Lung (2019) 197:147–153
https://doi.org/10.1007/s00408-019-00203-w

INTERSTITIAL LUNG DISEASE

Pirfenidone Therapy for Familial Pulmonary Fibrosis: A Real-Life Study

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Received: 23 November 2018 / Accepted: 6 February 2019 / Published online: 13 February 2019

Abstract

Introduction Familial pulmonary fibrosis (FPF) is defined as an idiopathic diffuse parenchymal lung disease affecting two or more members of the same primary biological family. The aim of this study was to compare disease progression and tolerance to pirfenidone in a population of FPF patients who presented with radiological and/or histological evidence of UIP, and a group of idiopathic pulmonary fibrosis (IPF) patients.

Methods Seventy-three patients (19 with FPF and 54 with IPF) were enrolled and data were collected retrospectively at 6, 12 and 24 months follow-up.

Results FPF patients were statistically younger and more frequently females. A significantly greater decline in FVC and DLCO was recorded in FPF than in IPF patients at 24 months follow-up. At the 6-min walking test, walked distance declined significantly in FPF patients than IPF at 24 months. No statistically significant differences in drug tolerance or side effects were recorded between groups.

Conclusion Different rate of progression was observed in patients with IPF and FPF on therapy with pirfenidone; our findings may not be due to lack of effectiveness of therapy, but to the different natural history and evolution of these two conditions. Pirfenidone was well tolerated by FPF and IPF patients. Specific unbiased randomized clinical trials on larger populations to validate our preliminary exploratory results are needed.

Keywords Pirfenidone · Familial pulmonary fibrosis · Idiopathic pulmonary fibrosis · Therapy

Introduction

Familial pulmonary fibrosis (FPF) is defined as an idiopathic diffuse parenchymal lung disease affecting two or more members of the same primary biological family [1]. The usual interstitial pneumonia (UIP) pattern is the most frequent radiological and/or histological finding among FPF patients, although other patterns have been observed (e.g., NSIP, COP, idiopathic pleuro-parenchymal fibroelastosis, micronodules) [1–3]. Some genetic variations have been documented in FPF and idiopathic pulmonary fibrosis (IPF), suggesting that the two conditions have a similar genetic background [2, 4–8]. FPF tends to develop at an earlier age than sporadic IPF (50–60 years) and to affect males and females alike. The two diseases share some common risk factors, such as tobacco smoking. Histological and radiological UIP pattern is the commonest finding [2, 3].

Two novel molecules, pirfenidone and nintedanib, have been shown to slow the progression of IPF and are now available for clinical use [9–11]. No data are available on the efficacy of antifibrotic therapies in patients with a familial form of IPF. The aim of this study was to compare disease progression—in term of FVC, DLCO and 6MWT—and tolerance to pirfenidone treatment in a population of FPF and IPF patients.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00408-019-00203-w) contains supplementary material, which is available to authorized users.

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Methods

Seventy-three patients were enrolled, 19 with FPF and 54 with IPF. All cases were reviewed by multidisciplinary discussion among a panel of experts on interstitial lung diseases (ILD), consisting of two pulmonologists, a radiologist and a pathologist. All FPF patients had radiological and/or histological UIP patterns according to the definition of the 2011 ATS/ERS/JRS/ALAT Guidelines for IPF [12].

The study was conducted at the Regional Referral Center for Sarcoidosis and other Interstitial Lung Diseases (ILD), Respiratory Disease and Lung Transplant Unit, AOUS, Department of Medical and Surgical Sciences & Neurosciences, University of Siena, Italy.

All patients were treated with pirfenidone at the usual dose. Nineteen patients (14 with IPF and 5 with FPF) were treated on compassionate use under the Pirfenidone Named Patient Access Program, while 54 patients (40 with IPF and 14 with FPF) were treated with pirfenidone under the Italian Agency for Pharmaceutics (AIFA) regulatory registry since June 2013. AIFA criteria only contemplate the use of pirfenidone in mild-to-moderate IPF, defined as having FVC ≥ 50% of predicted value, DLCO ≥ 35% of predicted value and age under 80 years.

