Teresa Bruni[1,2], Francesco Varone[2]

teresbruni@gmail.com

Journal club

The adoption of nintedanib in systemic sclerosis: the SENSCIS study

Commentary on:

Distler O, *et al*. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019; 380: 2518–2528.

Context

We live in an era of respiratory medicine in which there is increasing awareness of interstitial lung diseases (ILDs). This is probably due to the publication of evidence-based guidelines [1, 2] and the discovery of newer drugs [3, 4]. These advances are particularly evident for idiopathic pulmonary fibrosis (IPF), which is to date the only fibrotic disease with specific pharmacologic-approved treatments. The burgeoning interest in pulmonary fibrosis has recently shifted its focus to the possibility of using therapeutic interventions available for IPF on other non-IPF ILDs, including pulmonary fibrosis secondary to systemic sclerosis (SSc). ILD represents one of the most relevant complications of SSc [5], but a standard treatment has yet to be achieved. Currently, the therapeutic management of SSc-ILD includes a "wait and see" approach in patients with a slow functional decay, and an immunosuppressive strategy (cyclophosphamide or mycophenolate) in patients with progressive ILD [6]. The Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) trial [7] explored the use of nintedanib, an intracellular inhibitor of tyrosine kinases currently approved for IPF, in scleroderma patients.

Methods

The SENSCIS study was a 52-week randomised double-blind trial recruiting 580 patients with a diagnosis of SSc, according to the most recent American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria [5], with a secondary ILD recognised through a high-resolution computed tomography (HRCT) scan, involving at least 10% of the lungs. Forced vital capacity (FVC) and diffusing capacity for carbon monoxide (D_{LCO}) were required to be more than 40% and between 30% and 89% of their respective predicted values. Significant pulmonary hypertension (PH) was one of the key exclusion criteria.

After 1:1 ratio randomisation, patients were assigned to nintedanib 150 mg twice daily or placebo. Background treatment with up to 10 mg·day^{-1} of prednisone, or with a 6-month stable dose of mycophenolate (MMF) or methotrexate was also permitted.

The primary end point of the study was the annual rate of decline in FVC. Key secondary end points were absolute change from baseline in modified Rodnan skin score (mRSS) and St. George's

Cite as: Bruni T, Varone F. The adoption of nintedanib in systemic sclerosis: the SENSCIS study. *Breathe* 2020; 16: 200005.

@ERSpublications
Nintedanib shows a statistically significant effect on lung function decay in patients with ILD secondary to systemic sclerosis, but no effect on skin fibrosis and on health-related quality of life
http://bit.ly/2vfJRj7

Respiratory Questionnaire (SGRQ) at week 52. Other secondary endpoints were the percentage change of FVC and D_{LCO} and the absolute change in digital ulcer burden from baseline values.

Main results

Patients included in the trial had a mean age of 54.0±12.2 years; women were 76.7% and 73.6% of patients in nintedanib and placebo groups, respectively. The mean FVC and D_{LCO} were respectively 72.5±16.7% and 53.0±15.1% of their predicted values. Almost half of the patients in both nintedanib and placebo arms were background medications naive, while the remaining 50% were in treatment with MMF. The analysis was conducted in 576 patients who received at least one dose of nintedanib or placebo.

According to the primary analysis, the nintedanib group showed a lower annual rate of decline in FVC (–52.4±13.8 mL·year^{-1}) than the placebo group (–93.3±13.5 mL·year^{-1}). The difference was 41.0 mL per year (95% confidence interval 2.9–79.0; p=0.04), with a relative rate of reduction in FVC of 44% [fig. 1]. Moreover, in the nintedanib arm, patients who were taking mycophenolate at baseline presented a minor rate of change in FVC (–40.2 mL) than naive patients (–63.9 mL).

No significant absolute change from baseline was observed for mRSS and SGRQ.

