Pulmonary Pharmacology & Therapeutics 46 (2017) 48–53

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Safety and efficacy of pirfenidone in severe Idiopathic Pulmonary Fibrosis: A real-world observational study

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ARTICLE INFO

Article history:
Received 22 February 2017
Received in revised form
16 June 2017
Accepted 22 August 2017
Available online 24 August 2017

Keywords:
Pirfenidone
Safety
Efficacy
Idiopathic Pulmonary Fibrosis
Severe

ABSTRACT

Background: Pirfenidone is a novel anti-fibrotic drug that has shown efficacy in five randomized multicenter clinical trials enrolling patients with Idiopathic Pulmonary Fibrosis of mild-to-moderate disease severity. Scarce data supports the use of pirfenidone in IPF patients with more advanced disease.
Objective: To investigate the safety and efficacy profile of pirfenidone in IPF patients with severe lung function impairment.
Patients and methods: This was a retrospective study enrolling patients with advanced IPF (FVC%predicted < 50% and/or (DLco%predicted <35%) receiving pirfenidone for at least 6 months.
Results: Between September 2011 and March 2013, we identified 43 patients with severe IPF (baseline meanFVC%predicted±SD: 63.8 ± 20.3, meanDL_{CO}%predicted: 27.3 ± 8.2), of mean age±SD: 66.3 + 9.7, 34 males (81%) that received pirfenidone (2.403 mg/daily) for one year. Pirfenidone treatment was associated with a trend towards decrease in functional decline compared to 6-months before treatment initiation but failed to show any benefit after one year of treatment (ΔFVC: −3.3 ± 4.6 vs 0.49 ± 11.4 and vs. −5.8 ± 11.8, p = 0.06 and p = 0.04, respectively and ΔDL_{CO}: −13.3 ± 15.2 vs. −10.1 ± 16.6 and vs. 28.3 ± 19.2, p = 0.39 and p = 0.002, respectively). Gastrointestinal disorders (34.9%), fatigue (23.2%) and photosensitivity (18.6%) were the most common adverse events. Adverse events led to treatment discontinuation in 9 patients (20.9%) and dose reduction in 14 (32.5%).
Conclusion: Pirfenidone appears to be safe when administered in patients with advanced IPF. Pirfenidone efficacy in IPF patients with severe lung function impairment may diminish after 6 months of treatment.

1. Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a devastating chronic lung disease that is characterized by progressive lung scarring, ultimately leading to respiratory failure and death within 2.5–3 years of diagnosis [1]. With a gradually increasing incidence, clinical course largely unpredictable and pathogenesis yet elusive and controversial, IPF treatment still represents a major challenge for clinicians and researchers [2–9].

Until recently, no pharmaceutical treatment was available for the management of the disease and lung transplantation was the only therapeutic approach that could prolong patients' survival [10]. Pirfenidone was the first drug to be approved for the treatment of IPF in the European Union [11]. Pirfenidone is a pleiotropic molecule with anti-fibrotic, anti-inflammatory and anti-oxidant effects in experimental models of lung fibrosis [12–14]. It has been demonstrated to inhibit major anti-fibrotic signaling pathways including those of Transforming Growth Factor – beta1 (TGFβ1), Fibroblast Growth Factor (FGF) and Interleukin 1β (IL-1β) [15]. Importantly, pirfenidone has been clinically evaluated and has shown beneficial effects in patients with IPF in 5 randomized placebo controlled trials comprising an overall of 1710 patients [5,16–20]. In particular, it has been shown that pirfenidone was able to slow down disease progression, as assessed by decline in forced vital capacity (FVC), and reduce the risk of death at 1 year by

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http://dx.doi.org/10.1016/j.pupt.2017.08.011
1094-5539/

48% in a prespecified pooled analysis, including data from three independent cohorts of patients with IPF [18,19].

Despite the above encouraging data that led to reappraisal of the ATS/ERS guidelines for the diagnosis and treatment of IPF [21], current recommendations have been based on clinical trials that have excluded a significant proportion of patients seen in real-life clinical practice including those with more advanced disease; thus, current guidelines lack of major clinical applicability [11]. To this end, several groups of clinicians retrospectively assessed the safety and efficacy profile of pirfenidone in patients with advanced-stage IPF and produced rather conflicting data. In a recent study, patients with IPF who experienced the most severe decline in %FVC prior to treatment initiation were those who benefited the most from the treatment [22]. Findings were strengthened in a real-world clinical setting cohort that supported more favorable outcomes in patients with clear disease progression before treatment commencement [23]. Combination of oral pirfenidone with inhaled *N*-acetylcysteine exerted favorable effects by slowing down FVC decline in a Japanese cohort with severe IPF patients, as assessed by relative declines in FVC>10% within 6 months [24]. Similar benefits were also reported in a subgroup of patients with moderate-to-severe IPF enrolled in a retrospective real-life Italian study [25]. On the other hand, a better response to pirfenidone treatment by IPF patients with mild-to-moderate lung function impairment compared to those with more advanced disease has also been demonstrated [26] while a marginal change in %vital capacity (VC) at 3 months was associated with worse therapeutic outcomes in the pirfenidone arm [27]. Finally, long-term treatment with pirfenidone resulted in a similar rate of annual FVC decline in patients with severe lung function impairment compared to patients with more preserved lung function [28,29]. The above data suggests that the therapeutic spectrum of pirfenidone should be also extended to patients with more advanced-stage disease.

