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Real-life experiences in a single center: efficacy of pirfenidone in idiopathic pulmonary fibrosis and fibrotic idiopathic non-specific interstitial pneumonia patients

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Abstract

Background: Pirfenidone is the first antifibrotic drug approved for the treatment of idiopathic pulmonary fibrosis (IPF) and it is used in the treatment of other interstitial pneumonias, such as unclassifiable interstitial lung disease (ILD) and connective tissue-related ILD. This study examined the efficacy of pirfenidone in patients with IPF and fibrotic idiopathic non-specific interstitial pneumonia (f-iNSIP).

Methods: In a retrospective real-life study, 67 IPF and 24 f-iNSIP patients were enrolled and classified into a pirfenidone group and a non-antifibrotic group. The level of forced vital capacity (FVC) and diffusing capacity of lung for carbon monoxide (DLco) at baseline, 6, 12 and 24 months were recorded. The level of KL-6 in serum was detected by chemiluminescence enzyme immunoassay (CLEIA). The prognosis and safety outcomes were collected from patients.

Results: In IPF patients, pirfenidone decreased the mean change of FVC and DLco, and decreased the proportion of patients with a ⩾10% decline in FVC or a ⩾15% decline in DLco compared with the non-antifibrotic group. There was no difference in the mean change of FVC and DLco between smokers and non-smokers who received pirfenidone treatment. There was an improvement in progression-free survival, defined as the time to the first occurrence of acute exacerbation or death related to pulmonary fibrosis. Moreover, the ratio of patients who experienced acute exacerbation and death related to pulmonary fibrosis was lower in the pirfenidone group. There was no change in lung function and prognosis between the pirfenidone and non-antifibrotic groups in f-iNSIP patients. The KL-6 level slightly decreased after 1 year of pirfenidone treatment but not significantly. Gastrointestinal and skin-related adverse events were most common, and four patients ceased treatment due to the side effects.

Conclusions: Pirfenidone safely reduced disease progression by improving the lung function and progression-free survival in IPF patients, with acceptable side effects. The efficacy of pirfenidone on f-iNSIP was not significant, suggesting the need for further studies.

The reviews of this paper are available via the supplemental material section.

Keywords: disease progression, idiopathic pulmonary fibrosis, non-specific interstitial pneumonia, pirfenidone

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Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic interstitial lung disease (ILD) and characterized as an irreversible and progressive interstitial pneumonia with unknown etiology and having the usual interstitial pneumonia (UIP)-like pathological pattern.[1] The prognosis of IPF is poor and the 5-year survival rate ranges from 20% to 40%.[2] The current treatment strategies for IPF mainly consist of oxygen therapy, pulmonary rehabilitation, lung transplantation and antifibrosis drugs consisting of pirfenidone

and nintedanib.[3] Non-specific interstitial pneumonia (NSIP) is a major type of chronic idiopathic ILD and has been recognized as a disease entity since 2008.[4] It has a lower mortality rate and a better prognosis compared with IPF.[5] However, a subset of patients with fibrotic idiopathic non-specific interstitial pneumonia (f-iNSIP) do not respond to corticosteroids and have high mortality rates similar to IPF.[6] There is still no drug that will totally reverse the fibrosis pattern of IPF and f-iNSIP.

Pirfenidone, an active small molecule comprising phenyl pyridine, is the first orally administered drug approved for the treatment of IPF and has anti-inflammatory, anti-oxidative and anti-fibrotic effects by inhibiting the secretion of cytokines such as TGF-β.[7] The multinational, randomized, placebo-controlled phase III trials ASCEND and CAPACITY demonstrated that pirfenidone reduced the decline of forced vital capacity and slowed disease progression in patients with IPF.[8,9] Some gastrointestinal and skin-related adverse events occurred, but did not cause significant safety concerns.[10] Some clinical trials and real-life studies also showed that pirfenidone could slow disease progression and improve the prognosis in patients with IPF and some other interstitial pneumonias, such as rheumatoid arthritis-associated ILD and unclassifiable ILD.[11,12] Few studies have reported the efficacy of pirfenidone for f-iNSIP. In this study, we share our experiences with pirfenidone treatment in patients with IPF and f-iNSIP over the past 7 years.