Retrospective analysis concerned demographics, smoking history, comorbidities and family history of pulmonary fibrosis. Pulmonary Function Tests (PFT), 6-min Walking Test (6MWT) and Arterial Blood Gas Analysis (ABGA) were done at baseline and at follow-up 6, 12 and 24 months after the start of pirfenidone therapy. Follow-up data were available for 61 out of 73 patients at 6 months (18/19 FPF patients and 43/54 IPF patients), 54/73 patients at 12 months (14/19 FPF, 40/54 IPF) and 33/73 at 24 months (10/19 FPF, 23/54 IPF). Any new events and side effects were recorded during follow-up.

Bronchoalveolar lavage (BAL), performed at diagnosis for diagnostic purposes, was available in 9/19 patients with FPF and 21/54 patients with IPF. According to ATS Guidelines, differential cell count and lymphocyte typing were performed in all patients [13]. The local ethics committee approved the study; it has been conducted in compliance with ethical standards; all patients provided written informed consent to participation.

Statistics

Non-parametric statistical tests were applied to the data. The Mann–Whitney U test was used to compare the two groups, while the Kruskal–Wallis test and two-way ANOVA were used for more complex comparisons. The Wilcoxon and Friedman tests were used to detect differences between groups for repeated measurements. Survival was analyzed by the Kaplan–Meier test. Statistical significance was set at $p < 0.05$. All data were expressed as mean ± standard deviation. We used Stat Soft (2001) and GraphPadPrism 7.0 software packages.

Results

Baseline Characteristics

Demographic data and smoking history of our cohort of patients (FPF $n = 19$, IPF $n = 54$) are reported in Table 1. The mean age of FPF patients was significantly lower than that of IPF patients (FPF 63.32 ± 8.693 years vs. IPF 68.8 ± 7.175 years; $p = 0.0141$). There were more females among FPF than IPF patients and the difference was borderline significant (42.11% in FPF and 16.67% in IPF; $p = 0.05$; $U = 266$). No patient was still a smoker at the time of analysis; the prevalence of former smokers and tobacco exposure (packs/year) was not statistically different between the two groups (Table 1). Time interval between diagnosis of the diseases and start of therapy was shorter among patients with IPF than FPF, but it did not reach significance (290.21 ± 648.48 days for IPF and 674.38 ± 738.88 days for FPF, $p = 0.08$).

GERD and hiatal hernia were more frequent in FPF than IPF patients (26.3% in FPF vs. 5.5% in IPF, $p = 0.0246$; 36.84% in FPF vs. 7.4% in IPF, $p = 0.0050$, respectively). No other difference in comorbidities at diagnosis was found. At baseline, no statistically significant differences were found in PFT, 6MWT or ABGA parameters between FPF and IPF patients (Table 1). At the time of diagnosis, 30/73 patients (9/19 with FPF and 21/54 with IPF) underwent BAL. No statistically significant differences in cell composition or lymphocyte subtypes were found between the two groups.

Respiratory Function Analysis

Patients with FPF showed a greater decline in FVC than IPF patients at 12 months; the difference reached significance at 24 months (FPF 273.8 ± 339.6 ml vs. IPF 129.5 ± 326.0 ml, $p = 0.4069$; $U = 208$; FPF 383.3 ± 520.8 ml vs. IPF 193.6 ± 374.9 ml, $p = 0.0381$, $U = 51.50$ respectively) (Table 2; Fig. 1). Patients with a more than 10% decline in FVC with respect to baseline were 27.78% in the FPF group and 16.28% in the IPF group at 6 months; 42.8% and 34.2% at 12 months; 55.5% and 45.4% at 24 months, respectively (Fig. 2).

