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Pirfenidone in Idiopathic Pulmonary Fibrosis: Real-Life Experience from a German Tertiary Referral Center for Interstitial Lung Diseases

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Key Words
Idiopathic pulmonary fibrosis · Pirfenidone · N-acetylcysteine

Abstract
Background: Pirfenidone is a novel antifibrotic drug for the treatment of mild-to-moderate idiopathic pulmonary fibrosis (IPF). However, adverse events may offset treatment benefits and compliance. ***Objectives:*** To assess recent course of disease, adverse events and compliance in patients who started pirfenidone. ***Methods:*** In an observational cohort study, 63 patients with mild-to-moderate IPF who started pirfenidone between May 2011 and June 2013 were reviewed. Pulmonary function, adverse events and treatment compliance were recorded at each clinic visit. Disease progression was defined as a reduction of vital capacity ≥10% and/or diffusion capacity (DLCO) ≥15%. ***Results:*** Follow-up time on pirfenidone treatment was 11 (±7) months. Sixty-six percent of the patients continued with pirfenidone monotherapy and 34% of the patients received pirfenidone combined with corticosteroids (CCS) and/or N-acetylcysteine (NAC). There was a nonsignificant reduction in mean decline of percent predicted forced vital capacity after treatment start (0.7 ± 10.9%) compared to the pretreatment period (6.6 ± 6.7%, p = 0.098). Sixty-two percent of the patients had stable disease on pirfenidone treatment. Adverse events affected 85% of the patients, leading to discontinuation of pirfenidone in 20%. Adverse events and treatment discontinuation were seen more frequently in patients with concomitant CCS and/or NAC treatment. ***Conclusions:*** Adverse events affect the majority of patients treated with pirfenidone, but are mostly manageable with supportive measures. In this heterogeneous patient group, a nonsignificant effect of pirfenidone treatment on pulmonary function was seen, underlining the need for more data on patient selection criteria and efficacy of pirfenidone, particularly in patients with coexistent emphysema and concomitant NAC/CCS treatment.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic disease that ultimately leads to death by causing progressive decline of lung function. It is the most common disease

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among the idiopathic interstitial pneumonias and carries the worst prognosis with a median survival of only 2–3 years [1]. The estimated prevalence of IPF in the Western world ranges between 2 and 40/100,000 [2]. Men in their 6th or 7th decade of life are predominantly affected. The etiology of the disease is largely unknown, but ample evidence suggests that an initial insult to the alveolar epithelium sets off a complex cascade of repair mechanisms which ultimately results in abundant deposition of extracellular matrix within the pulmonary interstitium [3, 4].

Numerous trials with immunomodulatory and immunosuppressive drugs have been carried out in the past in order to identify an effective treatment that can stop the progressive course of the disease [5]. Until recently, however, no effective pharmacological intervention was available. Pirfenidone is a novel antifibrotic agent that has recently been licensed by the European authorities for the treatment of mild-to-moderate IPF. It is the first substance with proven clinical efficacy in the treatment of IPF [6]. In vitro and in vivo studies have shown that pirfenidone exhibits anti-inflammatory and antifibrotic properties by inhibiting fibroblast proliferation, inflammatory cell accumulation, and profibrotic and proinflammatory cytokine production, and by reducing extracellular matrix deposition [7, 8]. Various clinical trials including one phase II and three phase III trials have shown a clinically meaningful effect of pirfenidone on markers of disease progression such as forced vital capacity (FVC) decline, progression-free survival and distance in the 6-min walk test [9–11]. A Cochrane meta-analysis on the cumulative data of these phase II and III trials involving a total of 1,155 patients showed that pirfenidone slows down the decline of FVC and reduces the risk of disease progression by 30% [12]. Consequently, pirfenidone was given a weak positive treatment recommendation in the German guideline for the diagnosis and management of IPF [13]. In addition, the British National Institute for Health and Care Excellence (NICE) approved pirfenidone as a treatment option for mild-to-moderate IPF in a recent technology appraisal guidance [14]. However, support in favor of pirfenidone is not unanimous, in part due to an inconsistency in the primary endpoint results of two large clinical trials, while in a pooled analysis a significant treatment effect for pirfenidone versus placebo was observed [11, 15, 16]. In addition, there is the perception that a rather modest treatment benefit comes at the cost of significant adverse events which are experienced by a considerable proportion of patients and which may affect treatment compliance [17]. In view of the data available at that time, pirfenidone was given a weak negative recommendation by the consensus statement of the ATS/ERS/JRS/ALAT on the diagnoses and management of IPF [1]. The ongoing ASCEND trial is expected to provide further valuable information on the safety and efficacy profile of pirfenidone.