The aim of the current study was to report, on a retrospective basis, our clinical experience on the safety and efficacy profile of pirfenidone treatment in IPF patients with severe lung function impairment which represent a significant percentage of patients seen in the real-life clinical setting.

2. Methods

We conducted a retrospective multicenter study to investigate the safety and efficacy profile of pirfenidone in a sub-group of IPF patients with severe lung function impairment (as defined by predicted %FVC < 50% and/or diffusion capacity for carbon monoxide (%DLco < 35%) at the time of treatment initiation. Retrospective data analysis was approved by the institutional review board of the First Academic Department of Pneumonology, Hospital for Diseases of the Chest, "Sotiria", Medical School, and University of Athens, Greece (3876/21-2-2017). Patients that were visiting our outpatient clinic who met the ATS/ERS/JRS/ALAT criteria for IPF [30], had severe lung function impairment according to the criteria used by the CAPACITY trials [31] and received pirfenidone (2403 mg/day) were identified and included in the study. Patients with significant comorbidities (malignancy, liver failure, renal failure, or active infection), those who had used pirfenidone before and those who could not adhere to the visits plan were excluded from the study. Patients were informed for known adverse events and were instructed to avoid alcohol consumption and exposure to sunlight. Laboratory tests including Complete Blood Count (CBC), liver and renal panels were performed before administration of pirfenidone and also at monthly intervals for the first three months after treatment initiation and once every three months afterwards. All patients underwent Pulmonary Function Tests (PFTs) including body plethysmography and single breath test for determination of lung volumes and DLco 6 months before and 6 and 12 months post treatment initiation. Patients were divided based on changes in % FVC and %DLco into the following groups: stability (>-5% and −10%, respectively), marginal decline (−5 to −10% and −10 to −15%, respectively) and significant decline (≤-10% and ≤-15%, respectively).

Continuous data are presented as medians with ranges or mean ± SD. One-way ANOVA with Student-Newman-Keuls post-hoc test for pairwise comparisons and repeated measures ANOVA with Bonferroni correction were used to assess statistical significance between changes in %FVC (%ΔFVC) and $\%DL_{CO}$ ($\%\Delta DL_{CO}$) 6 months prior, as well as 6 and 12 months post pirfenidone treatment initiation. Chi square test was used for comparisons between different groups of IPF patients based on functional differences at different time points (6 months before treatment initiation to baseline-group 1, baseline to 6 months after treatment initiation-group 2, 6–12 months after treatment initiation-group 3) during study period. Statistical analysis was performed with Med Calc version 14, Ostend, Belgium.

3. Results

The baseline characteristics of patients involved in the study are summarized in Table 1. Between September 2011 and March 2013, we identified 43 IPF patients with severe lung function impairment (baseline mean %FVC±SD: 63.8 ± 19.3, mean $\%DL_{CO}$: 27.5 ± 7.5), of mean age±SD: 66.3 ± 9.7, median GAP score = 5 (stage II), 34 males (81%), that received pirfenidone (2.403 mg/daily) for at least 6 months. Twelve patients (27.9%) had %FVC predicted <50% and 41 patients (95.3%) had $\%DL_{CO}$ predicted<35%. Almost all of the patients were ex-smokers (n = 40, 93%) while the remaining 3 had never smoked. Histopathology was needed for 11 (25.6%) patients to establish diagnosis, while a definite UIP pattern was present on HRCT in the remaining 32 cases (74.4%). Combined pulmonary fibrosis and emphysema, as defined by extent of emphysematous lesions >10% of the affected lung, was present in 8 cases (18.6%). Underlying autoimmune disease was excluded by absence of compatible clinical presentation and negative autoimmune serology tests. Nine of the patients enrolled (20.9%) had respiratory failure and were under long term oxygen treatment. Pulmonary hypertension was present (as estimated by right ventricle systolic pressure (RVSP) > 35 + central venous pressure (CVP) measured by echocardiography) in 19 patients (44.2%).

Pirfenidone demonstrated a safety profile comparable to that reported in the 3 large randomized placebo controlled clinical trials

Table 1
Baseline characteristics of subjects included in study. Data are presented as no (total) or mean ± SD.

Characteristics	Baseline data
Total patients enrolled	43
Male/Female	35/8
Age (years ± SD)	66.25 ± 13.25
Never smokers	3
Current or ex-smokers	40
VATS	11
Prior treatment	0
CPFE	8
FVC %pred	63.80 ± 20.36
DLco %pred	27.26 ± 8.02
GAP score (median)	5

Abbreviations: CPFE: Combined Pulmonary Fibrosis and Emphysema; DLco: Diffusion capacity of lung for carbon monoxide; FVC: Forced Vital Capacity; TLC: Total Lung Capacity; VATS: Video-Assisted Thoracic Surgery; 6MWT: 6-min walk test; PH: Pulmonary Hypertension.