DLCO analysis showed a significantly greater decline among FPF than IPF patients at 24 months ($p = 0.04$, $U = 21$) (Table 2). Significance was not reached at 6 and 12 months, however, at 6 months the number of patients

Table 1 Demographic characteristics and tobacco smoking history and baseline lung function parameters (PFT, ABGA and 6MWT) of FPF and IPF patients (U = Mann–Whitney test)

	FPF	IPF	Statistics
Age at start therapy (years)	63.3 ± 8.7	68.8 ± 7.2	$p = 0.0141$; $U = 319.5$
Gender *n* (%)			$p = 0.05$; $U = 266$
Male	11 (57.89%)	45 (83.33%)	
Female	8 (42.11%)	9 (16.67%)	
Tobacco history *n* (%)			$p = 0.41$
Former	9 (47.37%)	33 (61.1%)	
Never	10 (52.64%)	21 (38.9%)	
Pack/year	17.8 ± 20.3	24.4 ± 20.6	$p = 0.21$; $U = 100.5$
Baseline PFT			
FEV1 (ml)	2038 ± 716.5	2196 ± 686.9	$p = 0.25$; $U = 421$
FEV1 (% pred.)	79.78 ± 19.7	82.57 ± 19.44	
FVC (ml)	2442 ± 874.5	2674 ± 823.5	$p = 0.21$; $U = 414.5$
FVC (% pred.)	76.84 ± 22.26	78.87 ± 19.78	
FEV1/FVC	84.05 ± 6.988	81.26 ± 6.316	$p = 0,07$; $U = 371$
TLC ml	4302 ± 1030	4762 ± 1194	$p = 0.22$; $U = 311.5$
TLC (% pred.)	76,6 ± 16.03	77.7 ± 16.3	
RV (ml)	1775 ± 327.2	2028 ± 561.8	$p = 0.09$; $U = 275$
RV (% pred.)	79.31 ± 12.8	83.23 ± 22.6	
DLCO (ml/min/mmHg)	3.971 ± 1.406	3.761 ± 1.374	$p = 0.99$; $U = 373$
DLCO (% pred.)	50.5 ± 16.5	46.70 ± 14.6	
KCO (ml/min/mmHg/VA)	1.141 ± 0.2278	0.9895 ± 0.2243	$p = 0.01$; $U = 223.5$
KCO (% pred.)	81.76 ± 17.7	75.14 ± 17.7	
Baseline ABGA			
FiO_2 (%)	21.18 ± 0.7	21.66 ± 2.16	$p = 0.55$; $U = 299$
PaO_2 (mmHg)	73.58 ± 9.845	77.19 ± 8.68	$p = 0.40$; $U = 269$
$PaCO_2$ (mmHg)	42.09 ± 11.4	38,81 ± 3.66	$p = 0.39$; $U = 268.5$
SpO_2 (%)	94.08 ± 3.235	95.16 ± 1.5	$p = 0.25$; $U = 254$
PaO_2/FiO_2	347.7 ± 47.46	359.1 ± 50.86	$p = 0.52$; $U = 280$
Baseline 6MWT			
Patients on O_2-therapy (*n*, %)	2/19 (10.53%)	9/54 (16.6%)	$p = 0.71$
O_2-therapy flow—l/min (FiO_2%)	7 ± 1.41 (23.84 ± 8.617)	3.4 ± 2.5 (23.52 ± 6.51)	$p = 0.14$; $U = 2$ $p = 0.48$; $U = 438$
Walked distance (m)	310 ± 124.1	313.6 ± 89.86	$p = 0.94$; $U = 445$
Final SpO_2 (%)	89.8 ± 3.7	91.54 ± 4.27	$p = 0.10$; $U = 353$

with a more than 15% decrease in DLCO with respect to baseline was significantly higher in FPF than IPF patients at 6 months (75% vs. 12%, $p = 0.001$).

