The role of pirfenidone in the treatment of interstitial pneumonia with autoimmune features

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Abstract

Objective

No approved pharmacotherapies are available for patients with interstitial pneumonia with autoimmune features (IPAF). In the present work, we aimed to evaluate the efficacy and safety of pirfenidone for the treatment of IPAF.

Methods

A retrospective cohort study consisting of patients who met diagnostic criteria for IPAF was performed after a multidisciplinary review, and the patients receiving pirfenidone were compared with those in the non-pirfenidone group. The baseline data and diagnostic characteristics of patients were assessed. Pulmonary function and prednisone dose were analysed by a mix-effects model.

Results

A total of 184 patients, who met the diagnostic criteria of IPAF, were divided into two groups: pirfenidone group (n=81) and non-pirfenidone group (n=103). Patients in the pirfenidone group had a lower forced vital capacity (FVC%, p<0.001) and a lower diffusion capacity for carbon monoxide (DLCO%, p=0.003). The pirfenidone group exhibited a greater increase of FVC% at 6 (p=0.003), 12 (p=0.013), and 24 (p=0.003) months. After adjustment for sex, age, UIP pattern, baseline FVC% and DLCO%, patients in the pirfenidone group continued to show a greater improvement in FVC% ($\chi^2(1)=4.59$, p=0.032). Subgroup analysis identified superior therapeutic effects of pirfenidone in patients with dosage >600 mg/day (p=0.010) and medication course >12 months (p=0.007). Besides, the pirfenidone group had a lower prednisone dose than the non-pirfenidone group after 12 months of treatment (p=0.002). Moreover, 17 patients (19.32%) experienced side effects after taking pirfenidone, including one case of anaphylactic shock.

Conclusion

Pirfenidone (600–1,800 mg/day) might help improve FVC, with an acceptable safety and tolerability profile in IPAF patients.

Key words

pirfenidone, interstitial pneumonia with autoimmune features, mix-effects model

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Introduction

As a heterogeneous collection of uncommon disorders, interstitial lung disease (ILD) is characterised by interstitial fibrosis and decline in lung function. A significant proportion of ILD patients demonstrate clinical features suggestive of a connective tissue disease (CTD) but fail to meet established CTD diagnostic criteria. Interstitial pneumonia with autoimmune features (IPAF) is used to label these patients according to a European Respiratory Society/American Thoracic Society research statement (1-2). This new classification system combines clinical, serological, and morphological domains, with an IPAF diagnosis requiring at least two of the three domains. Importantly, IPAF criteria are not diagnostic but standards for classification, which are used to interpret study findings and compare results between studies (3).

The majority of IPAF patients are females, with a mean age of 56.9–67.9 years (4-9). Moreover, 5–12% of IPAF patients may develop to definite CTD-ILD (1, 5). The most prevalent patterns in the three domains are Raynaud's phenomenon and inflammatory arthritis or polyarticular morning stiffness >60 min for the clinical domain, nonspecific interstitial pneumonia (NSIP) for the morphological domain, and antinuclear antibody (ANA) and rheumatoid factor (RF) for the serological domain. The prognosis of IPAF is superior to idiopathic pulmonary fibrosis (IPF) but worse than CTD-ILD (6-9). Usual interstitial pneumonia (UIP) pattern independently predicts poor survival in IPAF (7-10).

As IPAF patients do not have defined CTD, treatment may be similar to CTD-ILD for some IPAF patients (1). The INBUILD study has shown that nintedanib is beneficial to progressive fibrosing ILD from a variety of CTDs (11). Besides, nintedanib can slow down the annual rate of FVC decline in patients with systemic sclerosis-associated ILD (12, 13). On the other hand, pirfenidone also shows the potential treatment effects for IPAF. A multicentre clinical trial has demonstrated that pirfenidone can prevent the decline of FVC in patients with progressive fibrosing unclassifiable ILD (PF-ILD) (14), including IPAF patients. Li T *et al*. have reported that pirfenidone can improve the prognosis of patients with amyopathic dermatomyositis (15). Taken together, we postulated that pirfenidone was associated with the improvement of pulmonary function in IPAF patients. To verify such a hypothesis, we explored the efficacy and safety of pirfenidone capsules for the treatment of IPAF, and it was registered in the Chinese Clinical Trial Registry (ChiCTR-IPR-17010813).

Patients and methods

Screening process of patients

A total of 1,070 ILD patients diagnosed at Shanghai Pulmonary Hospital (Shanghai, China) from January 2014 to January 2019 were enrolled in this cohort. The screening process is illustrated in Figure 1. Finally, 242 patients met the diagnostic criteria of IPAF (2). Among these patients, there were 172 cases with UCTD-ILD, and 70 cases were diagnosed with idiopathic interstitial pneumonia (IIP), including four with biopsy-proven cryptogenic organic pneumonia (COP), eight with IPF, and 58 with unclassifiable IIP. Exclusion criteria were set as follows:

1. patients without follow-up data (n=30); 2. patients with other complications (n=15 including any active infection, heart or hepatic or renal impairment); 3. the duration of pirfenidone treatment was less than 3 months (n=7); 4. the follow-up interval was more than 40 months (n=6). This study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (approval no. K17-H1).