Methods and materials

Patients and study design

We conducted a retrospective observational study at the First Affiliated Hospital of China Medical University. Patients who were diagnosed with IPF and f-iNSIP from 2013 to 2019 were enrolled. Inclusion criteria were patients diagnosed with IPF and f-iNSIP by a multidisciplinary team including at least two pulmonologists and a radiologist according to American Thoracic Society and European Respiratory Society guidelines.[1,13] Patients were followed up for at least six disease progression months and those with malignant tumors, pulmonary hypertension and other systemic diseases were excluded. Patients with IPF or f-iNSIP who received consecutive oral pirfenidone treatment of 1800 mg/day, as recommended by the manufacturer's instructions, were classified as the pirfenidone group, and patients who received non-antifibrotic therapy such as corticosteroids and N-acetylcysteine were included in a non-antifibrotic group. Except for corticosteroids, no other disease-modifying agents were used in this study. The study was approved by the research ethics committees of the First Hospital of China Medical University.

Baseline data involving age, sex and smoking status were recorded and disease progression was followed up at least annually. Dyspnea was measured using the modified Medical Research Council (mMRC) dyspnea scale as described.[14] For pirfenidone-administered patients, liver and renal function were monitored every 3 months. Progression-free survival was defined as the time to the first occurrence of acute exacerbation or death related to pulmonary fibrosis according to the ASCEND trial with some modification.[9]

Pulmonary function test

Spirometry, whole-body plethysmography and diffusion capacity measurements were performed using a Jaeger MasterScreen system (Hoechberg, Germany) in the first affiliated hospital of China Medical University by two well-trained technicians according to American and European respiratory society guidelines. The tests were repeated at least three times and the best one reported as the result. Pulmonary function test including forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLco) were recorded at baseline and then approximately 6, 12 and 24 months after treatment. The change of FVC and DLco was calculated by their levels after treatment minus their basic level.

Serum Krebs von den Lungen-6 (KL-6) detection

Serum of patients was collected with written informed consent at the beginning and after 12 months of pirfenidone treatment, and stored at –80°C for KL-6 detection. These KL-6 levels were detected by chemiluminescence enzyme immunoassay (CLEIA) according to manuscript instruction. Lumipulse G1200 and Lumipulse KL-6 Eisai kits were obtained from Fujirebio Inc. (Japan).

Statistical analysis

All data were exhibited as the mean ± standard deviation. Data analysis was performed using SPSS software version 22.0 for Windows (IBM Corporation, Armonk, NY, USA). Student's *t*-test and the Mann–Whitney U test were used in continuous variables between two groups of independent samples based on whether the data were in normal distribution according to a Kolmogorov–Smirnov test. The Wilcoxon signed-rank test was used for the comparison of KL-6 levels. Fisher's exact test was used to test for differences in the measurement data between the pirfenidone and non-antifibrotic groups. A Kaplan–Meier curve was made to evaluate the progression-free survival, and differences were evaluated by a log rank test. $p < 0.05$ was considered statistically significant.

Results

Patients' baseline characteristics

Sixty-seven IPF patients and 24 f-iNSIP patients were enrolled in this study. In the pirfenidone group, 36 IPF and nine f-iNSIP patients received 31.3 ± 10.3 months and 31.3 ± 12.6 months pirfenidone treatment, respectively. In patients with IPF, the duration of follow-up was longer than that of the non-antifibrotic group, at 31.3 ± 10.3 compared with 22.5 ± 9.1 months ($p = 0.01$), respectively, while no difference was found in f-iNSIP patients at 31.3 ± 12.6 compared with 29.4 ± 14.5 months ($p = 0.74$). The age, male/female ratio, smoking status and the baseline level of FVC, FVC percentage predicted (FVC% pred) and DLco percentage predicted (DLco% pred) are shown in Table 1. In both IPF and f-iNSIP patients, no statistically significant

Table 1. Baseline characteristics of patients.