As a tertiary referral center for interstitial lung diseases (ILDs), we have treated patients with mild-to-moderate IPF with pirfenidone since its German approval in 2011. The aim of this study was to evaluate drug tolerability, treatment compliance and efficacy in patients treated with pirfenidone outside the tightly controlled conditions of a clinical trial.

Methods

Patients

Clinical records of all patients with mild-to-moderate IPF who were treated with pirfenidone in our ILD center between May 2011 and June 2013 were analyzed retrospectively. Prior approval from the local ethics committee was obtained. At first presentation in our ILD outpatient clinic, a full medical history including smoking history, occupational and drug history, comorbidities, oxygen requirements and previous IPF-specific treatment was recorded. In addition, a clinical examination, laboratory tests, full pulmonary function testing and arterial blood gas sampling were performed. A thin-section multislice computed tomography (MSCT) of the lungs was performed on all patients as part of the routine diagnostic workup in suspected interstitial lung disease. No patient received additional MSCT for the purpose of the study. Pulmonary function tests included body plethysmography with FVC, forced expiratory volume in 1 s (FEV_1), total lung capacity (TLC) in addition to carbon monoxide diffusion capacity of the lung (DLCO).

IPF was diagnosed according to the consensus statement of the ATS/ERS/JRS/ALAT on the diagnosis and management of IPF which includes the following criteria: (1) exclusion of other known causes of ILD, (2) the presence of a UIP pattern on MSCT in patients not subjected to surgical lung biopsy (SLB) and (3) specific combinations of MSCT and SLB patterns in patients subjected to SLB [1].

Every patient was reviewed individually, including medical history, comorbidities, radiological findings and serological markers, in our weekly multidisciplinary ILD (pulmonology, radiology and pathology) board, and pirfenidone treatment was started only after a consensual decision was achieved. Initially (from May 2011 to mid-September 2011), patients received pirfenidone within a named patient access program that was set up as an interim solution to facilitate access to therapy as pirfenidone was not yet commercially available after its approval by the European authorities.

Pirfenidone treatment was started according to the manufacturer's instructions by increasing the dose gradually over a 2-week period from 801 mg daily to 2,403 mg daily divided into 3 doses. Subsequently, patients followed standard care in our ILD department, which includes regular follow-up clinic visits at 1- to 3-month intervals with liver function monitoring, full pulmonary function testing and arterial blood gas sampling. In addition, treatment-related adverse events and treatment compliance were recorded at each clinic visit.

Data Evaluation and Statistical Analysis

Patients had to have >3 months of follow-up in order to be included in the analysis of pulmonary function data. Patients lost to follow-up after the initial presentation were not included in the evaluation of treatment-related adverse events, compliance and lung function data. Disease progression was defined as a reduction of FVC ≥10% predicted and/or diffusion capacity (DLCO) ≥15% predicted [1, 18]. Normal data distribution was tested using the Shapiro-Wilk normality test, and data are presented as means ± SD unless stated otherwise. A paired t test was used to compare pulmonary function data before and after the start of treatment. $p < 0.05$ was considered statistically significant. GraphPad Prism 6 software (San Diego, Calif., USA) was used for statistical analysis.

Results

Patient Characteristics

Demographic data, comorbidities, diagnostic criteria and pulmonary function data of the study population (n = 63) are shown in table 1. Patients were mostly in their 7th or 8th decade of life when pirfenidone treatment was started. The majority of patients were male (n = 47, 75%) and ex-smokers (n = 40, 64%). Comorbidities were frequent with a predominance of cardiovascular diseases. In addition to MSCT, more than half of the patients (n = 34, 54%) had SLBs as part of their diagnostic workup. Fifteen of the 34 (44%) patients who underwent SLB had a definitive UIP pattern on MSCT, but were diagnosed before the release of the 2011 ATS/ERS/JRS/ALAT consensus statement and underwent diagnostic procedures according to the previous statement [19]. The mean time from diagnosis to initiation of pirfenidone treatment was 21 (±24) months. Pulmonary function of the study population was restrictive with moderate reduction of diffusion capacity.

