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Double-Blind Randomized Trial of Pirfenidone in Chinese Idiopathic Pulmonary Fibrosis Patients

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Abstract: Idiopathic pulmonary fibrosis (IPF) lacks effective treatment. Pirfenidone has been used to treat IPF patients. *N*-acetylcysteine (NAC) exerts antioxidant and antifibrotic effects on IPF cases.

This study is a double-blind, modified placebo-controlled, randomized phase II trial of pirfenidone in Chinese IPF patients. We randomly assigned the enrolled Chinese IPF patients with mild to moderate impairment of pulmonary function to receive either oral pirfenidone (1800 mg per day) and NAC (1800 mg per day) or placebo and NAC (1800 mg per day) for 48 weeks. The primary endpoints were the changes in forced vital capacity (FVC) and walking distance and the lowest SPO₂ during the 6-minute walk test (6MWT) at week 48. The key secondary endpoint was the progression-free survival time. This study is registered in ClinicalTrials.gov as number NCT01504334.

Eighty-six patients were screened, and 76 cases were enrolled (pirfenidone + NAC: 38; placebo + NAC: 38). The effect of pirfenidone treatment was significant at the 24th week, but this effect did not persist to the 48th week. At the 24th week, the mean decline in both FVC and ΔSPO₂ (%) during the 6MWT in the pirfenidone group was lower than that in the control group (-0.08 ± 0.20 L vs -0.22 ± 0.29 L, $P = 0.02$ and $-3.44\% \pm 4.51\%$ vs $-6.29\% \pm 6.06\%$, $P = 0.03$, respectively). However, there was no significant difference between these 2 groups at the 48th week (-0.15 ± 0.25 L vs -0.25 ± 0.28 L, $P = 0.11$ and $-4.25\% \pm 7.27\%$ vs $-5.31\% \pm 5.49\%$, $P = 0.51$, respectively). The pirfenidone treatment group did not achieve the maximal distance difference on the 6MWT at either the 24th or the 48th week. But pirfenidone treatment prolonged the progression-free survival time in the IPF patients (hazard ratio = 1.88, 95% confidence interval: 1.092–3.242, $P = 0.02$). In the pirfenidone group, the adverse event (AE) rate (52.63%) was higher than that in the control group (26.3%, $P = 0.03$). Rash was more common in the pirfenidone group (39.5% vs 13.2%, $P = 0.02$).

Compared with placebo combined with high-dose NAC, pirfenidone combined with high-dose NAC prolonged the progression-free survival of Chinese IPF patients with mild to moderate impairment of pulmonary function. (ClinicalTrials.gov number, NCT01504334).

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Abbreviations: ABG = analyses of arterial blood gas, AE = adverse event, AE-IPF = acute exacerbation of IPF, DLCO = carbon monoxide diffusing capacity, EOT = end-of-treatment, ESR = erythrocyte sedimentation rate, FAS = full analysis set, FVC = forced vital capacity, HRCT = high-resolution computed tomography, IPF = idiopathic pulmonary fibrosis, 6MWT = 6-minute walk test, NAC = *N*-acetylcysteine, PFD = pirfenidone, PFS = progression-free survival, PFT = pulmonary function tests, PPS = per protocol set, RF = rheumatoid factor, SAS = Statistical Analysis System, SGRQ = St George's Respiratory Questionnaire, SS = safety set, UIP = usual interstitial pneumonia.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal disease that lacks an effective treatment. The median survival time for IPF patients is just 3 years.¹ A characteristic of the pathological manifestation of IPF is the presence of fibroblastic foci in the fibrotic lung. TGF-β is a central stimulator of collagen production during the pathogenesis of pulmonary fibrosis.^{2–4} Moreover, oxidative stress contributes to the pathogenesis of IPF and may coordinate with TGF-β during the progression of IPF.^{5–7}

Pirfenidone (PFD), or 5-methyl-1-phenyl-2-[1H]-pyridone, is a novel agent developed for the treatment of IPF. PFD and its metabolites 5-hydroxypirfenidone (PFD-OH) and 5-carboxypirfenidone (PFD-COOH) exert antifibrotic and antioxidant effects.^{8–11} After several phase II and III clinical trials for PFD,^{12–15} PFD has been used for IPF patients in Japan, Europe, and India. And in the new treatment guideline for IPF, both PFD and nintedanib are conditionally recommended for the treatment for IPF patients.¹⁶ *N*-acetylcysteine (NAC) also has antioxidant and antifibrotic effects, and high-dose NAC had been weakly recommended for IPF patients according to 2011 IPF guideline.^{1,17–20} But recent clinical trial has not showed the efficacy of high-dose NAC for IPF.²¹ In the new treatment guideline for IPF, NAC monotherapy is conditionally recommended against to use. But the ATS does recommend to keep patients on NAC if they are tolerating well.²¹ The evidence for or against the use of NAC is still not very clear.