(1) IPF	Pirfenidone (*n* = 36)	Non-antifibrotic treatment (*n* = 31)	*p*-value
Age (years)	62.2 ± 8.1	60.6 ± 10.2	0.56
Male, *n* (%)	34 (94.4)	27 (87.1)	0.4
Smoking status, *n* (%)			
Former smoker	18 (50)	16 (51.6)	1
Never smoker	9 (25)	10 (32.2)	0.59
Current smoker	9 (25)	5 (16.2)	0.55
mMRC-dyspnea grade ⩾2, *n* (%)	15 (41.7)	12 (38.7)	1
FVC (ml)	2607.5 ± 554	2456.1 ± 569.8	0.86
FVC%	68.7 ± 14	67.3 ± 15.3	0.91
DLco%	52.2 ± 16.3	54.7 ± 14.6	0.9
Duration of follow-up (months)	31.3 ± 10.3	22.5 ± 9.1	0.01
HRCT pattern, *n* (%)			
UIP	32 (88.8)	28 (90.3)	1
Probable UIP	4 (11.1)	3 (9.7)	1
Indeterminate for UIP	0 (0)	0 (0)	1
Alternative diagnosis	0 (0)	0 (0)	1

(Continued)

Table 1. (Continued)

(2) f-iNSIP	Pirfenidone ($n=9$)	Non-antifibrotic treatment ($n=15$)	p-value
Age (years)	58.4 ± 11.7	57.1 ± 9	0.76
Male, *n* (%)	3 (33.3)	6 (40)	1
Smoking status, *n* (%)			
Former smoker	3 (33.3)	6 (40)	1
Never smoker	5 (55.6)	9 (60)	1
Current smoker	1 (11.1)	0	0.38
mMRC-dyspnea score ⩾2, *n* (%)	3 (33.3)	5 (33.3)	1
FVC (ml)	2295.1 ± 640	2301 ± 605.5	0.67
FVC %	66.7 ± 14.1	68.9 ± 13.6	0.93
DLco %	48.3 ± 15.7	55.3 ± 19.5	0.29
Duration of follow-up (months)	31.3 ± 12.6	29.4 ± 14.5	0.74
Glucocorticoid history, *n* (%)	7 (77.7%)	14 (93.3%)	0.53
HRCT finding, *n* (%)			
GGO	7 (77.7%)	11 (73.3%)	1
Honeycombing	1 (11.1%)	2 (13.3%)	1
Intra-lobular reticular opacity	9 (100%)	13 (86.7%)	0.51
Consolidation	3 (33.3%)	4 (26.7%)	1

Data are number (%) or mean ± standard deviation.
DLco, diffusion capacity of carbon monoxide; f-iNSIP, fibrotic idiopathic non-specific interstitial pneumonia; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; mMRC, modified Medical Research Council.

differences in the baseline characteristics listed in Table 1 were found between the pirfenidone and non-antifibrotic groups.

Efficacy of pirfenidone on pulmonary function progression

The mean change of FVC and DLco was used to evaluate the lung function progression (Table 2). In patients with IPF, when compared with the non-antifibrotic group, the mean decline in FVC, FVC% pred and DLco% pred was significantly reduced in the pirfenidone group at 6, 12 and 24 months after treatment. In f-iNSIP patients, although pirfenidone was associated with a numerical reduction in lung function decline over the first 12 months of treatment, the difference was not statistically significant from the group not treated with an anti-fibrotic and no mean difference in the decline in FVC was observed at 24 months.

The percentage of patients who experienced lung function progression of greater than 10% decline in FVC% pred, or greater than 15% decline in DLco% pred at 6, 12 and 24 months were also compared (Table 3). The results showed that the percentages of patients having a lung function progression in the pirfenidone group were lower than the non-antifibrotic group, but the statistical difference was only significant in IPF patients at 24 months with 9.5% compared with 52.9% in ⩾10% FVC% pred decline ($p=0.01$) and 10% *versus* 43.8% with a greater than 15% DLco% pred decline ($p=0.05$).

Table 2. The lung function change in patients with (A) IPF and (B) f-iNSIP on pirfenidone and non-antifibrotic treatments.

