Safety and efficacy of pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis and carrying a telomere-related gene mutation

To the Editor:

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and deadly interstitial lung disease (ILD). Over the past decade, familial occurrence of IPF led to the identification of genetic susceptibility traits [1]. Germline pathogenic variations in telomere-related genes (TRG) such as *TERT*, *TERC TINF2*, *DKC1*, *RTEL1*, *PARN*, *NAF1*, *ZCCHC8*, *NHP2* and *NOP10* have been detected in 20–30% of patients with familial pulmonary fibrosis (FPF) and in 1–5% of sporadic IPF [2–4]. In comparison with IPF patients, carriers of a TRG mutation are significantly younger and show an accelerated decline of forced vital capacity (FVC) [5–7]. Two drugs, pirfenidone and nintedanib, have been shown to reduce the decline of FVC in IPF patients [8, 9]. So far, two studies have reported on the safety and effectiveness of pirfenidone in patients with a TRG mutation [6, 7] whereas no study has investigated nintedanib in this specific population. Thus, the aim of this retrospective study was to assess safety and efficacy of nintedanib and pirfenidone in IPF patients with a TRG mutation.

Patients from specialised European ILD centres from France (OrphaLung network), the Netherlands, Spain, Greece, Belgium and Switzerland were included in the study if they fulfilled the following criteria: 1) a multidisciplinary team diagnosis of IPF, 2) carrier of a TRG variant interpreted as pathogenic and referred to as a mutation in the remaining manuscript, and 3) received at least one dose of pirfenidone or nintedanib.

Demographical data, clinical status, treatment continuation (as assessed by the physician in charge), adverse events (clinical and biological) and all lung function test results available were collected, at diagnosis, at antifibrotic treatment initiation and during treatment follow up. Time zero was set to the date of first antifibrotic treatment.

In a first analysis, the impact of the first antifibrotic treatment on the evolution of FVC was analysed by modelling the longitudinal FVC measurement with a mixed-effects model. The evolution after treatment was then compared to what a model fit with pre-treatment data only would predict. Confidence intervals were obtained by nonparametric bootstrap. In a second analysis, the post-treatment evolution was compared between groups of patients receiving pirfenidone or nintedanib using inverse probability of treatment weighting. The evolution of FVC was then compared between groups using a weighted linear mixed effects model, where the treatment effect on the slope of FVC was represented by the time by group interaction. All analyses were carried out using the R statistical software version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria), with the Hmisc, lme4, WeMix and boot packages.

We identified 89 patients with IPF and who were carriers of a TRG mutation: *TERT* (n=65), *TERC* (n=16), *RTEL1* (n=5) or *PARN* (n=3). The mean±SD age at diagnosis was 59.8±9.4 years. At treatment initiation, median (interquartile range) FVC was 84.3% (70.0–94.2%) of the predicted value and median diffusing capacity of the lung for carbon monoxide was 45.8% (38.0–53.0%) pred. At treatment initiation, patients treated with pirfenidone (n=55) or nintedanib (n=34) were similar in terms of age, smoking, mutation status, delay between diagnosis and treatment initiation or disease severity.

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This study suggests that pirfenidone and nintedanib can be used safely in IPF patients with a telomerase related gene mutation and that both drugs reduce FVC decline. These results should be confirmed in a larger prospective study. https://bit.ly/3k7b4Zx

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The median (interquartile range) transplant-free survival was 64.9 months (3.0–117.2 months) and the duration of treatment was 22.0 months (13.5–36.5 months), without significant difference between the two groups (figure 1a). No patient from this analysis received danazole. While being treated, 12 patients experienced an acute exacerbation, nine patients received a lung transplantation and 22 patients died. All deaths were caused by respiratory insufficiency due to progression of lung fibrosis.

During the follow-up, nine patients treated with pirfenidone (25.9%) and 12 patients treated with nintedanib (32.4%) stopped treatment due to gastrointestinal disorders. Three patients (3.7%), two treated with pirfenidone and one with nintedanib, showed an increase in liver enzymes, leading to treatment termination. Three patients treated with pirfenidone (5.6%) showed a skin-related side-effect leading to treatment cessation. Whilst 27 (30.3%) patients presented initially with blood abnormalities in the context of TRG mutation, none of the 89 patients experienced a haematological adverse event.

To assess anti-fibrotic efficacy, we collected 581 lung function test results. The longitudinal change in FVC (in litres), modelled in a linear mixed effects model, was significantly reduced compared to the predicted evolution of the FVC (figure 1). The mean FVC decline was 39 mL per month (95% CI 23–55 mL per month) before treatment, and 22 mL per month (95% CI 17–28 mL per month) in the next 30 months after treatment initiation (p=0.026).

We compared the slope of FVC in patients receiving pirfenidone and nintedanib, with a weighting on the propensity score to correct any differences in baseline characteristics. After adjustment for confounders, the slope of FVC in the 30 months following treatment was 15 mL per month (95% CI 5–24 mL per month) with nintedanib and 25 mL per month (95% CI 17–32 mL per month) with pirfenidone (p=0.12).