Based on the results of these clinical trials and new treatment guideline for IPF, we performed a double-blind, modified placebo-controlled, randomized phase II trial of PFD in Chinese IPF patients. In our trial, the baseline treatment was high-dose NAC (600 mg 3 times daily), and PFD or placebo was added to the enrolled patients. To our knowledge, this may be the first registered clinical trial to use a PFD and NAC combination therapy for IPF.

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METHODS PATIENTS

The diagnosis of IPF was in accordance with evidence-based guidelines for the diagnosis and management of IPF published in 2011.¹ All patient high-resolution computed tomography (HRCT) images and lung-biopsy specimens were reviewed centrally (in our hospital) by 2 experienced radiologists and 2 experienced pathologists, respectively, to verify eligibility. The diagnosis for each enrolled case in our trial was approved based on a multidisciplinary discussion of experienced interstitial lung disease experts in respiratory, pathology, and radiology departments. The eligible patients were 18 to 75 years of age. Patients younger than 50-years old were required to exhibit a characteristic usual interstitial pneumonia (UIP) pattern based on a surgical lung biopsy. After the diagnosis of IPF was acquired, the patient was enrolled to this trial for further screening. In addition to the diagnosis of IPF, all enrolled cases met the following lung function criteria: percentage of predicted forced vital capacity (FVC) of at least 45%, percentage of predicted carbon monoxide diffusing capacity (DLCO) of at least 30%, and PaO₂ of at least 50 mmHg when the patient is at rest and breathing room air.

The exclusion criteria were as follows:

- (1) aggravated dyspnea during the preceding 6 months;
- (2) currently in a period of acute exacerbation of IPF (AE-IPF);
- (3) fasting blood glucose level of more than 11.1 mmol/L
- (4) comorbid conditions including malignancy, bleeding tendency, severe hepatic dysfunction (alanine transaminase or aspartate transaminase level 2-fold above the upper limit of normal), or renal (serum creatinine level above the upper limit of normal) or cardiac disease (New York Heart Association grade 3–4);
- (5) use of immunosuppressants, antifibrotic drugs including interferon, D-penicillamine and colchicine, or oral corticosteroids at a dose \geq 15 mg/day or the equivalent during the preceding 3 months;
- (6) current pregnancy or breastfeeding;
- (7) enrollment in another clinical trial during the preceding 1 month; or
- (8) denied by the researchers.

All enrolled patients provided written informed consent, and the protocol for our study was approved by the ethics committee of each center.

Study Design

The study was a double-blind, placebo-controlled, randomized, multicenter clinical trial that was conducted at 5 sites in northern China, including Beijing (3 centers), Tianjin (1 center), and Shenyang (1 center). The study was approved by the State Food and Drug Association of China (number 2010L03738). The trial is also registered in ClinicalTrials.gov (number NCT01504334).

Beijing Kawin Technology Share-Holding Co., Ltd. provided 200 mg PFD and matching placebo tablets, as well as NAC, for oral use. All patients were treated with 600 mg of NAC (Fluimucil, Zambon Group) 3 times daily as a baseline treatment. The patients were randomly assigned to the PFD or placebo (1:1) group using a modified permuted-block centralized dynamic randomization method with block sizes of 4. A dose titration schedule for PFD/placebo was arranged for all enrolled patients: the patients received oral tablets (PFD/

placebo) at a dose of 200 mg 3 times daily for the first 7 days, 400 mg 3 times daily for the 2nd week, and 600 mg 3 times daily (target dose) for the 3rd week. The target dose was maintained in patients who tolerated it throughout the subsequent study period. If the patients did not tolerate 1800 mg of PFD daily, their treatment was modified to a reduced regimen according to the Standards for Classification of Serious Adverse Drug Reactions.¹³ It was suggested to administer PFD/placebo and NAC with food. The enrolled patients were advised to use sunscreen and/or long sleeves and hats during exposure to direct sunlight. All patients were asked to take a reliable method of contraception during the clinical trial when they and/or their partners were fertile.