Both arms presented an analogous rate of mortality and a comparable number of severe adverse events. The safety and tolerability profile of nintedanib in scleroderma patients was similar to that of patients with IPF. Gastrointestinal (GI) adverse events were more common in SSc patients (regardless the arm of the study) than in IPF, probably due to the known GI involvement of scleroderma. Diarrhoea, vomiting and elevation in liver enzymes were the main adverse events reported in the nintedanib group. The percentage of patients who discontinued the assigned intervention because of adverse events was 16% in the nintedanib arm and 8.7% in the placebo arm.

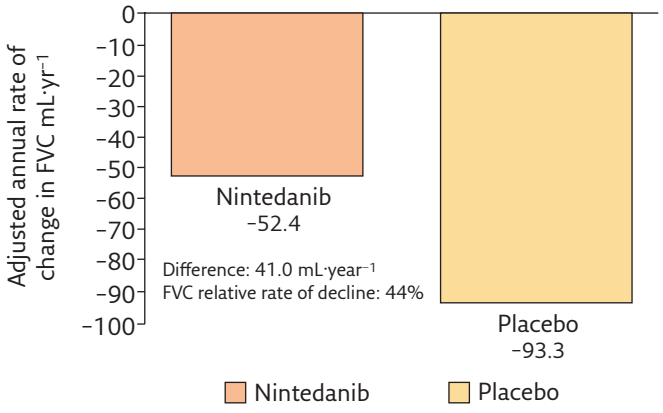

Figure 1 *Annual rate of decline in FVC: Nintedanib* versus *placebo.*

Commentary

SSc-ILD is mainly characterised by the nonspecific interstitial pneumonia radiological and/or histological pattern [5]; only a minority of patients with scleroderma may exhibit the usual interstitial pneumonia (UIP) pattern, which is typical of IPF. Nevertheless, since similarities have been demonstrated in some phases of the pathogenetic cascade between IPF and SSc-ILD (such as epithelial and/or endothelial cell injury and platelet-derived growth factor receptor overexpression [8]), it was hypothesised that nintedanib could show benefit also in patients with SSc-ILD.

Nintedanib is a multi-target tyrosine kinase inhibitor, approved for use in IPF by the U.S. Food and Drug Administration (FDA) in 2014 and by the European Medicines Agency (EMA) in 2015. The two INPULSIS studies clearly showed efficacy of this drug in slowing the rate of functional decline [3]. The most commonly reported adverse events from patients treated with nintedanib are diarrhoea, hepatic enzyme elevation and increased risk of bleeding [9]. The efficacy and safety profile of nintedanib described in patients with IPF also prompted the SENSCIS study design.

The design of SENSCIS and INPULSIS studies was very similar. The main endpoint of SENSCIS, namely the annual rate of decline in FVC measured in millilitres per year, was the same of INPULSIS, while in the most important SSc-ILD trials [10, 11] the change in the percentage value of FVC compared to baseline was the primary outcome. Other key secondary endpoints were the absolute change from baseline of mRSS and SGRQ score. The mRSS, a feasible score of skin thickness which generally reflects an associated internal organ involvement and increased mortality risk [12], is also an almost universally used endpoint in SSc clinical trials [13]. The SGRQ is a tool designed to assess the health-related quality of life in patients with chronic respiratory diseases, which correlates with the perceived breathlessness, exertional capacity and HRCT abnormalities also in patients with SSc-ILD [14].

The SENSCIS trial was a positive study, due to the statistically significant effect of nintedanib on lung function decay. Moreover, even if patients where not randomised to MMF use, the combination of nintedanib and mycophenolate has shown the lowest decline in pulmonary function.

Nonetheless, important elucidation on its results are necessary. The first comment regards the difference between the populations studied. In the SENSCIS trial, patients were younger and mostly women, while in INPULSIS, the patients were older and largely men.

