# Safety and efficacy of pirfenidone in patients carrying telomerase complex mutation

*To the Editor:*

The most frequent mutations in familial pulmonary fibrosis (FPF) involve genes of the telomerase complex such as *TERT*, *TERC*, *RTEL1*, *PARN* or *DKC1* [1]. Mutations within *TERT* and *TERC* are found in 15–20% of FPF and are associated with blood, liver and skin disorders. Idiopathic pulmonary fibrosis (IPF) is the most frequent multidisciplinary diagnosis in *TERT* and *TERC* mutation carriers [1, 2]. Treatment of IPF in patients who carry a *TERT* or *TERC* mutation has not been previously defined. Recently, danazol, a synthetic androgen, was shown to increase telomere length, and seemed to stabilise forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (*D*LCO) in telomerase complex mutation carriers [3]. Pirfenidone has been shown to reduce FVC decline and to improve progression-free survival in IPF [4, 5]; however, pirfenidone has not been specifically evaluated in telomerase complex mutation carriers. The aim of this multicentre retrospective study was to evaluate the safety and efficacy of pirfenidone in patient carriers of *TERT*/*TERC* mutations.

All patients from France, Athens (Greece) and Barcelona (Spain) with pulmonary fibrosis and a pathogenic mutation within *TERT* and *TERC*, who received at least one dose of pirfenidone, were included in the study. We collected clinical status data, self-reported adherence, adverse events and pulmonary function test results, at initial diagnosis, at pirfenidone initiation, and at each visit up to pirfenidone stopping or the last follow-up visit. Disease progression was defined by an acute exacerbation [6] or a relative decrease of FVC >10% or a relative decrease of *D*LCO >15% compared to baseline. In order to assess pirfenidone efficacy, we compared the rate of FVC and *D*LCO decline before and after treatment initiation, using a nonlinear mixed effect model [7]. Random-coefficient models with a random intercept and a random slope were fitted to assess the rate of change in the main parameters (FVC in litres, FVC as % predicted and *D*LCO as % predicted) over the study period. In these models, interaction of pirfenidone treatment and time were introduced in the model to assess the impact of treatment on the rates of change over time. The random slopes were based on time of lung function test assessment. Effect estimates were adjusted for sex and age at study entry. Deaths and drop-outs were considered as missing data. No attempt was made to impute missing data. Annualised declines in the main parameters were assessed by the empirical Bayes estimates. The R software (3.0.2) (www.r-project.org) was used together with the "nlme" package.

We identified 33 patients meeting the inclusion criteria, including 12 patients previously reported [1]. Among them 21 had a familial history of interstitial lung disease (ILD) and/or liver cirrhosis and/or haematological disease. All the patients had a pulmonary fibrosis, including 31 (93.9%) IPF, one (3.0%) rheumatoid arthritis-ILD and one (3.0%) pleuropulmonary fibroelastosis. 13 (39.3%) patients had blood abnormalities and 10 (30.3%) patients showed liver abnormalities.

The follow-up data were available for all patients at 3 and 6 months (figure 1a). 24 patients were male and the mean±SD age at diagnosis was 59.8±6.0 years. 31 patients carried a *TERT* mutation and two patients carried a *TERC* mutation. At treatment initiation, the mean±SD FVC was 78.6±17.1% of the predicted value and the mean±SD *D*LCO value was 46.6±15.7% of the predicted value. The median survival time was 5.76 years (range: 0.25–8.42 years) and the median transplant-free survival time was 3.0 years (range: 0.25–7.00 years). During follow-up the mean±SD FVC decline was 314.5±107.6 mL per year. Eight patients

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**In this retrospective study, a beneficial effect of pirfenidone on lung function decline could not be demonstrated in patients carrying *TERT/TERC* mutation** http://ow.ly/VYpJ30i5wSr

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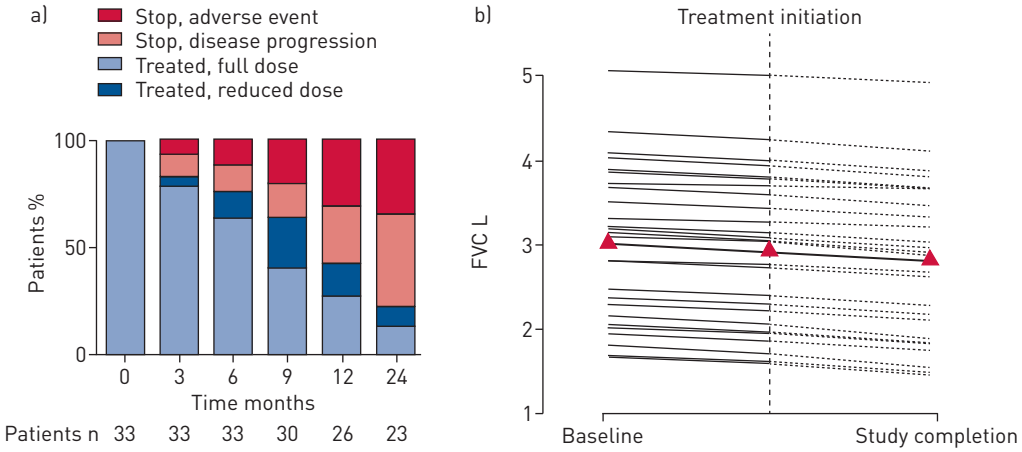