Data collection

Clinical data were collected from patient-visit records, including demographic characteristics, body mass index (BMI), smoking history, RFs and autoantibodies (ANA, anti-CCP, anti-double-stranded DNA, anti-SSA, anti-SSB, anti-RNP, anti-smith, anti-Scl-70, anti-tRNA synthetase), arterial oxygen saturation, and pulmonary function test (PFT). Medication history included glucocorticoids, immunosuppressive agents, and pirfenidone (dos-

age and duration of therapy). Baseline data were recorded at the time when the patient started pirfenidone or corticoid therapy (allowable range was 0–3 months to permit the inclusion of patients). The time table began with the time of baseline for all analyses. PFT was recorded at baseline and after 3 months of pirfenidone treatment, and then it was performed every 6 months as clinically indicated.

Pirfenidone treatment

Patients with the following situations were recommended to pirfenidone treatment: 1. patients exhibited more than 10% fibrosis on high-resolution computed tomography (HRCT); 2. patients had a more than 5% absolute decline in percent predicted FVC within the previous 6 months. All the patients started the pirfenidone therapy with a dose of 600 mg/day, and such a dose was increased to 1,800 mg/day in 6 months unless the patients experienced serious side effects. The final dose (1,800 mg/day) was decided based on the clinical trial of pirfenidone (16). A severe side effect was defined as an event that caused an inability to work or perform daily activity.

Treatment of prednisone and immunosuppressants

The dose of prednisone was adjusted according to disease severity and body weight. A sufficient dose of prednisone was administered at the beginning, and then it was gradually reduced. Unless the patients experienced an exacerbation, the dose of prednisone would be maintained at a relatively low level. All the immunosuppressants were administered by rheumatologists.

Diagnostic criteria

The final diagnosis was made by a multidisciplinary discussion (MTD) (three experienced pulmonologists, two rheumatologists, two chest radiologists, and two pathologists). The diagnosis of ILD was made according to the diagnostic criteria described previously (17, 18). Diagnosis of IPAF was made based on the evaluation of three diagnostic domains (clinical, serological, and morphological domains) (2). The morphological domain referred to HRCT or in combination with pathological results when lung biopsies were performed. All patients with CTD-ILD or UCTD-ILD were confirmed by rheumatologists. The diagnostic criteria for CTD in this study followed the recommendations by the American Rheumatism Association and the American College of Rheumatology (19-24). UCTD was defined as patients who showed systemic autoimmune features but did not meet definite classification criteria (1).

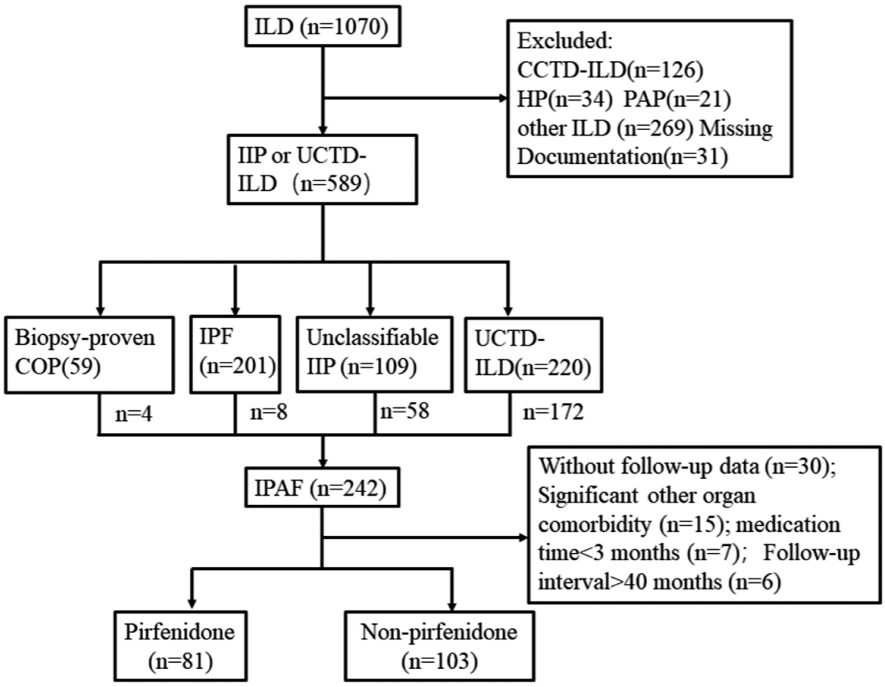

Fig. 1. Flowchart of patients' selection process.
Of 1070 patients diagnosed with ILD, 184 patients with IPAF (81 received pirfenidone therapy, while 103 did not) were enrolled in this study.
CCTD-ILD: confirmed connective tissue disease-associated ILD; COP: cryptogenic organic pneumonia; HP: hypersensitivity pneumonitis; IIP: idiopathic interstitial pneumonia; ILD: interstitial lung disease; IPAF: interstitial pneumonia with autoimmune features; IPF: idiopathic pulmonary fibrosis; PAP: pulmonary alveolar proteinosis; UCTD-ILD: undifferentiated connective tissue disease-associated ILD.