The second comment regards the rate of progression of SSc-ILD as compared to IPF. In the INPULSIS trials, the nintedanib and placebo arms showed an annual rate of decline in FVC of –113.6 mL·year^{-1} and –223.5 mL·years^{-1}, respectively [fig. 2]. In the SENSCIS study, the same

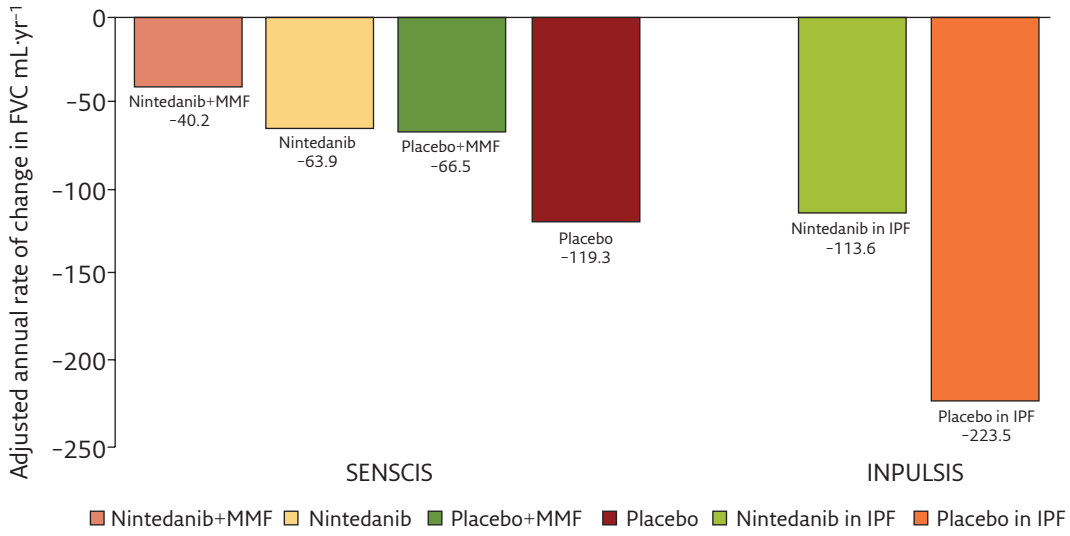

Figure 2 *Annual rate of decline in FVC: SENSCIS* versus *INPULSIS.*

measurement in nintedanib and placebo arms was of –52.4 mL·year^{-1} and –93.3 mL·year^{-1}, respectively. Even if the relative rate of reduction in FVC compared to placebo was similar (49% *versus* 44% in INPULSIS and SENSCIS, respectively), the difference in the annual rate of decline in FVC in the placebo arms between the two trials was 130.2 mL·years^{-1}. In other words, the rate of decline of the placebo arm from SENSCIS was lower than the nintedanib arm from the INPULSIS. This implies that the two populations studied are markedly different and no convincing comparison between them could be done.

Moreover, nintedanib revealed no effect on skin fibrosis and on health-related quality of life, evaluated through the mRSS and the SGRQ, respectively. These results highlight how nintedanib does not seem to play any role on the multiorgan involvement of SSc. Furthermore, the quality of life of SSc patients might be compromised by the presence of the side effects of the drug, despite a reduced deterioration of lung function.

The SENSCIS trial showed the best efficacy in patients taking both nintedanib and MMF, with no described increase in side effects. This result could pave the way to newer studies exploring the efficacy of the combination of the two drugs in SSc and other connective tissue disease-associated ILDs, such as rheumatoid arthritis-associated ILD, that are currently lacking well-designed clinical research. Combination therapy has been advocated by experts as an option for future management of IPF [15] and has already been explored in phase 2 [16], phase 3 [17, 18] and phase 4 studies [19].

Implications for practice

Currently, ILD and PH are the main causes of death in patients with SSc. To date, the management of SSc-ILD has been based on the use of immunosuppressants. In September 2019, after the SENSCIS study, nintedanib was approved by FDA for the treatment of SSc- ILD in the USA, while in Europe the approval by EMA is still pending. An open-label extension of SENSCIS study to evaluate the long-term effectiveness of nintedanib in patients with SSc-ILD is currently ongoing. Furthermore, the results of the INBUILD trial [20] showed outstanding results for the use of nintedanib in progressive fibrosing ILDs, including pulmonary fibrosis secondary to scleroderma. The positive results of the SENSCIS trial on lung function could pave the way for a newer therapeutic approach to these patients, including combination or sequential regimens.