Thirty-eight (60%) patients had a trial of immunosuppressive or anti-inflammatory treatment before starting pirfenidone treatment (table 2). Combined treatment with corticosteroids (CCS) and N-acetylcysteine (NAC) was the most common (n = 14, 22%) treatment followed by single use of NAC (n = 10, 16%) or CCS (n = 8, 12%) and triple therapy including azathioprine, CCS and NAC (n = 6, 10%). Two patients (3%) had participated in the ARTEMIS trial [20]. Once started on pirfenidone, the majority of patients (n = 40, 66%) continued on pirfenidone as monotherapy. The remaining patients were treated concomitantly with NAC (n = 12, 19%), CCS (n = 4, 7%) or a combination of both (n = 5, 8%; table 2). Patients on pirfenidone monotherapy had a higher percent predicted FVC and DLCO at baseline compared to patients on combined pirfenidone treatment (FVC 74 ± 22% vs. 64 ± 11%, DLCO 43 ± 15% vs. 35 ± 11%).

Table 1. Demographic data, comorbidities, diagnostic criteria and pulmonary function data of the study population

Patients	63
Sex, male/female	47/16 (75/25)
Age, years	68±7
Comorbidities	
Arterial hypertension	33 (52)
CAD	28 (44)
Gastroesophageal reflux disease	17 (27)
Diabetes mellitus	16 (25)
Pulmonary emphysema	11 (17)
Malignancy	9 (14)
Obstructive sleep apnea	5 (8)
Cerebrovascular accident	4 (6)
Depression	4 (6)
Smoking history	
Never smoker	20 (32)
Ex-smoker	40 (64)
Current smoker	1 (1.6)
Pack-years	24±25
Diagnosis	
Definite UIP pattern on MSCT	46 (73)
SLB	34 (54)
Time from first diagnosis to treatment start, months	21±24
Lung function	
FVC (% predicted)	70±19
FEV_1 (% predicted)	78±20
TLC (% predicted)	65±18
DLCO (% predicted)	40±14
Blood gas analysis	
PaO_2 (mm Hg)	68±11
$AaDO_2$ (mm Hg)	37±16
Oxygen therapy	14 (22)

Data are presented as absolute number of patients (%) or means ± SD.

Table 2. Treatment of IPF prior to starting pirfenidone and coexisting IPF treatment of the study population while taking pirfenidone

Prior to pirfenidone treatment (n = 63)	
None	25 (40)
CCS	8 (12)
NAC	10 (16)
CCS and NAC	14 (22)
AZT, NAC and CCS	6 (10)
Clinical trial[1]	2 (3)
While on pirfenidone treatment (n = 61)[2]	
Pirfenidone alone	40 (66)
Pirfenidone and NAC	12 (19)
Pirfenidone, NAC and CCS	5 (8)
Pirfenidone and CCS	4 (7)

Values represent n (%). AZT = Azathioprine. [1] Two patients participated in the ARTEMIS trial before pirfenidone treatment was started. [2] Two patients were lost to follow-up after treatment start and were not included in subsequent analysis.