Chest HRCT evaluation

HRCT patterns were blindly reviewed and interpreted by two dedicated chest radiologists. HRCT diagnosis referred to proposed criteria for IPAF by ERS/ATS guidelines (2), including NSIP, organic pneumonia (OP), NSIP in combination with OP, and UIP (Supplementary Fig. S1). NSIP pattern was defined as basal predominant reticular abnormalities with traction bronchiectasis, which was frequently associated with ground-glass attenuation. OP pattern was defined as bilateral patchy areas of consolidation with a subpleural and lower lung zone predominance or peribronchovascular distribution. NSIP in combination with OP was defined as basal predominant consolidation, which was associated with features of fibrosis. UIP pattern was defined as basal and subpleural predominant honeycombing opacities associated with traction bronchiectasis. No lymphoid interstitial pneumonia (LIP) HRCT pattern was found in this cohort.

Data processing

Continuous variables were presented as mean (standard deviation) and compared by two-tailed Student's *t*-test. Categorised variables were expressed as frequency (percentage) and compared using the Chi-square test or Wilcoxon rank-sum test. All analyses were performed using GraphPad Prism 6 and SPSS 24 software (IBM, Armonk, NY, USA).

The PFT results were recorded at baseline and follow-up visits. The differences between the follow-up value and baseline value were calculated (change

= follow-up value - baseline value), and then the changes in FVC absolute value, FVC%, and DLCO% were compared using a mixed-effects model. Fixed effects included gender, age, UIP pattern, baseline FVC%, and DLCO%. The mixed-effects model has been proved reliable in other retrospective studies (25-27). The prednisone doses were compared by the same method. These analyses were carried out by R software.

Results

Baseline characteristics of patients

Table I shows that 184 patients were finally included in the analysis, including 81 (44.0%) patients in the pirfenidone group, and 103 (56.0%) patients in the non-pirfenidone group. The mean age of the cohort was 59.4 years old, 54.3% were females, and 53 (28.8%) patients had a history of smoking. There were no differences in gender, smoking history and UIP pattern. However, both FVC% and DLCO% were lower in the pirfenidone group compared with the non-pirfenidone group (FVC%, $p<0.001$; DLCO%, $p=0.003$). As for the treatment, the baseline data of glucocorticoid and immunosuppressant treatment were not different between the two groups. Generally speaking, 151 (82.1%) patients received oral glucocorticoid, and 13 (7.1%) patients received immunosuppressants. The duration of prednisone treatment was 2.25–40 months, with an average of 28.8 months. The mean duration of pirfenidone treatment was 14.4 months, and the dose of pirfenidone ranged from 600 to 1,800 mg/day, with an average of 1,492 mg/day.

Diagnostic characteristics of IPAF patients

Table II shows the diagnostic characteristics. Overall, 66 (35.9%) patients met the diagnostic criteria of IPAF using a combination of serological and morphological domains, 53 (28.8%) patients met the diagnostic criteria of IPAF using clinical and morphological domains, 34 (18.5%) patients met the diagnostic criteria of IPAF using clinical and serological domains, and 31 (16.8%) patients met the diagnostic criteria of IPAF using all the three domains.

Table I. Baseline characteristics of patients.

Characteristics	Total	Pirfenidone	Non-pirfenidone	*p*-value
	n=184	n=81	n=103	
Age (year)	59.4 ± 9.5	58.0 ± 10.3	60.5 ± 8.7	0.077
Female, n (%)	100 (54.3)	49 (60.5)	51 (49.5)	0.176
BMI	24.8 ± 2.9	25.0 ± 3.1	24.7 ± 2.8	0.521
Smoking status				
Ever, n (%)	53 (28.8)	20 (24.7)	33 (32.0)	0.326
Current, n (%)	30 (16.3)	9 (11.1)	21 (20.4)	0.109
Observation periods (months)	15.0 ± 11.4	14.6 ± 10.3	15.4 ± 12.4	0.649
Pulmonary function				
FVC (litres)	2.00 ± 0.67	1.86 ± 0.67	2.10 ± 0.65	0.013*
FVC, %predicted	64.7 ± 16.6	59.7 ± 15.8	68.6 ± 16.3	<0.001*
DLCO, %predicted	59.3 ± 18.7	54.3 ± 17.9	63.0 ± 18.6	0.003*
PaO_2	83.0 ± 17.9	81.4 ± 1.9	84.3 ± 1.7	0.266
SaO_2%	95.5 ± 4.0	95.5 ± 2.5	95.6 ± 4.8	0.881
UIP pattern on CT	57 (31.0)	21 (25.9)	36 (33.3)	0.337
Treatment				
Corticosteroids n (%)	151 (82.1)	69 (85.2)	82 (79.6)	0.342
Maximal dose of prednisone (mg/day)	31.9 ± 1.3	33.2 ± 1.2	30.9 ± 1.4	0.198
Time for prednisone (months)	28.8 ± 5.6	29.7 ± 4.3	28.1 ± 6.2	0.438
Immunosuppressant n (%)	13 (7.1)	7 (8.6)	6 (5.8)	0.459

BMI: body mass index; FVC: forced vital capacity; DLCO: carbon monoxide diffusing capacity.
*$p<0.05$

Table II. Proportion of each domain of IPAF.