The patients were observed in the clinic weekly for 2 weeks; after 2 weeks, they were asked to follow-up in the clinic at the 4th, 12th, 24th, 36th, and 48th weeks after they were enrolled. A complete blood count, urine analysis, the erythrocyte sedimentation rate (ESR), the C-reactive protein level, a blood chemistry panel (including hepatic and kidney function and lipid levels), an auto-antibody panel (including antinuclear antibodies, antiextractable nuclear antigen, antineutrophil cytoplasmic antibodies, rheumatoid factor [RF], and antiphospholipid antibodies) were tested. Complete blood count, urine analysis, and the blood chemistry panel were repeated on the 4th, 24th, and 48th weeks. All HRCT scans, pulmonary function tests (PFTs), 6-minute walk tests (6MWTs), analyses of arterial blood gas (ABG), electrocardiography, dyspnea, and St George's Respiratory Questionnaire (SGRQ) were performed in accordance with the predetermined protocol at baseline and at 24-week intervals.

The HRCT findings were graded on a scale of 1 to 6 based on the classification by Ichikado et al²² for areas with ground-glass attenuation, reticular changes, or honeycombing.

Efficacy Endpoints

The primary endpoints were defined as the change in FVC from baseline to week 48, and the change in the maximal distance on the 6MWT and the change in the lowest SPO₂ during the 6MWT from baseline to week 48. The secondary endpoints were defined as the change in the result on the resting PFT, including the percentage predicted FVC, FEV1 and the percentage predicted FEV1, total lung capacity (TLC) and the percentage predicted TLC, DLCO and the percentage predicted DLCO, DLCO/VA from baseline to week 48; the change in ABGs including PaCO₂, PaO₂, and SaO₂; episodes of AE-IPF;¹ progression-free survival (PFS) duration, which was defined as the time until the first occurrence of any one of the following:¹⁵ a confirmed \geq 10% decline in the percentage predicted FVC, a confirmed \geq 15% decline in the percentage predicted DLCO (corrected based on the patient's actual hemoglobin levels), a confirmed progression of fibrosis defined by the HRCT fibrosis score, AE-IPF, or death; change in the dyspnea score; change in fibrosis according to HRCT; and change in the SGRQ score.

Safety was assessed based on clinical and laboratory evaluations at all visits and adverse events (AEs) recorded by investigators.

Statistical Analysis

Statistical analysis was performed using Statistical Analysis System (SAS) software version 9.2 (SAS Institute Inc., Cary, NC). The means and the 95% confidence intervals were calculated. Differences in the means were examined using 2-sided *t*-tests, and statistical significance was defined as

$P < 0.05$. Baseline data were analyzed for each full analysis set (FAS). Efficiency variables were calculated for each FAS and per protocol set (PPS). Safety analyses were performed using each safety set (SS). Quantitative data regarding the clinic visits of the 2 groups were expressed as the means and standard deviations. Paired t -tests were employed to test the difference between the basic characteristics at baseline. Analysis of variance was performed to compare the parameters before and after treatment. Qualitative data were expressed as frequencies, and differences between the groups were examined using the χ^2 test or a nonparametric test.

RESULTS

Enrolled Cases and Follow-Up

Eighty patients were screened from January 10, 2012 to July 6, 2012, and 76 cases were enrolled in this study (PFD: 38, placebo: 38) (Figure 1). Among the 38 cases in the PFD group,

34 cases were included in the PPS, and 38 cases were included in the FAS and the SS. Among the 38 cases in the control group, 37 cases were included in the PPS, and 38 cases were included in the FAS and the SS. Six cases withdrew from the study, including 3 cases that withdrew consent and 3 cases that had trial-associated AEs. Four cases died during the study, including 2 cases in the PFD group and 2 cases in the control group. Sixty-six cases completed the entire study.