Nowadays SSc-ILD is managed primarily by rheumatologists in many institutions, but, since nintedanib is a drug already prescribed for patients with IPF, pulmonologists are already familiar with its handling.

The use of nintedanib for SSc-ILD patients will desirably imply a partnership between pulmonologists - who better know the drug - and rheumatologists – who better know the disease. As for IPF, multidisciplinarity and cooperation among different specialities might better improve the overall management of these fragile patients.

Affiliations

Teresa Bruni[1,2], Francesco Varone[2]

[1]Malattie dell'apparato Respiratorio, Università Cattolica del Sacro Cuore Sede di Roma, Rome, Italy. [2]Respiratory Medicine, Policlinico Universitario Agostino Gemelli, Rome, Italy.

Conflict of interest

T. Bruni has nothing to disclose. F. Varone reports personal fees from Boehringer Ingelheim and Roche outside the submitted work.

References

1. Raghu G, Remy-Jardin M, Myers JL, *et al.* Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.
2. Raghu G, Rochwerg B, Zhang Y, *et al.* An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. an update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med* 2015; 192: e3–e19.
3. Richeldi L, du Bois RM, Raghu G, *et al.* Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2071–2082.
4. King TE, Bradford WZ, Castro-Bernardini S, *et al.* A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2083–2092.
5. Schoenfeld SR, Castelino FV. Interstitial lung disease in scleroderma. *Rheum Dis Clin North Am* 2015; 41: 237–248.
6. Cottin V, Brown KK. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). *Respir Res* 2019; 20: 13.
7. Distler O, Highland KB, Gahlemann M, *et al.* Nintedanib for systemic sclerosis-associated interstitial lung disease. *N Engl J Med* 2019; 380: 2518–2528.
8. Herzog EL, Mathur A, Tager AM, *et al.* Review: interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: how similar and distinct? *Arthritis Rheumatol* 2014; 66: 1967–1978.
9. Varone F, Sgalla G, Iovene B, *et al.* Nintedanib for the treatment of idiopathic pulmonary fibrosis. *Expert Opin Pharmacother* 2018; 19: 167–175.
10. Tashkin DP, Elashoff R, Clements PJ, *et al.* Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; 354: 2655–2666.
11. Tashkin DP, Roth MD, Clements PJ, *et al.* Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 2016; 4: 708–719.
12. Khanna D, Furst DE, Clements PJ, *et al.* Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. *J Scleroderma Relat Disord* 2017; 2: 11–18.
13. Mendoza FA, Keyes-Elstein LL, Jimenez SA. Systemic sclerosis disease modification clinical trials design: Quo vadis? *Arthritis Care Res* 2012; 64: 945–954.
14. Beretta L, Santaniello A, Lemos A, *et al.* Validity of the Saint George's Respiratory Questionnaire in the evaluation of the health-related quality of life in patients with interstitial lung disease secondary to systemic sclerosis. *Rheumatology* 2007; 46: 296–301.
15. Wuyts WA, Antoniou KM, Borensztajn K, *et al.* Combination therapy: the future of management for idiopathic pulmonary fibrosis? *Lancet Respir Med* 2014; 2: 933–942.
16. Vancheri C, Kreuter M, Richeldi L, *et al.* Nintedanib with add-on pirfenidone in idiopathic pulmonary fibrosis. Results of the INJOURNEY trial. *Am J Respir Crit Care Med* 2018; 197: 356–363.
17. Kolb M, Raghu G, Wells AU, *et al.* Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2018; 379: 1722–1731.
18. Behr J, Nathan SD, Harari S, *et al.* Sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: a phase IIb, randomised, double-blind, placebo-controlled study – rationale and study design. *Respir Med* 2018; 138: 13–20.
19. Flaherty KR, Fell CD, Huggins JT, *et al.* Safety of nintedanib added to pirfenidone treatment for idiopathic pulmonary fibrosis. *Eur Respir J* 2018; 52: 1800230.
20. Flaherty KR, Wells AU, Cottin V, *et al.* Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med* 2019; 381: 1718–1727.