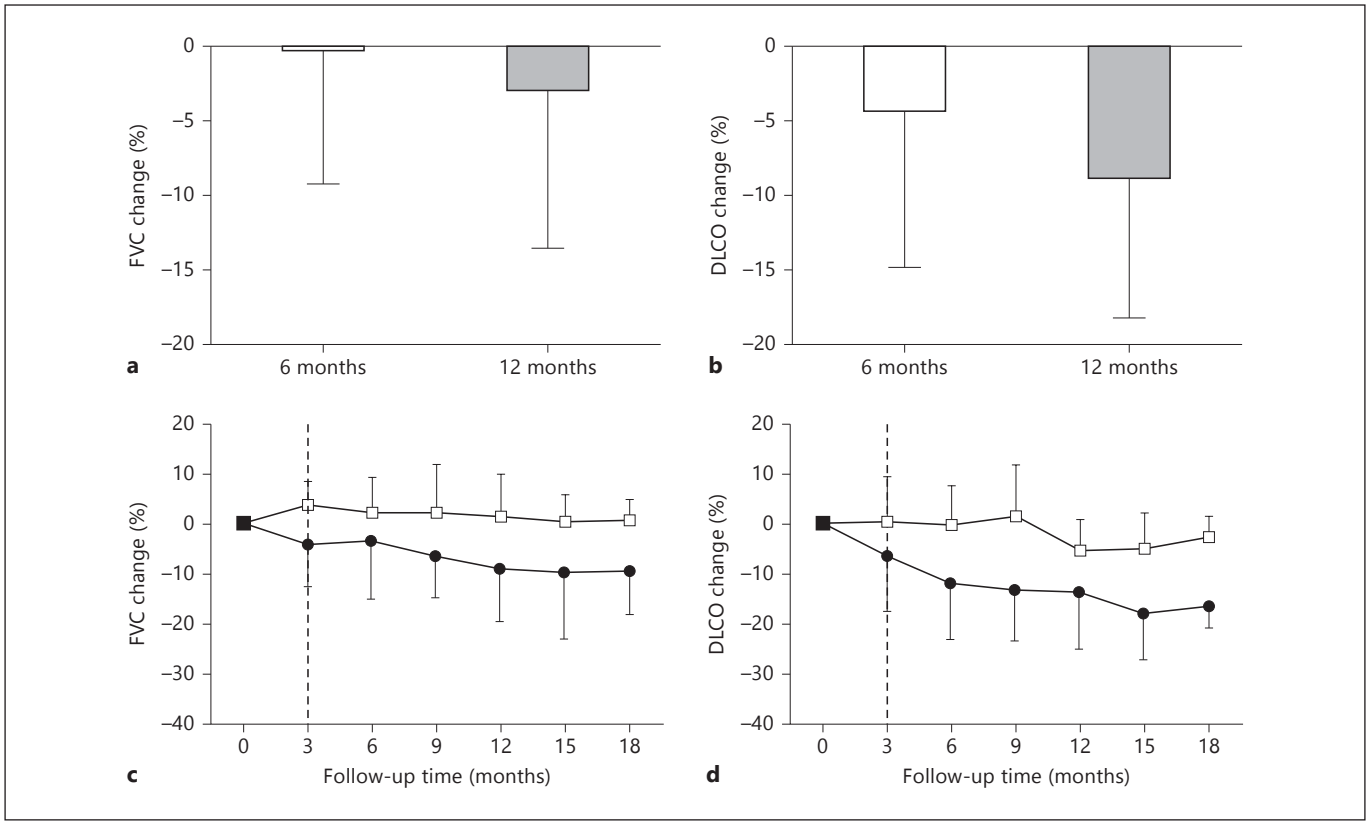

Fig. 1. Change of percent predicted FVC (**a**) and DLCO (**b**) 6 and 12 months after pirfenidone treatment was started. Course of FVC (**c**) and DLCO (**d**) decline in patients with progressive disease (n = 15, circle) compared to patients with stable disease (n = 24, open squares) with follow-up time >3 months (dotted line) after pirfenidone treatment was started. Data are presented as means ± SD.

Table 3. Follow-up course of the study population (n = 61)

Follow-up time on treatment, months	11±7
Progress while on treatment[1]	15 (38)
Time to progress on treatment, months	8±5
Termination of treatment	28 (46)
Side effect	12 (20)
Death	7 (11)
Disease progression	5 (8)
Patient wish	2 (3)
Lung transplantation	1 (2)
Other	1 (2)
Death	12 (20)
IPF-related	5 (8)
Cardiovascular	4 (7)
Multimorbidity	2 (3)
Not known	1 (2)
Time to death from first diagnosis, months	31±20

Data are presented as means ± SD or absolute patient number (%). [1] Only patients with pulmonary function data available >3 months after starting pirfenidone treatment were included in this analysis (n = 39).

Treatment Effect on Pulmonary Function

Pulmonary function data of patients with clinical follow up for >3 months after starting pirfenidone treatment (n = 39) were analyzed and the number of patients with progressive and stable disease was assessed. The mean decline in percent predicted FVC from baseline at 6 and 12 months after treatment start with pirfenidone was 0.3 ± 9% and 3 ± 11%, respectively (fig. 1). Percent predicted DLCO declined by 4 ± 10% after 6 months and 9 ± 9% after 12 months of treatment. Most patients (n = 24, 62%) had stable disease during pirfenidone treatment; however, 15 patients (38%) showed a decline of percent predicted FVC and/or DLCO that indicated disease progression (table 3). Five of these patients (33%) developed progression of disease as early as 3 months after treatment start but remained stable afterwards. The rate of disease progression in patients with pirfenidone monotherapy was 20% (n = 8) and 33% (n = 7) in those with concomitant CCS and/or NAC treatment. Mean time to progression while on pirfenidone treatment was 8 ± 5 months.