	Total n (%)	Pirfenidone n (%)	Non-pirfenidone n (%)	*p*-value
Subjects	184	81	103	
Clinical and serological	34 (18.5)	11 (13.6)	23 (22.3)	0.180
Clinical and morphological	53 (28.8)	25 (30.9)	28 (27.2)	0.625
Serological and morphological	66 (35.9)	31 (38.3)	35 (34.0)	0.547
All three domains	31 (16.8)	14 (17.3)	17 (16.5)	1.000
Clinical domain	118 (64.1)	50 (61.7)	68 (66.0)	0.643
Mechanical hands	14 (7.6)	5 (6.0)	9 (8.7)	0.472
Distal digital tip ulceration	3 (1.6)	1 (1.2)	2 (1.9)	0.684
Inflammatory arthritis or polyarticular morning joint stiffness ≥60min	45 (24.5)	20 (24.7)	25 (24.3)	0.948
Palmar telangiectasia	8 (4.3)	5 (6.0)	3 (2.9)	0.307
Raynaund's phenomenon	49 (26.6)	23 (28.4)	26 (25.2)	0.737
Unexplained digital oedema	7 (3.8)	3 (3.7)	4 (3.9)	0.950
Gottron's sign	2 (1.1)	1 (1.2)	1 (1.0)	0.864
Serological domain ^	131 (71.2)	56 (69.1)	75 (72.8)	0.625
I	80 (43.5)	31 (38.3)	49 (47.6)	0.240
II	26 (14.1)	12 (14.8)	14 (13.6)	
III	18 (9.8)	10 (12.3)	8 (7.8)	
IV	7 (3.8)	3 (3.7)	4 (3.9)	
Antinuclear antibody #	81 (44.0)	38 (46.9)	43 (41.7)	0.550
Rheumatoid factor ≥2 upper limit normal	49 (26.6)	17 (21.0)	32 (31.1)	0.125
Anti-cyclic citrullinated peptide (CCP)	1 (0.5)	1 (1.2)	0 (0)	0.258
Anti-double stranded DNA	6 (3.3)	2 (2.5)	4 (3.9)	0.592
Anti-SSA	27 (14.7)	14 (17.3)	13 (12.6)	0.375
Anti-SSB	15 (8.2)	8 (9.9)	7 (6.8)	0.448
Anti-ribonucleoprotein (RNP)	3 (1.6)	2 (2.5)	1 (1.0)	0.426
Anti-smith	11 (6.0)	5 (6.2)	6 (5.8)	0.921
Anti-topoisomerase (Scl-70)	4 (2.2)	3 (3.7)	1 (1.0)	0.207
Anti-tRNA synthetase	17 (9.2)	7 (8.6)	10 (9.7)	0.804
Morphological domain	150 (81.5)	70 (86.4)	80 (77.7)	0.180
NSIP	114 (62.0)	51 (63.0)	63 (61.2)	0.879
OP	26 (14.1)	13 (16.0)	13 (12.6)	0.508
NSIP+OP	10 (5.4)	6 (7.4)	4 (3.9)	0.295

NSIP: non-specific interstitial pneumonia; OP: organising pneumonia.
^ I, II, III, IV respectively represent one, two, three or four different kinds of auto-antibodies are positive with the patients. #ANA ≥1:320 titre, diffuse, speckled, homogeneous patterns or **a**. ANA nucleolar pattern (any titre) or **b**. ANA centromere pattern (any titre). *$p<0.05$