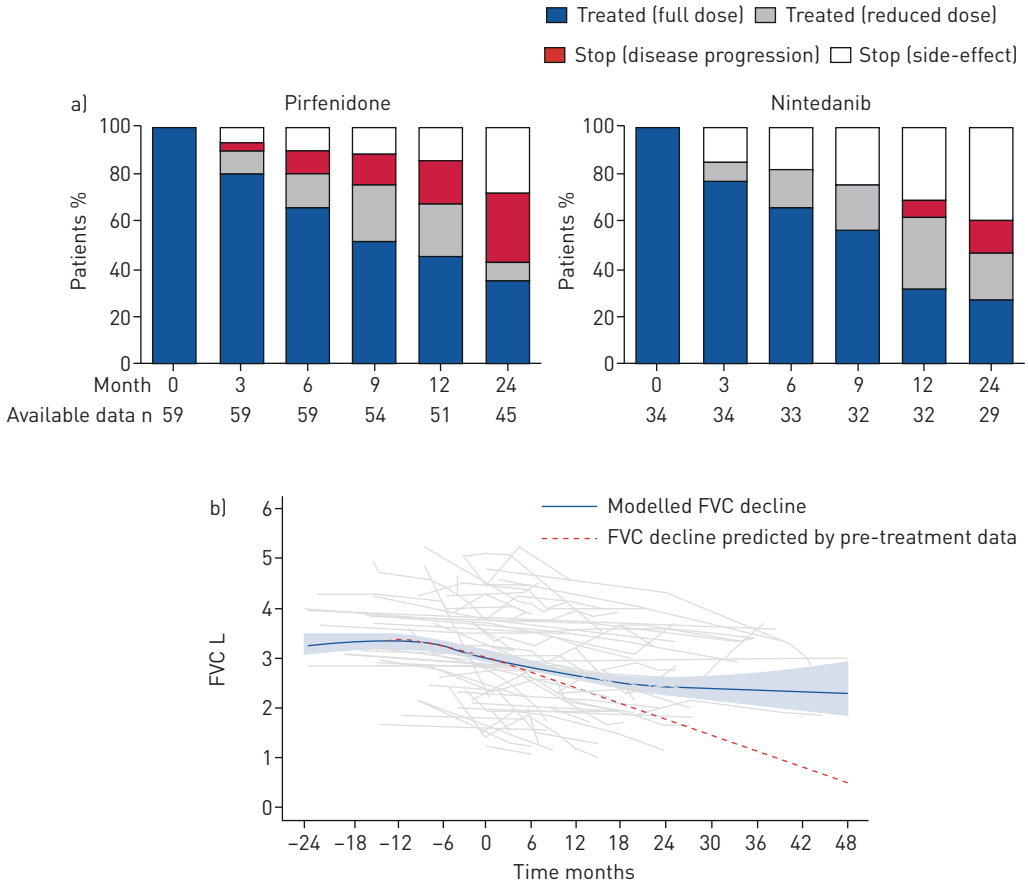

FIGURE 1 a) Treatment continuation of pirfenidone and nintedanib. This figure shows the percentage of patients treated by pirfenidone (left panel) or nintedanib (right panel). Blue column represents the percentage of patients treated by antifibrotic treatment at full dose (blue background) or reduced dose (grey background). Red column represents the percentage of patients who stopped the treatment due to disease progression (including patients that died or received a lung transplantation) (red background) or due to a side-effect (white background). b) Longitudinal forced vital capacity (FVC) decline of idiopathic pulmonary fibrosis (IPF) patients carrying TRG mutation treated by nintedanib or pirfenidone. The blue curves shows the FVC data collected for each patient, with a flexible model of the mean estimated by splines, in a mixed effects model. The curve represented by red dashes shows the predicted evolution of the FVC obtained with data before treatment only (until time zero).

In this multicentre European retrospective study, we observed that antifibrotic treatment was associated with a reduced decline of FVC in IPF patients with TRG mutations. We did not observe any unexpected adverse event, nor any difference between pirfenidone and nintedanib in terms of efficacy.

As previously reported in patients with TRG mutations [6, 7], patients in this cohort were younger and showed a more rapid decline of lung function as compared to previous cohorts of sporadic IPF patients [10]. Because of specific haematological and liver diseases associated with TRG mutation [11], we were concerned about an increased risk of liver toxicity and haematological adverse events [8, 9]. Fortunately, our data suggest that the side-effect profile of pirfenidone or nintedanib in patients with TRG mutation is similar with those observed in the general IPF population [8, 9]. 27 patients (30.3%) had to stop the treatment due to a side-effect, mostly gastrointestinal. These results correspond to the usual proportion of patients stopping use of antifibrotic drugs in reported retrospective and prospective cohorts of IPF patients [10, 12–14].

We observed that antifibrotic drugs were associated with a reduced decline of FVC in IPF patients carrying TRG mutations. Our results are in line with a *post hoc* analysis of the INSPIRE, CAPACITY and ASCEND trials in patients carrying a rare TRG variant. Patients with a rare TRG variant had a more rapid decline of FVC than IPF patients without a TRG variant [6], though pirfenidone was still associated with a reduced decline of FVC compared to placebo in this subpopulation [6].

Our study is the first to assess the benefit of nintedanib in this specific population, highlighted by the number of rare and unique mutations, and our results support the safety and efficacy of nintedanib in these patients.

This study has several limitations. Treatment continuation was self-reported by the patient, and we cannot ensure the presence of unreported adverse events due to the retrospective nature of the study. In addition, due to the limited number of patients included, we were neither able to evaluate the efficacy of antifibrotic treatment according to the nature of the mutation status nor to compare the efficacy of pirfenidone and nintedanib. With respect to the very limited number of patients who switched from pirfenidone to nintedanib, we did not assess efficacy or safety of the second line of anti-fibrotic treatment. Finally and most importantly, we compared the observed decline of FVC to predicted decline, a comparison which can suffer many biases, and which cannot replace a randomised control trial.

In conclusion, this study suggests that pirfenidone and nintedanib can be used safely in IPF patients with a TRG mutation and that both drugs reduce FVC decline. These results should be confirmed in a larger prospective study.

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In an exception to usual *ERJ* policy, a supplementary file containing a tabulated summary of the pathogenic telomerase-related gene mutations reported in this research letter is available from erj.ersjournals.com

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