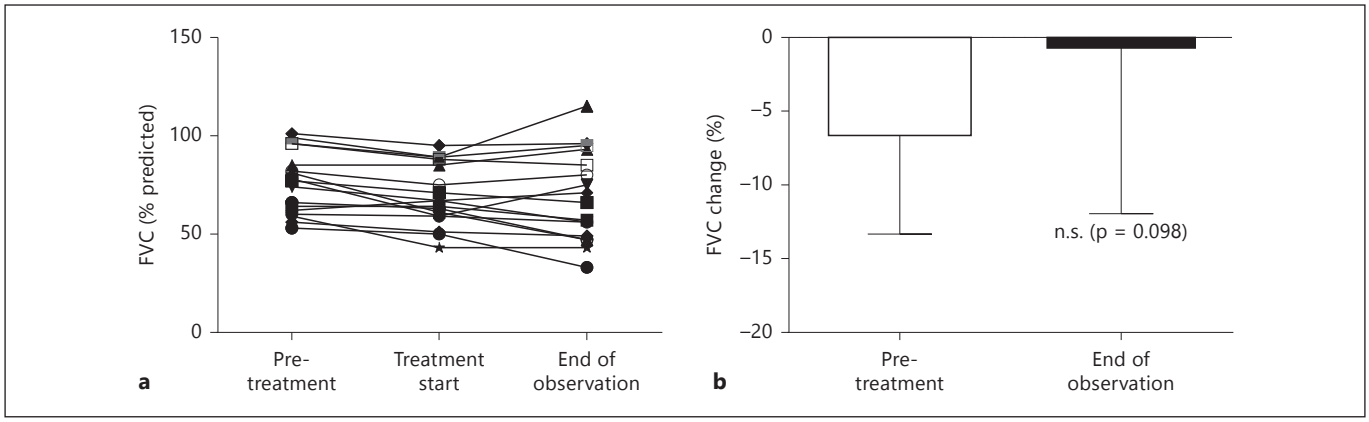

Fig. 2. Change of percent predicted FVC in patients with >3 months of follow-up clinic attendance and pulmonary function data available 3–12 months prior to starting pirfenidone treatment (n = 17). Data are shown as individual data points (**a**) and means ± SD (**b**). n.s. = Not statistically significant (p > 0.05; paired t test).

In a subgroup of patients who had technically comparable pulmonary function data available 3–12 months before and >3 months after starting pirfenidone therapy (n = 17), the change of percent predicted FVC before and after treatment start was compared (fig. 2). There was a tendency towards a reduced decline of mean FVC% predicted after treatment was started (0.7 ± 10.9%) compared to the pretreatment period (–6.6 ± 6.7%); however, this difference was not statistically significant (p = 0.098).

Treatment Compliance, Adverse Events and Termination

Two patients, who were lost to follow-up after treatment with pirfenidone was commenced, were excluded from analysis of treatment compliance and adverse events. Mean follow-up time on pirfenidone treatment in the remaining study population (n = 61) was 11 ± 7 months (table 3). Treatment compliance was high with 54 (89%) patients taking pirfenidone at the prescribed dose of 2,403 mg per day (table 4). Seventeen patients (28%) noted decreased coughing after starting pirfenidone treatment. However, adverse events were common, affecting 52 (85%) patients. In order of frequency, the reported adverse events were gastrointestinal symptoms (n = 36, 59%), fatigue (n = 33, 54%), weight loss (n = 18, 30%), skin reactions (n = 17, 28%), raised transaminases (n = 12, 20%) and sleep disturbance (n = 4, 7%). Transaminases were only mildly elevated (<3 times the upper limit of normal) in all but one patient [21]. Preexistent mildly elevated transaminases in 3 patients remained stable after treatment start with pirfenidone and were not considered to be drug-related adverse events. Most patients (n = 36, 59%) experienced more than one category of adverse events. Adverse events were usually mild and manageable with supportive measures such as temporary dose reduction, prokinetic agents, skin lotion or close observation. Temporary interruption of treatment due to adverse events was necessary in 12 patients (20%). In addition, one patient stopped treatment temporarily because of planned surgery (not excluded). Intolerable adverse events caused treatment termination in 12 patients (20%). More patients on combined treatment with pirfenidone and CCS and/or NAC experienced adverse events (n = 20, 95%) and had to stop pirfenidone treat-