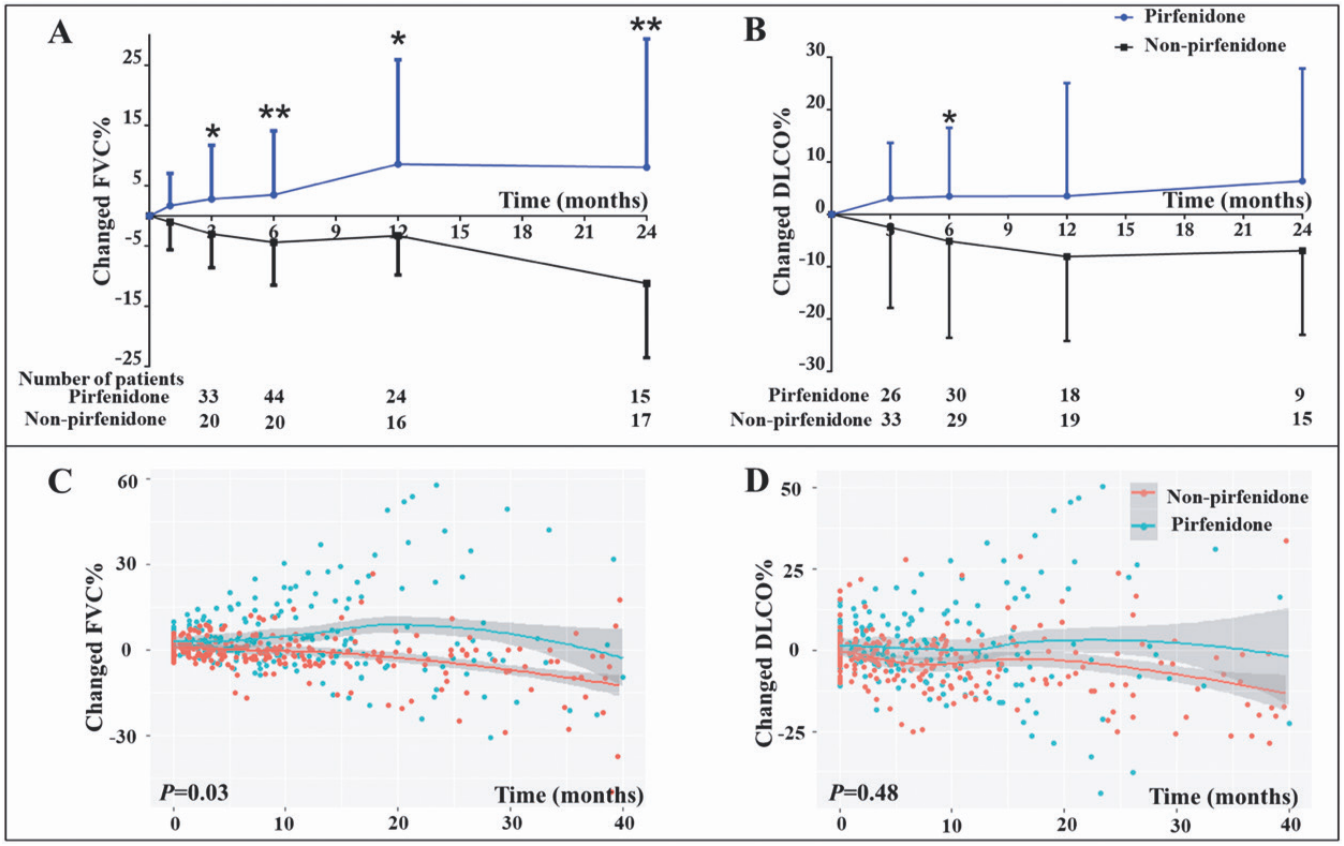

Fig. 2. Changes of FVC% and DLCO% for two groups of IPAF patients.
A-**B**: Changes of FVC% (A) and DLCO% (B) in the corresponding time point for two groups of IPAF patients.
C-**D**: Adjusted changes in FVC% (C) and DLCO% (D) in the two groups of patients. The adjustment was performed by mix-effect model for gender, age, UIP pattern, baseline FVC% and DLCO%.

Table III. Analysis of change in forced vital capacity (litres) outcome [#]

	Pirfenidone		Non-pirfenidone		Pirfenidone *vs.* non-pirfenidone
	n	Estimated FVC change in 1 year (95%)	n	Estimated FVC change in 1 year (95%)	*p*-value
Total	81	0.0390 (-0.0545,0.1326)	103	-0.0769 (-0.1250,-0.0288)	0.038*
FVC% <70%	58	0.0697 (-0.0541,0.1935)	56	-0.0574 (-0.1416,0.0269)	0.021*
FVC% >70%	23	-0.0533 (-0.1550,0.0483)	47	-0.1001 (-0.1550,-0.0453)	0.745
Pirfenidone = 600mg	33	-0.0369 (-0.1379,0.040)	103	-0.0848 (-0.1307,-0.0390)	0.125
Pirfenidone > 600mg	48	0.1251 (-0.0440,0.2942)	103	-0.0848 (-0.1307,-0.0390)	0.010*
Time ≤12 month[◊]	37	-0.0164 (-0.1435,0.2307)	103	-0.0848 (-0.1307,-0.0390)	0.224
Time >12 month	44	0.0960 (-0.0388,0.2307)	103	-0.0848 (-0.1307,-0.0390)	0.007*
M+C+S[Δ]	14	0.0612 (-0.0959,0.2183)	17	-0.1669 (-0.3340,0.0003)	0.407
C+S	11	-0.1957 (-0.3643,-0.0270)	23	-0.1174 (-0.1711,-0.0637)	0.149
M+C	25	0.2075 (-0.0471,0.4621)	28	-0.0051 (-0.1747,0.1646)	0.246
M+S	31	0.0229 (-0.1368,0.1826)	35	0.0005 (-0.0673,0.0684)	0.033*

FVC%- forced vital capacity% predicted. [#]Adjusted for age, sex, baseline forced vital capacity% predicted and baseline carbon monoxide diffusing capacity% predicted. [◊]Grouped by the time of pirfenidone therapy. [Δ]Grouped according to the diagnostic domain. M-morphological domain, C-clinical domain, S-serological domain. * $p<0.05$.