Regarding the 6MWT, the walked distance decline was significantly greater in FPF than IPF patients at 24 months (61.42 ± 106.8 m vs. 52.14 ± 127.4 m, $p = 0.0393$, $U = 30.50$) (Table 2; Fig. 3). In line with this, the percentage of patients who showed a more than 50 m reduction in distance walked at 12 months was significantly higher among FPF than IPF patients (77.7% vs. 33.33%, $p = 0.0262$). The number of patients who needed oxygen during the 6MWT was higher in the FPF group, almost reaching significance at 24 months ($p = 0.066$) (Supplementary Material, Table 1 SM). Other variables recorded during the 6MWT, such as amount of oxygen required, final test SpO_2 and final BORG Scale Index, are also reported in Table 1 SM.

Survival

A total of 16 patients died during the observation period (6 FPF patients and 10 IPF patients): 8 died from disease progression (5 FPF, 3 IPF), 6 from acute exacerbation (1 FPF, 5 IPF) and 2 from lung cancer (all patients were affected by IPF). Kaplan–Meier survival did not show any statistically significant differences between the two groups (median survival 893 days for FPF vs. 1108 days for IPF patients).

Table 2 FVC, DLCO and distance walked in 6 min reduction (expressed as ml, ml/min/mmHg and m, respectively) and % of loss with respect to baseline at 6, 12 and 24 month follow-up (FU)

	Time 0	6 months FU	Statistics	12 months FU	Statistics	24 months FU	Statistics
FVC (ml)							
IPF	2720.5 ± 798.9 (79.0 ± 19.9% pred.)	− 10.2 ± 289.9 (0.5 ± 11.7%) (*n* = 43)	*p* = 0.4729 *U* = 341 CI − 320.0 to 720.0	− 129.5 ± 326.0 (− 4.2 ± 12.6%) (*n* = 38)	*p* = 0.4069 *U* = 208 CI − 270.0 to 750.0	− 193.6 ± 374.9 (− 6.7 ± 14.0%) (*n* = 22)	*p* = 0.0381 *U* = 51.50 CI 40.00–1130
FPF	2503.8 ± 872.1 (77.6 ± 20.9% pred.)	− 66.1 ± 228.2 (− 2.4 ± 8.3%) (*n* = 18)		− 273.8 ± 339.6 (− 9.9 ± 11.8%) (*n* = 13)		− 383.3 ± 520.8 (− 15.2 ± 19.9%) (*n* = 9)	
DLCO (ml/min/mmHg)							
IPF	3.761 ± 1.374 (46.70 ± 14.62% pred.) (*n* = 44)	− 0.21 ± 0.39 (− 5.08 ± 11.06) (*n* = 33)	*P* = 0,7133 *U* = 194.5 CI − 0.5800 to 0.9300	− 0.37 ± 0.56 (− 9.6 ± 14.4) (*n* = 29)	*P* = 0.1333 *U* = 109.5 CI − 0.2500 to 1.190	− 0.66 ± 0.57 (− 16.5 ± 14.5) (*n* = 16)	*P* = 0.0468 *U* = 21 CI − 0.02000 to 2.150
FPF	3.971 ± 1.406 (50.5 ± 16.56% pred.) (*n* = 17)	− 0.45 ± 0.62 (− 11.2 ± 14.3) (*n* = 12)		− 0.69 ± 0.8 (− 17 ± 16) (*n* = 11)		− 0.80 ± 0.47 (− 27.4 ± 17.9) (*n* = 6)	
Walked distance (m)							
IPF	310 ± 124.1 (*n* = 18)	− 76.4 ± 136.6 (− 15.5 ± 66.2) (*n* = 14)	*p* = 0,9321 *U* = 268.5 CI − 60.00 to 70.00	− 53.3 ± 85.84 (− 6.9 ± 58.4%) (*n* = 9)	*p* = 0.1328 *U* = 105.5 CI − 20.0 to 150.0	− 61.42 ± 106.8 (− 4.19 ± 79.2) (*n* = 8)	*p* = 0.0393 *U* = 30.50 CI = 0.0–160.0
FPF	313.6 ± 89.86 (*n* = 50)	− 35.69 ± 7.,8 (− 9.7 ± 30.6%) (*n* = 39)		− 31.87 ± 74.3 (− 8.9 ± 31.25%) (*n* = 35)		− 52.14 ± 127.4 (− 11.6 ± 25.16%) (*n* = 16)	