		Pirfenidone	Non-antifibrotic treatment	*p*-value
(A) IPF				
6 months	Patients numbers	30	24	
	Change in FVC	92 ± 247.9	−58.8 ± 274.8	0.022
	Change in FVC% predicted	3.2 ± 7.9	−1.4 ± 9.5	0.028
	Change in DLco% predicted	3.2 ± 11.3	−6.3 ± 10.3	0.004
12 months	Patients numbers	27	19	
	Change in FVC	27.4 ± 247.6	−64.7 ± 400.6	0.055
	Change in FVC% predicted	0.8 ± 6.7	−3.4 ± 7.6	0.061
	Change in DLco% predicted	2.9 ± 15.7	−10.9 ± 9.8	0.001
24 months	Patients numbers	21	17	
	Change in FVC	−25.7 ± 346.2	−358.2 ± 458.3	0.019
	Change in FVC% predicted	0.4 ± 8	−10.4 ± 12.5	0.005
	Change in DLco% predicted	1.7 ± 22	−15.7 ± 16	0.008
(B) f-iNSIP				
6 months	Patients numbers	9	11	
	Change in FVC	49.6 ± 189.4	−143.2 ± 320.2	0.114
	Change in FVC% predicted	1.5 ± 5.8	−3.3 ± 11.5	0.246
	Change in DLco% predicted	2.3 ± 9.4	6.8 ± 11.8	0.536
12 months	Patients numbers	8	8	
	Change in FVC	18 ± 210.9	−150.6 ± 386.2	0.302
	Change in FVC% predicted	−0.3 ± 5.6	−5.3 ± 10.5	0.262
	Change in DLco% predicted	4.5 ± 11.1	5 ± 14.4	0.941
24 months	Patients numbers	7	8	
	Change in FVC	−222.3 ± 320.3	−271.9 ± 326.5	0.772
	Change in FVC% predicted	−7.1 ± 8.9	−6.8 ± 9.2	0.954
	Change in DLco% predicted	9.1 ± 14.3	−5.9 ± 14.6	0.091

Data are mean ± standard deviation.
DLco, diffusion capacity of carbon monoxide; f-iNSIP, fibrotic idiopathic non-specific interstitial pneumonia; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.

Table 3. The number and percentages of IPF (A) and f-iNSIP (B) patients who experienced lung function progression.

		Pirfenidone	Non-antifibrotic treatment	*p*-value
(A) IPF				
6 months	Patients with ⩾10% decline in FVC%	1 (3.3%)	4 (16.7%)	0.16
	Patients with ⩾15% decline in DLco%	1 (3.7%)	3 (17.6%)	0.28
12 months	Patients with ⩾10% decline in FVC%	2 (7.4%)	4 (21.1%)	0.21
	Patients with ⩾15% decline in DLco%	2 (7.4%)	4 (25%)	0.17
24 months	Patients with ⩾10% decline in FVC%	2 (9.5%)	9 (52.9%)	0.01
	Patients with ⩾15% decline in DLco%	2 (10%)	7 (43.8%)	0.05
(B) f-iNSIP				
6 months	Patients with ⩾10% decline in FVC%	0 (0%)	4 (36.3%)	0.09
	Patients with ⩾15% decline in DLco%	0 (0%)	0 (0%)	1
12 months	Patients with ⩾10% decline in FVC%	0 (0%)	2 (25%)	0.47
	Patients with ⩾15% decline in DLco%	0 (0%)	1 (12.5%)	1
24 months	Patients with ⩾10% decline in FVC%	1 (14.3%)	2 (25%)	1
	Patients with ⩾15% decline in DLco%	0 (0%)	3 (42.9%)	0.19

Data are number (%).
DLco, diffusion capacity of carbon monoxide; f-iNSIP, fibrotic idiopathic non-specific interstitial pneumonia; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.

The mean change of lung function was compared for smoking status in patients receiving pirfenidone treatment (Table 4). The results showed that no difference was found in the mean change in lung function between smokers and non-smokers ($p > 0.05$). Non-smokers with IPF seemed to benefit more from pirfenidone treatment compared with smokers at 24 months, with a change of 1.6% in non-smokers FVC% pred compared with 0.1% in smokers ($p = 0.72$) and 11.5% compared with –1.6% for DLco% pred, ($p = 0.26$). This needs more investigation in future studies.

Dyspnea during pirfenidone treatment

Dyspnea measured by the mMRC score after pirfenidone treatment is showed in Table 5. Patients with mMRC scores greater than two were regarded as experiencing severe dyspnea. At baseline level, 15 (41.7%) IPF and three (33.3%) f-iNSIP patients had severe dyspnea, 16 (45.7%) IPF and three (33.3%) f-iNSIP patients had severe dyspnea at 12 months and 16 (54.5%) IPF and four (44.4%) f-iNSIP patients had severe dyspnea at 24 months. Although the percentage of IPF and f-iNSIP patients who had severe dyspnea increased with time, no statistical difference was found after 24 months of pirfenidone treatment compared with the baseline level, which indicated that pirfenidone prevented the worsening of dyspnea as a symptom.