A breakdown of features into each IPAF domain showed that the most common clinical findings were Raynaud's phenomenon (49, 26.6%) and inflammatory arthritis or polyarticular morning joint stiffness lasting ≥60 min (45, 24.5%). Moreover, 131 patients had positive serum autoantibody (71.2%), and 51 cases had two or more positive antibodies. An ANA ≥1:320 (or nucleolar or centromere pattern of any titer) was the most common serological finding (81, 44.0%). Apart from the autoantibodies listed in table 2, the antineutrophil cytoplasmic antibodies were positive in 12 patients (11 p-ANCA and 1 c-ANCA). Within the morphological domain (150, 81.5%), the NSIP pattern by HRCT was found in 62.0% (114) of patients, while the OP pattern was found in 14.1% (26) patients. There

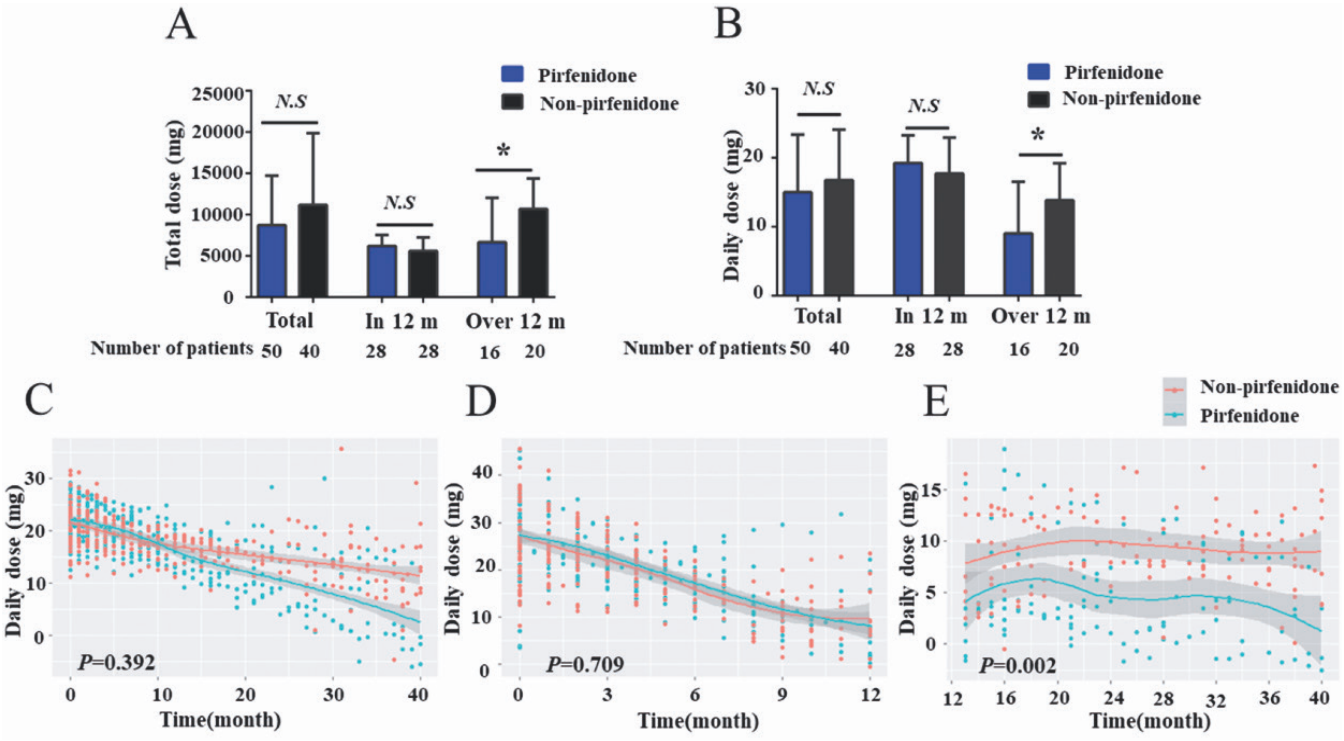

Fig. 3. Prednisone dose over time for IPAF patients treated with or without pirfenidone.
A-**B**: Total dose (A) and average daily dose (B) of prednisone in the two groups of patients.
C-**D**-**E**: The adjusted prednisone doses through overall observation time (C), in 12 months (D), and during month 12-40 (E). The adjustment was performed by mix-effect model for sex, age, UIP pattern, baseline FVC%, and baseline DLCO%.

were no differences in the diagnostic characteristics between the pirfenidone group and the non-pirfenidone group.