Statistical comparison of FPF and IPF patients is indicated at each observation time

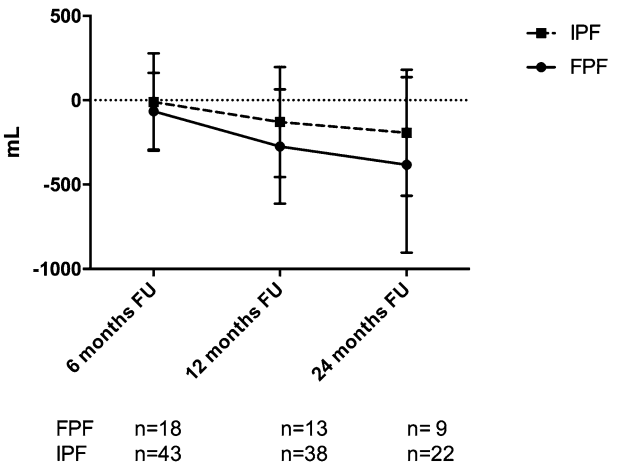

Fig. 1 Decline in FVC expressed as decrement in ml (mean ± standard deviation) with respect to baseline for FPF and IPF patients. The number of patients is indicated at each observation time

Drug Tolerance

Twenty-six of the 73 patients enrolled (35.62%) experienced side-effects or drug toxicity during treatment with pirfenidone. The most common were skin rash and photosensitivity (together 12.33%). Six out of 73 patients (8.22%) had gastrointestinal disorders (dyspepsia, abdominal distension, bloating, gastric pyrosis), 5/73 (6.85%) weight loss, 5/73 (6.85%) increased transaminase activity and 1/73 (1.37%) dizziness. For some, it sufficed to briefly reduce or discontinue therapy (11/73 patients), whereas others had to suspend treatment (4/73 patients). No statistically significant differences were observed between the FPF and IPF groups (Supplementary Material, Table 2 SM).

Fifteen patients discontinued therapy during the observation period: four due to drug intolerance (one FPF and three IPF patients) and six due to significant progression of fibrosis (all these patients changed to nintedanib) (two FPF, four IPF); five patients discontinued treatment because they underwent lung transplant (two FPF, three IPF).

Discussion

The present study is a real-life experience in which patients with FPF (presenting with UIP pattern) and IPF were treated with pirfenidone at a single Institution. Pirfenidone is a powerful antifibrotic agent that demonstrated to reduce fibroblast proliferation and collagen synthesis. The drug has been shown to reduce disease progression in patients with mild-to-moderate IPF as measured by lung function (significant reduction in FVC), exercise tolerance and progression-free