Progression-free survival and mortality outcomes

Figure 1 shows that, at 24 months for patients with IPF, pirfenidone improved the progression-free survival and reduced the risk of death or acute exacerbation compared with non-antifibrotic treatment with a hazard ratio of 2.04 [95% confidence interval (CI) = 1.03–4.04, $p = 0.032$]. Fewer patients treated

Table 4. The lung function change in smokers and non-smokers who received pirfenidone treatment in patients with (A) IPF and (B) f-iNSIP.

		Smoker (current and former)	Non-smoker	*p*-value
(A) IPF				
6 months	Patient numbers	21	9	
	Change in FVC% predicted	3.3 ± 7.9	3.1 ± 8.4	0.96
	Change in DLco% predicted	1.6 ± 8.7	6.4 ± 15.3	0.3
12 months	Patient numbers	20	7	
	Change in FVC% predicted	1.2 ± 6.7	−0.1 ± 7.4	0.68
	Change in DLco% predicted	2 ± 15.6	5.4 ± 17.2	0.64
24 months	Patient numbers	16	5	
	Change in FVC% predicted	0.1 ± 7.2	1.6 ± 11.1	0.72
	Change in DLco% predicted	−1.6 ± 21.9	11.5 ± 21.4	0.26
(B) f-iNSIP				
6 months	Patient numbers	6	3	
	Change in FVC% predicted	0.4 ± 5.8	3.7 ± 6.4	0.46
	Change in DLco% predicted	−2.5 ± 3.7	8.7 ± 11.7	0.12
12 months	Patients numbers	5	3	
	Change in FVC% predicted	−1.8 ± 4.6	2.1 ± 7.2	0.38
	Change in DLco% predicted	3.3 ± 12.3	6.1 ± 11.6	0.78
24 months	Patients numbers	4	3	
	Change in FVC% predicted	−8.5 ± 9.2	−3.9 ± 8.8	0.54
	Change in DLco% predicted	11.4 ± 16.3	6.7 ± 15.3	0.74

Data are mean ± standard deviation.
DLco, diffusion capacity of carbon monoxide; f-iNSIP, fibrotic idiopathic non-specific interstitial pneumonia; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis.

Table 5. The number and percentages of IPF and f-iNSIP patients who had a ⩾2 mMRC dyspnea score.

	IPF		f-iNSIP	
	mMRC dyspnea score ⩾ 2, *n* (%)	*p*-value	mMRC dyspnea score ⩾ 2, *n* (%)	*p*-value
Baseline	15 (41.7)	–	3 (33.3)	–
12 months	16 (45.7)	0.81	3 (33.3)	1
24 months	16 (54.5)	0.34	4 (44.4)	1

Data are number (%).
f-iNSIP, fibrotic idiopathic non-specific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; mMRC, modified Medical Research Council.

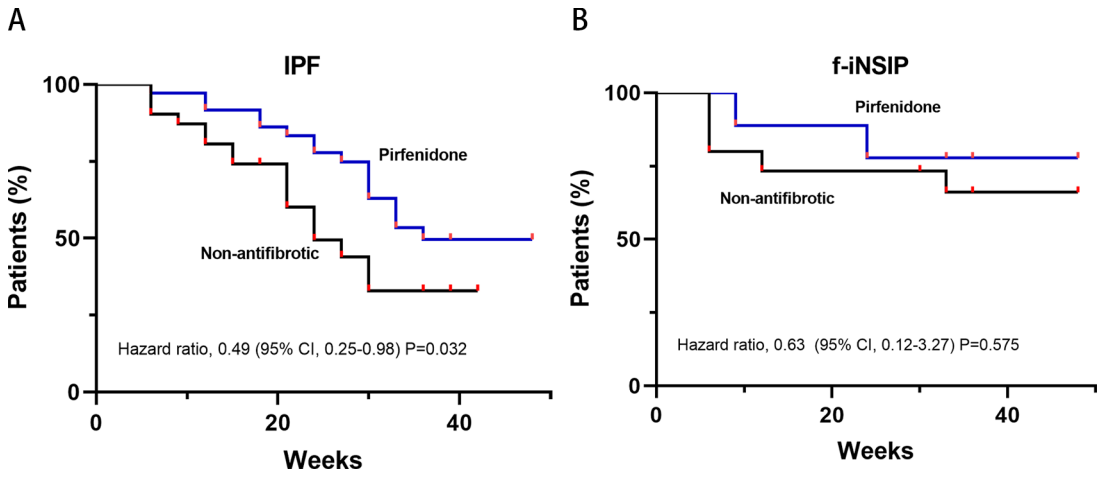

Figure 1. Kaplan–Meier distribution of progression-free survival time in patients with IPF (A) and f-iNSIP (B).
f-iNSIP, fibrotic idiopathic non-specific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis.

