized to nintedanib and placebo in subgroups based on use of a stable dose of mycophenolate at baseline (46).

FVC that would be expected in healthy individuals of the same age (26.2 mL) (18).

The relative effect of nintedanib versus placebo on reducing the rate of decline in FVC was consistent across subgroups based on baseline characteristics including age, sex, race, time since first non-Raynaud symptom, ATA status, dcSSc vs lcSSc, mRSS, FVC % predicted, GAP stage, CPI, extent of fibrotic ILD on HRCT, and the presence of cough or dyspnoea at baseline (12, 17, 31, 37, 38, 47, 48). Data from SENSCIS-ON, the open-label extension of the SENSCIS trial, showed that over 148 weeks of SENSCIS-ON, FVC declined at a similar rate to that observed in the nintedanib group of the SENSCIS trial, supporting the long-term efficacy of treatment (49, 50). Taken together, these findings suggest that nintedanib should be considered as a treatment option for patients with fibrosing SSc-ILD.

Learning 5: The side-effects of nintedanib need to be managed

Consistent with the adverse event profile of nintedanib observed in patients with other ILDs (42, 43), the side-effects of nintedanib in patients with SSc-ILD in the SENSCIS trial were mainly gastrointestinal events (12, 13). In the nintedanib and placebo groups, respectively, diarrhoea was reported in 75.7% and 31.6% of patients, nausea in 31.6% and 13.5% of patients, and vomiting in 24.7% and 10.4% of patients over 52 weeks (12). Clinicians should be aware of these potential side-effects of nintedanib, but should also investigate other potential causes of gastrointestinal problems such as intestinal dysmotility, bacterial overgrowth, gastroparesis, and side-effects of other drugs used to treat SSc (51-54).

The investigators in the SENSCIS trial were advised on how to manage the adverse events that may be associated with nintedanib through symptom management, treatment interruptions, and dose reductions from 150 mg bid to 100 mg bid (13). Over 52 weeks, 37.8% of patients treated with nintedanib had treatment interruptions and 40.6% had dose reductions, compared to 11.5% and 4.5% of patients in the placebo group, respectively. Adverse events led to permanent discontinuation of trial drug in 16.0% of patients treated with nintedanib and 8.7% of the placebo group (13). Diarrhoea was the most common reason for nintedanib treatment interruption (41.2% of interruptions), dose reduction (59.2% of dose reductions) and permanent treatment discontinuation (43.5% of permanent treatment discontinuations) (13).

The adverse events associated with nintedanib were generally consistent across subgroups by age, sex, race and weight, but nausea, vomiting and hepatic adverse events, and dose adjustments, were reported more frequently in female than male patients (13). Similar observations have been made in patients with other ILDs (55). Patients in the SENSCIS trial who had a predisposition to gastrointestinal or intestinal events at baseline were not more likely to have gastrointestinal adverse events during the trial compared with patients without such a predisposition (13). The adverse event profile of nintedanib was generally similar between subgroups by use of mycophenolate at baseline (46). The proportion of patients who reported diarrhoea, or who had adverse events leading to permanent discontinuation of nintedanib, were no more common in the patients who were taking mycophenolate (46).

The safety profile of nintedanib in SENSCIS-ON was consistent with that reported in the nintedanib group of the SENSCIS trial (49, 50). Over 148 weeks, adverse events led to permanent discontinuation of nintedanib in 14.7% of patients who continued nintedanib in SENSCIS-ON (having taken nintedanib in the SENSCIS trial) and 29.1% of patients who initiated nintedanib in SENSCIS-ON (50).

Learning 6: Management of SSc-ILD requires a holistic approach

SSc is a heterogeneous disease associated with a variety of manifestations. In the SENSCIS trial, nintedanib did not have a significant effect on skin fibrosis as measured using the mRSS (12). Treatment with nintedanib did not improve patients' quality of life (12). Nintedanib should not be regarded as a treatment for manifestations of SSc other than ILD. The management of patients with SSc requires a holistic mindset. A multidisciplinary approach is likely to provide the best results (56). Screening for comorbidities such as pulmonary hypertension (41) or cardiac involvement (57) is an important element of care. In addition to drug therapies to manage manifestations of the disease and comorbidities, supportive care, pulmonary rehabilitation and individualised patient education and support should be part of the package of care (58, 59).

Conclusions

The SENSCIS trial provided valuable insights into the course and impact of SSc-ILD. Patients had impaired FVC at baseline and experienced a marked decline in FVC over 52 weeks, which was largely unpredictable based on baseline characteristics. Treatment with

nintedanib reduced the rate of decline in FVC when used as monotherapy or as add-on to mycophenolate. The side-effects of nintedanib were mostly gastrointestinal and were manageable for most patients. These data support the importance of prompt identification and treatment of SSc-ILD and the consideration of nintedanib as a treatment option.

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Competing interests

S. Assassi reports consultancy fees from Boehringer Ingelheim, CSL Behring, AstraZeneca, TeneoFour and aTyr, and grant support to his institution from Boehringer Ingelheim and Janssen.

S. Tumuluri is on the speakers' bureau for Boehringer Ingelheim, Lilly, Janssen, AstraZeneca, Scipher Medicine, Labcorp, ANI Pharmaceuticals, Amgen, Sanofi.

R.W. Levin reports being a member of the speakers bureau for Boehringer Ingelheim, Scipher, Exagen, AbbVie, GlaxoSmithKline and acting as a consultant for Janssen, AbbVie, AstraZeneca, Scipher, Exagen.

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