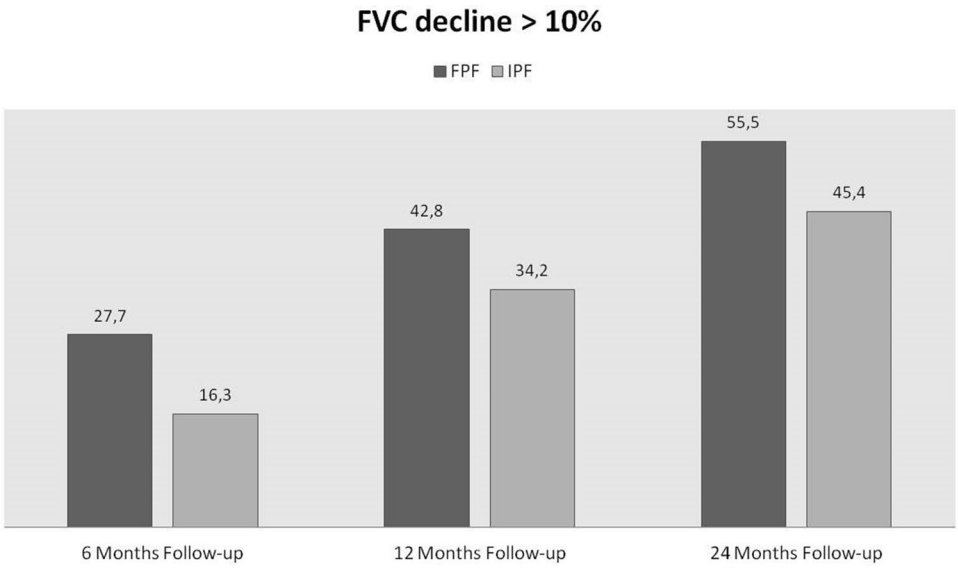

Fig. 2 Percentage of patients with a more than 10% of reduction in FVC with respect to baseline

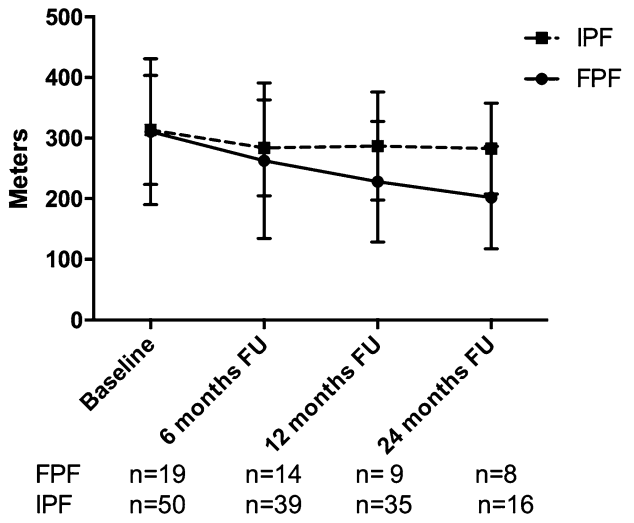

Fig. 3 Decline in distance walked expressed as decrement in meters (mean ± standard deviation) with respect to baseline in FPF and IPF patients. The number of patients is indicated at each observation time

survival [9, 10, 14]. Our aim was to evaluate the efficacy of pirfenidone in patients with FPF (with radiological and/or histological UIP pattern), defined as familial on the basis of at least two first-degree relatives with idiopathic interstitial lung disease [1]. To our knowledge, no specific pharmacological trials on FPF have been conducted; the present study is the first investigation of pirfenidone treatment of such patients.

In line with previous observations [2, 3, 15], patients with FPF included in the present study were significantly younger than those with IPF ($p = 0.0141$). No other differences between basal clinical, time interval between diagnosis of the diseases and start of therapy and functional characteristics were found between the FPF and IPF cohorts, except for a significantly higher prevalence of symptomatic GERD and hiatal hernia in FPF patients. This finding was somewhat unexpected: GERD and chronic microaspiration are considered a risk factor for the development of IPF [16]. There is no data on GERD and hiatal hernia impact in FPF; their potential effect in patients genetically predisposed to pulmonary fibrosis is intriguing and needs to be specifically investigated.

In the present study, patients with FPF on therapy with pirfenidone showed a greater decline in terms of FVC, DLCO and 6MWT parameters respect to patients with sporadic IPF.

In the FPF group, FVC at 12 months declined more than in the IPF group, reaching significance at 24 months ($p = 0.0381$). Moreover, there was an evident trend of more patients with a significant FVC decrease (> 10% below baseline) in the FPF than in the IPF group at 6, 12 and 24 months. Similarly, DLCO showed a greater decline among FPF than IPF patients at 24 months ($p = 0.04$). The 6-min walking test showed a significantly greater decline in walked distance after 24 months of treatment in the FPF group ($p = 0.0393$) and the percentage of patients with a decline exceeding 50 m at 12 months was significantly higher among FPF patients ($p = 0.0262$).