Table 4. Summary of reported adverse events of the study population while on pirfenidone treatment

Adverse events (total)	52 (85)
Gastrointestinal	36 (59)
Fatigue	33 (54)
Weight loss	18 (30)
Skin	17 (28)
Phototoxicity	7 (11)
Nonphototoxicity	8 (13)
Both	2 (3)
Raised transaminases[1]	12 (20)
Sleep disturbance	4 (7)
Full-dose treatment	54 (89)
Interruption[2]	13 (21)

Data given as n (%). [1] Termination of treatment due to a raised liver function test (>5 ULN) required in 1 patient. [2] Interruption due to adverse events in 12 patients and stopped perioperatively in 1 patient.

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ment due to these (n = 8, 38%) compared to patients on pirfenidone monotherapy (n = 32, 80% and n = 4, 10%, respectively).

Overall, 28 (46%) patients stopped pirfenidone therapy during the observation period. Apart from adverse events, reasons for treatment discontinuation were death (n = 7, 11%), disease progression (n = 5, 8%), individual patient wish (n = 2, 3%) and lung transplantation (n = 1, 2%; table 3). Twelve patients (20%) died during the observation period. Of these, 7 patients died during pirfenidone treatment and 5 patients had stopped treatment between 2 weeks and 5 months before their death. The most common reasons for death were progression or acute exacerbation of IPF (n = 5, 8%) and cardiovascular diseases (n = 4, 7%).

Pirfenidone in Patients with Coronary Artery Disease

Coronary artery disease (CAD) was a frequent comorbidity in the study population (n = 28, 44%). In order to assess treatment tolerance and outcome in this subgroup of patients, the rate of adverse events, treatment discontinuation and deaths were compared to patients without CAD (n = 35; table 5). Two patients with CAD were lost to follow-up and therefore excluded from this analysis. Patients with CAD less frequently reported adverse events compared to non-CAD patients (n = 19, 77% and n = 32, 91%, respectively). The rate of treatment discontinuation (CAD n = 12, 46%; non-CAD n = 16, 46%) and the rate of treatment discontinuation due to adverse events (CAD n = 5, 19%; non-CAD n = 7, 20%) were similar in both groups. However, there was a higher death rate during the observation period in the CAD group (n = 8, 31%) compared to non-CAD patients (n = 4, 12%). Death was related to CAD in 3 (12%) patients of the CAD group compared to none in the non-CAD group.

Pirfenidone in Patients with IPF and Coexistent Emphysema

Patients with IPF and coexistent emphysema on MSCT (n = 11, 17%) had a more extensive smoking history compared to nonemphysematous patients (45 ± 37 and 11 ± 15 pack-years, respectively). Comparison of pulmonary function data at the time pirfenidone treatment was started, including FVC, FEV_1, TLC and DLCO, showed mildly elevated FVC and TLC and mildly decreased DLCO in patients with emphysema compared to nonemphysematous patients (fig. 3). Three patients with emphysema (27%) had evidence of disease progression compared to 12 patients without emphysema (24%).

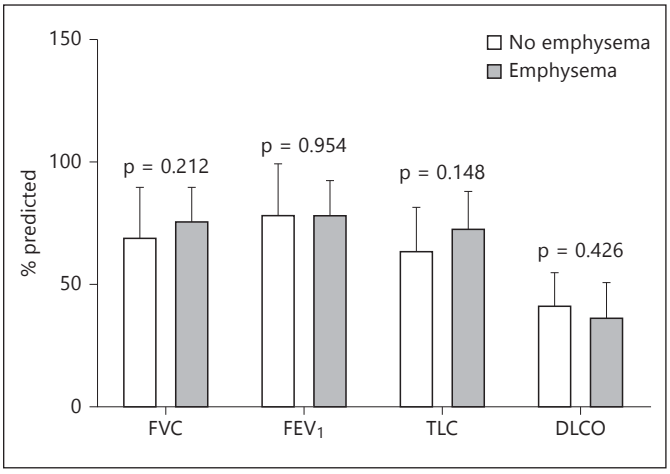

Fig. 3. Pulmonary function data at start of treatment with pirfenidone of IPF patients without emphysema (n = 50) and with coexistent emphysema (n = 11). Data are presented as means ± SD. Lung function parameters were not significantly different between patients with and without emphysema (p > 0.05; unpaired t test).