Table 6. Acute exacerbation and death related to pulmonary fibrosis at 24 months in patients with IPF (A) and f-iNSIP (B).

	Pirfenidone	Non-antifibrotic treatment	*p*-value
(A) IPF			
Acute exacerbation	8 (22.2%)	13 (41.9%)	0.11
Death related to pulmonary fibrosis	6 (16.7%)	10 (32.3%)	0.16
(B) f-iNSIP			
Acute exacerbation	2 (22.2%)	4 (26.7%)	1
Death related to pulmonary fibrosis	0 (0%)	2 (13.3%)	0.51

Data are number (%).
f-iNSIP, fibrotic idiopathic non-specific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis.

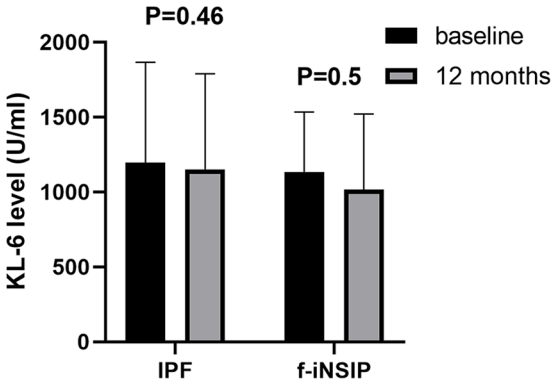

Figure 2. The serum KL-6 level in IPF and f-iNSIP patients at baseline and 12 months of pirfenidone treatment.
f-iNSIP, fibrotic idiopathic non-specific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6.

with pirfenidone experienced acute exacerbation, at 22.2% compared with 41.9% ($p=0.11$) or death related to pulmonary fibrosis, at 16.7% compared with 32.3% ($p=0.16$), although the differences were not statistically significant (Table 6). Table 4 shows that, for patients with f-iNSIP at 24 months, although pirfenidone reduced the percentages of patients who experienced acute exacerbation to 22.2% from 26.7% ($p=1$) or death related to pulmonary fibrosis to 0% from 13.3% ($p=0.51$) as seen in in Figure 1. No significant difference in the risk of death or acute exacerbation was found between the pirfenidone and non-antifibrotic groups, with a hazard ratio of 1.58, at 95% CI=0.31–8.17 ($p=0.575$).

Effect of pirfenidone on serum KL-6 level

The serum KL-6 level at baseline and 12 months in the pirfenidone group was recorded in 17 IPF and five f-iNSIP patients. Compared with baseline, the KL-6 levels at 12 months decreased in both IPF at 1216 ± 654 U/mol at baseline compared with 1171 ± 623 U/mol at 12 months ($p=0.463$) and f-iNSIP patients, measured at 1056 ± 395 U/mol compared with 920 ± 501 U/mol. However, the difference was not statistically significant ($p=0.5$), as seen in Figure 2.

Adverse events

The adverse events occurring during pirfenidone treatment are listed in Table 7. Skin and

Table 7. Treatment-emergent adverse events.

	IPF	f-iNSIP	*p*-value
Total events occurred	13 (36%)	4 (44.4%)	0.71
Rashes/ photosensitivity	8 (22.2%)	2 (22.2%)	1
Nausea/ vomiting	3 (8.3%)	0 (0%)	1
Dyspepsia	3 (8.3%)	1 (11.1%)	1
Anorexia	4 (11%)	1 (11.1%)	1
Diarrhea	2 (5.6%)	1 (11.1%)	0.5
Dizziness	1 (2.8%)	0 (0%)	1
Hepatotoxicity	3 (8.3%)	1 (11.1%)	1
Fatigue	4 (11%)	2 (22.2%)	0.58

Data are number (%).
f-iNSIP, fibrotic idiopathic non-specific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis.

gastrointestinal-related events were most common in both IPF and f-iNSIP patients. Dizziness, hepatoxicity and fatigue also occurred in some patients. Three (8.3%) patients with IPF and one (11.1%) patient with f-iNSIP discontinued the therapy due to side effects.