Despite the relative small number of patients with IPF in the present study, FVC progression substantially overlapped with published RCT data (such as results of the ASCEND and CAPACITY studies) [9, 10], confirming the positive impact of pirfenidone on this population. On the other hand, our FPF patients showed a worse progression of FVC even compared to published data of the ASCEND and CAPACITY studies (at 12 months of observation reported FVC progression was − 3.3% and − 192.8 ml, respectively; while in

our FPF cohort FVC declined 273.8 ± 339.6 ml, equivalent to 9.9 ± 11.8%). Similarly, regarding 6MWT data, our FPF patients showed a greater decrease in walked distance at 12 (53.3 ± 85.84 m) and 24 months (61.42 ± 106.8 m) compared to IPF patients of the CAPACITY study, who scored a mean decrease of 52.8 m at 72 weeks of follow-up [13–15]. Pirfenidone tolerance was not different between groups; no significant differences in SAE between the FPF and IPF cohorts were observed and the data were similar to that reported in the literature [13–15].

Our result should be interpreted with caution. Natural history and respiratory functional progression of FPF patients, presenting with UIP pattern, has not yet been investigated sufficiently; it is known it can have an aggressive behavior, even more rapid than sporadic IPF and with shorter survival [3]. In a recent study, our research group analyzed the clinical course of FPF patients with different radiological patterns, concluding that FPF patients with radiological UIP pattern had a significantly worse decline in FVC and DLCO at 12 months follow-up than FPF patients without UIP radiological pattern [15]. These consideration could be at the basis of different rate of progression over time of FVC, DLCO and 6MWT we observed in the present study and not interpreting it as a lack of effectiveness of therapy with pirfenidone, but due to the different natural history and evolution of these two conditions.

Our study has some limitations: it is a retrospective single-center real-life experience on a relatively small number of patients and no control or placebo group was available. These limits make results interpretation difficult and no clear recommendations on the use of pirfenidone in FPF patients can be made, nevertheless our findings raised important questions about the role of antifibrotic therapy in such patients. Moreover, since genetic analysis was only available for a minority of our FPF patients, it was not taken into consideration. The hypothesis that some but not all genetic mutations associated with IPF and FPF may induce a different response to antifibrotic therapies is interesting and needs to be specifically investigated. In future, personalized medicine may respond to individual needs and enable the role of such molecules to be re-evaluated for specific genetic subsets of FPF. Multicenter studies are needed to better understand the context of diagnosis of FPF and the possibility of an early diagnosis by using screening in families with FPF that could have a significant impact on an early treatment debut.

In conclusion, the present study showed different rate of respiratory functional progression of patients affected by IPF and FPF on therapy with pirfenidone, despite both presenting with UIP pattern. This may not be due to lack of effectiveness of pirfenidone, but to the different natural history and evolution of these two conditions. Specific unbiased randomized multicenter clinical trials on larger populations to validate our preliminary exploratory results are needed to better identify which patients will take advantage from antifibrotic therapies.

Compliance with Ethical Standards

Conflict of interest Dr. Bennett reports personal fees from Boehringer Ingelheim, personal fees from Roche, personal fees from Biotest, outside the submitted work. Prof. Rottoli reports personal fees and other from Roche, personal fees from Boehringer ingelheim, grants and personal fees from Novartis, personal fees from TEVA, other from Menarini, outside the submitted work. Dr. Rosa Metella Refini, Dr. Maria Lucia Valentini, Dr. Annalisa Fui, Dr. Antonella Fossi, Dr. Maria Pieroni and Prof. Maria Antonietta Mazzei and have nothing to disclose.

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