Table 5. Adverse events, treatment discontinuation and death rate of IPF patients with and without CAD

	CAD	Non-CAD
Patients, n	26	35
AE	19 (77)	32 (91)
Termination	12 (46)	16 (46)
AE	5 (19)	7 (20)
Death	4 (15)	3 (9)
Progress	1 (4)	4 (11)
Other	2 (8)	2 (6)
Death	8 (31)	4 (12)
IPF-related	2 (8)	3 (9)
CAD	3 (12)	0
Multimorbidity	3 (12)	0
Unknown	0	1 (3)

Data are presented as absolute number of patients (%). AE = Adverse events.

Discussion

This study summarizes the experience of a tertiary referral center for ILDs with pirfenidone, a novel drug for the treatment of mild-to-moderate IPF. The results show that the majority of patients, including those with cardiovascular comorbidities and emphysema, tolerated pirfenidone well and had a stable course of disease on treatment. Adverse events were mostly manageable with

supportive measures, dose reductions or temporary interruption of treatment. Patients with concomitant treatment with CCS and/or NAC had worse baseline lung function, reported more adverse events and had a higher rate of disease progression than patients on pirfenidone monotherapy. The effect of pirfenidone on FVC decline after the start of treatment compared to the pretreatment period was not significant.

The demographic characteristics, including gender distribution, age and smoking status, of our study population were very similar to two previous phase III clinical trials [11]. A higher rate of patients in our study had SLB as part of their diagnostic process, and half of these had a definitive UIP pattern on MSCT. The explanation for this is that these patients were diagnosed prior to publication of the new ATS/ERS IPF guidelines which now obviate the need for SLB if diagnostic radiological criteria are present on MSCT [1]. A significant proportion of our study population had echocardiographic evidence of pulmonary hypertension (30%) and/or radiological features of emphysema (17%), which may account for the lower percent predicted DLCO and the higher alveolar-arterial oxygen tension gradient ($AaDO_2$) in our study population compared to the CAPACITY trials [11, 22].

It is generally accepted that a decline of FVC reflects disease progression and is a reliable predictor of mortality in IPF [18]. A decline in FVC of 10% or more over a 6-month period is associated with a more than fourfold increased risk of mortality [18]. Similarly, a decline in DLCO indicates disease progression and an increased risk of death. Analysis of lung function data in our study population showed that the rate of FVC decline before the start of pirfenidone treatment was comparable to the expected average FVC decline in untreated IPF patients, taking into consideration the pooled placebo group lung function data of the CAPACITY program and other clinical trials [11, 23]. Following the start of treatment, a reduced FVC decline similar to the FVC decline of the pooled high-dose CAPACITY treatment group was seen [11]. A higher rate of disease progression on pirfenidone treatment was seen in our study population (38%) compared to previous phase III trials. It is important to note, however, that a third of these patients developed progression of disease as early as 3 months after the start of treatment start, but remained stable afterwards, indicating that these patients stabilized on pirfenidone treatment. This is consistent with results from previous clinical trials which show a time interval of at least 3 months before the clinical benefits of pirfenidone treatment become apparent [11].

A small proportion of patients in our study group had coexistent radiological features of IPF and emphysema. This coexistence is increasingly recognized in patients with an extensive smoking history and associated with pulmonary hypertension and severely impaired gas exchange [24]. Not much is known about the efficacy of pirfenidone in this group of patients. Our results show that patients with IPF and emphysema had a similar rate of disease progression compared to patients without emphysema.