Changes in pulmonary function

The changes in FVC% (Fig. 2A) and DLCO% (Fig. 2B) between the two groups were compared at the time points of 3, 6, 12, 18, and 24 months. After 12 months of treatment, FVC% in the pirfenidone group was increased by 10.44%, while such value was decreased by 1.18% in the non-pirfenidone group (p=0.013). Besides, a greater increase of FVC% was observed in the pirfenidone group after 6 (p=0.003) and 24 months (p=0.003). A greater improvement of DLCO% was also observed in the pirfenidone group after 6 months (p=0.043).

Considering the potential confounders, we estimated the changes of FVC% (Fig. 2C) and DLCO% (Fig. 2D) using a mixed-effects model. After adjustment for sex, age, UIP pattern, baseline FVC%, and DLCO%, patients in the pirfenidone group continued to show a greater improvement in FVC% [1.49%, 95% CI (0.14%, 2.84%)] compared with the non-pirfenidone group (χ^2 (1) =4.59, p=0.032). However, no difference was observed in the change of DLCO% (χ^2 (1) =0.49, p=0.48). In conclusion, pirfenidone was associated with the improvement of FVC% in IPAF patients.

Subgroup analysis of the pulmonary function

To further explore the effect of pirfenidone in different subgroups, subgroup analysis was performed. Table III shows the average annual change in FVC absolute value**.** The volume of FVC (litres) was increased by 0.0390 L/year in the pirfenidone group, while such value was decreased by 0.0769 L/year in the non-pirfenidone group (p=0.038). The association between pirfenidone use and greater improvement in FVC showed a qualitatively same trend in patients with FVC <70% (p=0.021), with pirfenidone >600 mg/day (p=0.010), and with total medication time >12 months (p=0.007). Moreover, pirfenidone also showed superior effects in patients diagnosed by morphological and serological domains (p=0.033). Consequently, pirfenidone treatment had superior effects on FVC improvement when dose >600 mg/day and treatment time >12 months.

IPAF patients can reduce the dose of prednisone after 12 months

In our cohort, the prednisone dose ranged from 2.5 to 50 mg/day, with an average of 14.4 mg/day. The total dose (Fig. 3A) and daily dose (Fig. 3B) had no difference between the two groups when assessing the full duration of 40 months. However, when we separated the period into the initial 12 months and the remaining 12–40 months, both the total dose and daily dose of prednisone were significantly lower in the pirfenidone group (total dose, p=0.012; daily dose, p=0.032) during 12-40 months. After adjustment for potential confounders (sex, age, UIP pattern, baseline FVC%, and baseline DLCO%) in the mixed-effects model, patients in the pirfenidone group continued to show a reduced dose of prednisone by 6.27 mg per day (Fig. 3C-D-E χ^2 (1) =9.8385, p=0.002, pirfenidone n=34, non-pirfenidone n=27).

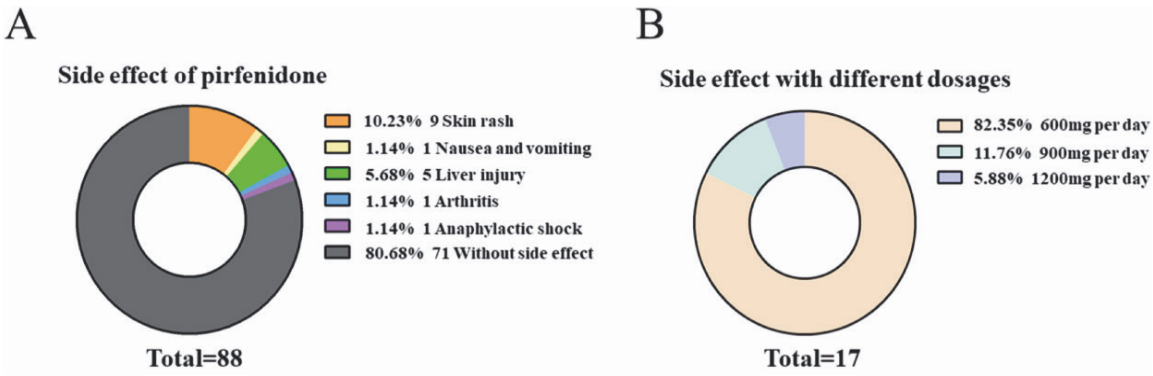

Fig. 4. Side effects of pirfenidone.
A: 17 (19.32%) patients in the pirfenidone group suffered from side effects, and 7 (7.95%) patients stopped the pirfenidone therapy due to side effects.
B: Side effects occurred in 14 patients (82.35%) with initial dosage (600 mg/day). 3 patients experienced side effects, while increasing pirfenidone dose.