Discussion

In this study, we share our real-life experience of pirfenidone administration in IPF and f-iNSIP patients. Consistent with previous studies, pirfenidone treatment reduced the decline of lung function and improved the progression-free survival in patients with IPF with an acceptable safety profile.

Pirfenidone is an oral antifibrotic drug shown to slow down the progression and improve the prognosis in patients with IPF. In the CAPACITY and ASCEND trials, pirfenidone reduced the decline in FVC and 6-minute walk distance and improved progression-free survival compared with the placebo treatment in IPF patients.[8,9] Some researchers showed that pirfenidone could also decrease the risk of acute exacerbation and death in IPF patients.[15] A meta-analyses study found that the all-cause mortality and IPF-related mortality were significantly lower in the pirfenidone group compared with the placebo group at weeks 52 and 120,[16] and patients could benefit from pirfenidone irrespective of their disease stages and basic level of lung function.[17] As our study was a retrospective observation based on real-world cases, the patients who did not receive antifibrotic treatment of pirfenidone and nintedanib were chosen as the control group. In our study, pirfenidone also reduced the decline of FVC and DLco and decreased the percentages of patients who experienced a $\geqslant$10% decline in FVC% pred or a greater than 15% decline in DLco% pred in IPF patients compared with the non-antifibrotic group. Pirfenidone also improved the progression-free survival and decreased the proportion of patients with acute exacerbation or death related to pulmonary fibrosis at 24 months. These results further confirmed the efficacy of pirfenidone treatment in IPF patients. One interesting finding that was different from the results of the CAPACITY and ASCEND trials was that pirfenidone slightly increased the level of FVC and DLco at 6 and 12 months in our study and this may be an accidental result due to the insufficient number of patients enrolled. Pirfenidone might have better effects on the Asian population which were not the main subjects in the CAPACITY and ASCEND trials, and finally IPF is a heterogeneous disease, and pirfenidone might exert better efficacy on some special subtypes of interstitial pneumonia, similar to *N*-acetylcysteine which was reported to be an efficacious therapy for the IPF patients with the rs3750920 (TOLLIP) TT genotype.[18]

As lung function progression might be affected by smoking status besides pulmonary fibrosis,[19,20] the mean change of FVC% pred and DLco% pred between smokers and non-smokers in patients who received pirfenidone treatment was compared. Although no statistical difference was found between different smoking status, non-smokers had the tendency to benefit more from pirfenidone treatment, reflected by the reduction in their lung function decline. This might be due to the damage to lung function caused by smoking being unable to benefit from pirfenidone treatment, as pirfenidone mainly prevents lung function decline induced by pulmonary fibrosis, and cigarette smoking exposure might interfere with the antifibrotic effect of pirfenidone, but this conclusion could not be supported by the results from previously published articles.

It is interesting to note that IPF patients in the pirfenidone group were followed up for longer

than patients in the non-antifibrotic group. In our opinion, patients who received pirfenidone treatment had better preserved lung function and suffered from fewer acute exacerbations, so they were able to be followed up for a longer time.

In recent years, more and more studies have reported the use of pirfenidone in the treatment of ILDs besides IPF. Maher *et al.* reported that pirfenidone attenuated the decline of FVC, DLco and 6-minute walking distance compared with the placebo group in unclassifiable ILD.[12] Patients with rheumatoid arthritis-associated ILD could also benefit from pirfenidone treatment.[11] The INBUILD trial demonstrated that another antifibrotic drug, nintedanib, attenuated the annual rate of decline in the FVC in patients with progressive fibrosing ILDs other than IPF.[21] Although the antifibrotic mechanism differs between pirfenidone and nintedanib, it was still worthwhile to explore the efficacy of pirfenidone on other fibrotic ILDs. The morbidity of idiopathic NSIP is only inferior to IPF among the idiopathic interstitial pneumonias. The efficacy of corticosteroids on f-iNSIP is limited and pirfenidone is a promising treatment for these patients. In this study, nine fibrotic patients who received pirfenidone treatment were enrolled and analyzed. Although their mean decline of lung function and progression-free survival was slightly improved compared with the non-antifibrotic group, the difference was not significant. This may be because the quantity of patients enrolled was not large enough to show the statistical differences, and although patients with the UIP pattern could benefit from pirfenidone treatment, the same efficacy might not happen in patients with the NSIP pattern. Whether patients with f-iNSIP could benefit from pirfenidone still needs to be explored in a randomized controlled trial. Finally, despite client education, poor patient compliance could contribute to the lack of effectiveness of pirfenidone in the f-iNSIP treatment group.