A high number of patients in the CAPACITY trials experienced pirfenidone-related adverse events (98%), which led to dose reduction and treatment discontinuation in a significant number of patients (46 and 15%, respectively). Two recently published retrospective analyses on the experience of pirfenidone in the treatment of IPF reported adverse events in 58 and 84% of their study population and treatment discontinuation rates of 18 and 13% [25, 26]. In our study population, the number of patients complaining of adverse events (85%) and the treatment discontinuation rate (20%) was at the high end of this spectrum. The adverse event profile was very similar to previous reports and included gastrointestinal symptoms, fatigue, weight loss, skin reactions, raised liver function tests and sleep disturbance. Similarly to Bonella et al. [25] and Okuda et al. [26], patients in our study noted weight loss more frequently than in the CAPACITY program [11]. In addition, fatigue was an early and frequent complaint that affected more than half of the patients. Skin reactions were seen less frequently in our study population, probably a result of strict sun protection carried out by most patients following our advice. The mortality rate on pirfenidone treatment in our study group (11%) was only minimally higher than in the CAPACITY trials [11].

In contrast to the CAPACITY trials, a third of our study population was concomitantly treated with CCS and/or NAC. Most of these patients were unable to completely discontinue preexisting CCS treatment. Others started CCS and/or NAC treatment while on pirfenidone treatment because of increased symptoms or acute exacerbation of IPF [27]. Baseline pulmonary function in this group of patients was worse than patients on pirfenidone monotherapy, which is partially due to the fact that some patients started pirfenidone treatment while still recovering from an acute exacerbation of IPF. Patients with concomitant CCS and/or NAC treatment in our study experienced more adverse events than patients on pirfenidone monotherapy and had a higher rate of disease progression. This is an important finding that raises questions

about the safety of combining CCS and/or NAC with pirfenidone. Results of an ongoing trial on the safety and tolerability of combined NAC and pirfenidone (PANORAMA) should provide further valuable information on this issue.

Despite a considerable rate of adverse events, treatment compliance was high at 89%, and a significant number of patients noted a clinical meaningful improvement of cough symptoms within a few weeks of starting pirfenidone treatment. A beneficial effect of pirfenidone treatment on cough and dyspnea scores was noted before in a subgroup analysis of a Japanese phase III clinical trial [28]. The exact mechanisms of the cough-suppressing effect of pirfenidone are not known, but may be linked to reduced prostaglandin and leukotriene release as shown in a recent animal model where pirfenidone reduced capsaicin-induced cough [29].

There are clearly some limitations to our study. Most importantly, this is a retrospective data analysis of a heterogeneous group of patients. Interpretation of lung function data in our study is limited in view of the small patient number in the subgroup analysis and in the absence of a placebo group. In addition, patients with a broad spectrum of comorbidities and cotreatments were included which almost certainly had an impact on drug tolerance and effectiveness. However, this is a scenario that is frequently encountered in the daily routine of an ILD center where most patients do not fit the specific criteria of a controlled clinical trial.

Among clinicians from all over the world, support for pirfenidone treatment in IPF is not unanimous, and the ongoing debate concerning clinical efficacy and safety is fueled further by the high expenses associated with pirfenidone treatment. This was also demonstrated in a recent cost-effectiveness analysis which showed unfavorable cost ratios for any quality-adjusted life year gained by pirfenidone treatment [30]. Nonetheless, it has to be acknowledged that the advent of pirfenidone has brought about a series of clinical trials with novel drugs that specifically interfere with cellular and molecular pathways implicated in the fibrosing process in IPF [4]. This is an important step forward towards a targeted therapy in IPF, and hopefully in the future there will be a range of pharmacological interventions to choose from when having to decide on appropriate treatment strategies for patients with IPF.

In conclusion, our results show that pirfenidone is tolerated well in the majority of patients with mild-to-moderate IPF, including those with significant comorbidities. Adverse events are common, but mostly manageable with supportive measures. Within the limitations of this retrospective observational cohort study, no significant effect of pirfenidone on lung function decline was observed. Along with the substantial costs and adverse events associated with pirfenidone treatment, this finding has to be balanced carefully against the clinical benefits when considering starting pirfenidone treatment. In this respect, results of ongoing trials (ASCEND, PANORAMA and PASSPORT) are expected to provide additional valuable information on the efficacy and safety of pirfenidone, particularly in patients with concomitant NAC treatment. In addition, future research should aim at identifying selection criteria that will help to predict which patient may benefit from pirfenidone treatment.

Financial Disclosure and Conflicts of Interest

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