Side effects of pirfenidone

In the present study, 17 (19.32%) patients had side effects after taking pirfenidone (Fig. 4A) with seven (7.95%) cases of severe side effects (one case of anaphylactic shock, one case of arthritis, one case of liver injury, one case of photosensitivity, and three cases of skin rash) who stopped the medication. Skin rash (10.23%) and liver injury (5.68%) were the most common side effects, which were similar to those of IPF patients (12). Moreover, 14 (14/17, 82.35%) patients experienced side effects at the initial dose (600 mg), and three (17.65%) patients experienced side effects after the dose of pirfenidone was increased (Fig. 4B).

Discussion

Several clinical trials have confirmed the efficacy of pirfenidone in IPF, demonstrating that pirfenidone can delay the decline of FVC and increase the progression-free survival rates (16, 28-29). However, no study has explored the effects of pirfenidone in IPAF patients. Our observational study identified that the use of pirfenidone was associated with the improvement of FVC and the reduction of prednisone dose. The strengths of the study included the longitudinal data of PFT and prednisone dosage throughout 40 months as well as subgroup analyses of lung function.

The pathological features of IPAF are autoimmune inflammatory exudation and interstitial fibrosis. Therefore, the treatment for IPAF would cover both of the two sides. Wiertz *et al*. (30) have reported that IPAF patients may benefit from cyclophosphamide treatment. Besides, McCoy *et al*. (31) have shown that mycophenolate therapy can attenuate disease progression in IPAF patients. Nevertheless, all these published studies are designed to explore the effect of immunosuppressive therapy. No studies have yet explored the effect of anti-fibrosis treatment in IPAF patients. In the present study, we, for the first time, reported that the anti-fibrosis treatment of pirfenidone could improve the pulmonary function of IPAF patients.

The average dosage of pirfenidone was 1,492 mg/day, suggesting that the dosage of pirfenidone for IPAF was not necessarily as high as that for IPF. Reasons might be as follows: 1) IPAF patients are relatively younger than IPF patients, as the mean age is 57–68 for IPAF (4-9) and 68–79 for IPF (18, 28-29) at diagnosis; 2) IPAF patients have more inflammatory exudative lesions on chest CT scans (*e.g*. NSIP and OP); 3) pirfenidone is mostly prescribed in combination with glucocorticoids; and 4) effective dose for East-Asian patients may be lower than Caucasian. In a phase-III clinical trial in Japan (29), the effective dose of pirfenidone is 1,800 mg/day or 1,200 mg/day for IPF patients, which is lower than that in clinical trials (CAPACITY and ASCEND) in Caucasians (2,400 mg/day) (28, 29). Besides, we began with a low dose (600 mg/day) for the following considerations. 1) We observed that a low dose could achieve a certain effect on IPAF patients. 2) Low dose could help prevent side effects. 3) There is a heavier financial burden for some patients in China if they take a high dose of pirfenidone. The duration of pirfenidone treatment was similar between our study and the IPF clinical trials (16, 28, 29). Both indicated that the change of FVC was noted when the medication course was longer than 12 months.

The overall incidence of side effects was lower (19.32%) in the present study compared with other IPF clinical trials (28, 29). Only 10.23% of the patients had skin rash in our study, while such proportion is 28.1–32% in other IPF clinical trials (28, 29), which could be explained by the lower dose of pirfenidone (average 1,492 mg/day) in our study. The side effects of pirfenidone were dose-related in this study. Three (3.4%) patients experienced skin rash and liver damage when the pirfenidone dose was increased. These results further demonstrated the benefits of lower-dose pirfenidone for IPAF patients.

Corticosteroids are widely used in IPAF patients. In the present study, the steroid dose was significantly reduced when pirfenidone was used for initial steroid-sparing therapy. Specifically, the dose of prednisone was reduced by 6.27 mg per day in the pirfenidone group after 12 months of pirfenidone treatment. Consistent with this, Huapaya *et al*. have reported the use of immunosuppressants (azathioprine and mycophenolate) in 110 patients with myositis-related ILD (M-ILD) is associated with the reduction of prednisone dose (32). The reduction of prednisone dose prevents the side effects of corticoids, therefore improving the medication compliance and treatment outcomes in IPAF patients.

Our study has several limitations. First, the study is limited to reporting associations, but unable to identify causal relationships due to the retrospective, single-center, and observational nature. Second, patients were not randomised to pirfenidone treatment. Therefore, pirfenidone exposure might cause an indication bias. Patients receiving pirfenidone were more likely to have a progressive fibrosing ILD. However, the subgroup analysis identified the same effect of pirfenidone in patients with FVC%<70%. Besides, limited follow-up of subjects over time might lead to misleading estimates of beneficial drug effects. Nevertheless, the follow-up bias could be weakened by adding the time interval as a random effect into the mixed-effects model. Last, although the analysis was adjusted by the mixed-effects model, system differences in the cohorts could not be ignored. Therefore, our current findings need to be confirmed by prospective studies. However, multi-center clinical trials cannot be accomplished in a short time. Therefore, in the meantime, our study might help provide suggestions for therapy in IPAF patients.

Conclusion

Collectively, our findings indicated that low-dose pirfenidone (1,492 mg/day) might help improve FVC with an acceptable safety and tolerability profile in IPAF patients.

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