FIGURE 1 a) Adherence to treatment and cause of discontinuation. The numbers at the bottom represent the number of patients with available data at each time. b) Model of annualised decline of forced vital capacity (FVC) before (solid lines) and after (dotted lines) pirfenidone initiation. Red triangles indicate the mean FVC.

experienced an acute exacerbation, four patients received lung transplantation and nine patients died, all from respiratory failure, all of them where then considered as progressors.

The median time between diagnosis and treatment initiation was 10.1 months (range: 0–66.5 months) and the median duration of treatment was 237 days (range: 31–1461 days). After 3 months, 27 (81.8%) out of 33 patients still received pirfenidone, including 26 at the full dose (2403 mg daily). One year after pirfenidone initiation, 15 (57.7%) out of 26 patients had stopped the treatment, including seven (26.9%) due to disease progression and eight (31%) because of adverse events or poor tolerance (figure 1a).

28 patients (84.8%) experienced at least one adverse event, including gastro-oesophageal reflux (33.3%), nausea (30.3%), diarrhoea (30.3%), weight loss (24.2%), anorexia (24.2%) and photosensitivity (12.1%). Seven patients experienced adverse events leading to termination of treatment (gastrointestinal, n=2; increased transaminases, n=2; weight loss, n=1; toxidermia, n=2). We did not observe any haematological complications in this cohort [8].

Regarding efficacy, we included in the analysis the patients who received pirfenidone for at least 3 months, *i.e.* 27 (82%) patients. All the patients included in efficacy analysis had data available at 3 months and 6 months. At 9 months and 12 months, the data are missing for two and four patients (*i.e.* a total of six patients at 12 months), respectively. The median time between diagnosis and pirfenidone initiation was 9.1 months (range: 0.0–71.0 months). The median duration of efficacy data available for this group was 10.0 months (range: 5.0–48.2 months).

Adjusted decline of FVC was 161.8±31.2 mL per year (3.47±1.06% of predicted value) before and 235.0±49.7 mL per year (4.65±1.06% of predicted value) after pirfenidone initiation (figure 1b). There was no difference between annualised FVC decline before and after treatment initiation in ultimate value (p=0.15) or as a percentage of predicted value (p=0.43). Adjusted decline of $D_{LCO}$ was 7.52±1.65% per year before and 9.06±1.87% per year after the initiation of pirfenidone (p=0.12). There was no trend and no statistical difference between the nonprogressors (n=14) and the progressors (n=19) at initiation, with regards to sex, smoking status, age at diagnosis (data not shown). The median lead-time until pirfenidone initiation was 7.5 months (range: 0.0–55.0 months) in the nonprogressors, whereas it was 10.0 months (range: 0.0–71.0 months) in the progressors (p=0.21).

This is the first assessment of lung function decline in patients with *TERT/TERC* mutation who received pirfenidone. We observed that neither FVC decline nor $D_{LCO}$ decline was improved by pirfenidone in patients with lung fibrosis and a *TERT/TERC* mutation. The safety of pirfenidone in *TERT/TERC* mutation carriers was similar to that observed in sporadic IPF [9]. The retrospective nature and the limited number of patients included are the major limitations of this study that preclude definitive conclusions on the safety and efficacy of pirfenidone in this population. We may presume that a larger number of patients would have allowed us to show a difference in the lead-time until pirfenidone initiation between the progressors and the nonprogressors. Another limitation of the study was the self-reported adherence. However, adverse events were similar to those observed in prospective studies and in real life cohorts of sporadic IPF [10]. Despite these limitations, similar methodology to ours was previously used in retrospective works in order to demonstrate pirfenidone efficacy [9, 11]. Interestingly, the mean rate of FVC decline with pirfenidone in this cohort was numerically higher than that measured in the treated group in patients included in recent

clinical trials assessing the efficacy of pirfenidone [5] and similar to that recently measured by NEWTON *et al.* [12] in a series of 115 patients with pulmonary fibrosis and telomerase complex mutations (mean value: 300 mL per year). This series confirms our previous report that patients with *TERT* and *TERC* mutation present a poor transplant-free survival [1] and suggests that patients with *TERT* and *TERC* mutation present an increased decline of FVC when compared to sporadic IPF [10].

In conclusion, a beneficial effect of pirfenidone on lung function decline could not be demonstrated in this study, highlighting the urgent need for a prospective work to validate efficacy and safety of pirfenidone in patients carrying *TERT/TERC* mutation.

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