The high molecular weight glycoprotein KL-6 is classified as MUC1 mucin. The expression of KL-6 was increased in the serum and bronchoalveolar lavage fluid of ILD patients compared with the healthy population, and the serum KL-6 level is a reliable biomarker for the diagnosis and prognostic indication of ILD.[22,23] In IPF patients, it was reported that the serum KL-6 level was continuously increased as fibrosis progressed and that a high KL-6 level might indicate poor prognosis.[24] In our study, the serum KL-6 level was found to be decreased after 12 months' pirfenidone treatment in patients with IPF and f-iNSIP although no statistical difference was found. Although we did not compare the KL-6 change between pirfenidone and the non-antifibrotic group because the serum KL-6 level in the non-antifibrotic group was not available, these results still indicated that pirfenidone could maintain a stable serum KL-6 level in patients with IPF and f-iNSIP. Whether the stable KL-6 level in serum indicated better prognosis still needs further research as Volkmann *et al.* found that patients with higher baseline KL-6 levels were more likely to experience disease progression despite treatment.[25]

Gastrointestinal effects including nausea, vomiting, dyspepsia, anorexia and diarrhea and skin-related effects such as rashes and photosensitivity were the most frequent adverse events in both IPF and f-iNSIP patients, and some patients also had other adverse reactions such as dizziness, fatigue and aminotransferase elevations. Four patients discontinued pirfenidone treatment because of adverse reactions, and the damage was reversible. The level of adverse events does not seem to differ between the two diseases. The incidence of total adverse events in our study was nearly 40%, which was lower than previous studies.[8,9,26] This might be due to the dose of pirfenidone used in our study at 1800 mg/day, which is the manufacturer's instructed dose in China, after being determined in a series of clinical trials in China and Japan.[27,28] Overall, the safety of pirfenidone was moderate and acceptable.

There were some limitations in our study. Although pirfenidone could maintain the dyspnea symptom stable measured by the mMRC dyspnea scale in our study, the 6-minute walk test and high-resolution computed tomography (HRCT) score were not analyzed during pirfenidone treatment. The 6-minute walk test can predict the quality of life and long-term mortality in IPF patients and the HRCT score is used to quantify fibrosis in HRCT images. However, these items were not collected completely in this retrospective study. Our criteria of patient enrollment did not contain the restriction in the basic range of lung function. In the ASCEND trial, patients with FVC% pred less than 50% or DLco% pred less than 30% were excluded, but this study did not set such restrictions in order to demonstrate the effect of pirfenidone in the real world. Poor client compliance might also interfere with

the results of our study, despite patients being contacted every 3 months to remind them to take medicine in a timely and adequate manner. Finally, the factors which might affect the efficacy of pirfenidone were not analyzed. One study reported that IPF patients with a $>25\,kg/m^2$ in body mass index (BMI) or a >30% in DLco had a higher progression-free survival rate,[28] but similar analyses were not performed in our study due to the limited quality and information of patients.

Conclusion

This retrospective real-life study described our experience with pirfenidone in the treatment of IPF and f-iNSIP patients. Consistent with previous studies, our results demonstrated that pirfenidone maintained the development of lung function and improved the progression-free survival of patients with IPF. The serum KL-6 level decreased after pirfenidone treatment with no statistical difference. The safety profile was acceptable and some acceptable adverse events occurred. However, the efficacy of pirfenidone still requires further evidence to support its use in f-iNSIP in the future.

Author contribution(s)

Haoshen Feng: Conceptualization; Formal analysis; Investigation; Methodology; Writing-original draft.

Yabin Zhao: Formal analysis; Methodology; Writing-review & editing.

Zhenhua Li: Investigation; Methodology; Resources; Writing-review & editing.

Jian Kang: Conceptualization; Formal analysis; Funding acquisition; Writing-review & editing.

Conflict of interest

The authors declare that there is no conflict of interest.

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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