Among these 76 IPF cases, 56 cases were diagnosed with a definite UIP pattern according to HRCT, and the others were diagnosed with a probable UIP pattern. Four cases underwent a surgical lung biopsy and were found to exhibit a characteristic pathological UIP pattern. There were no significant differences in the baseline characteristics between the PFD group and the control group (Table 1). Most of the enrolled cases were male (86.8% in the PFD group and 100% in the control group, $P = 0.05$). On the baseline 6MWT, the maximal distance was 459.87 ± 100.86 m in the PFD group and 469.58 ± 81.56 m in

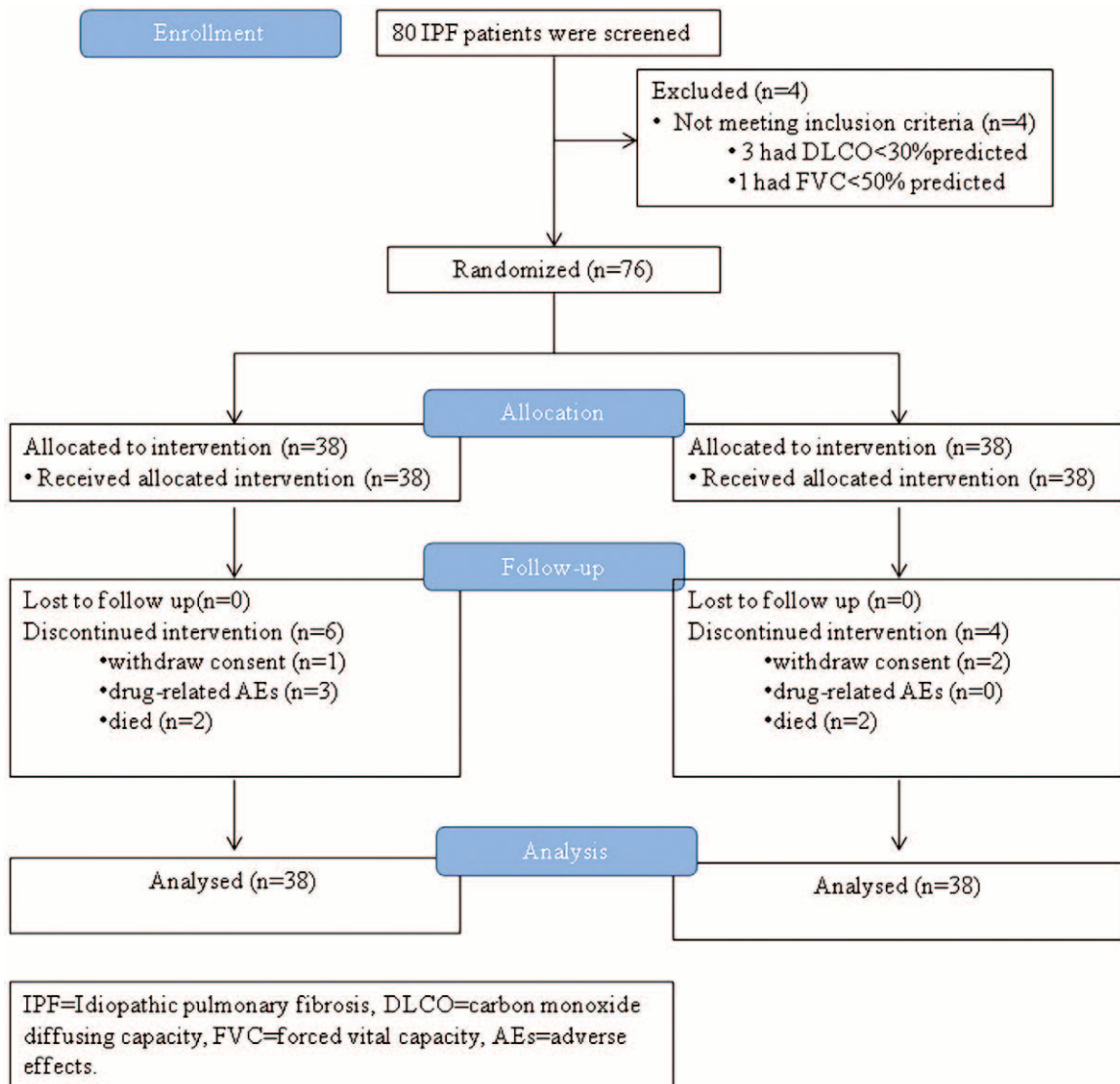


FIGURE 1. Enrollment and outcomes.

TABLE 1. Baseline Characteristic of the Enrolled Patients

Characteristics	PFD Group (n = 38)	Placebo Group (n = 38)	P Value
Age	59.03 ± 5.94	61.61 ± 6.39	0.07
Man	33/86.84%	38/100.00%	0.05
BMI, kg/m ²	26.53 ± 3.94	26.49 ± 3.32	0.97
Han nationality	38/100.00%	35/92.11%	0.24
Course of IPF, m	6.00 ± 23.00	12.00 ± 23.00	0.58
Smoking status			
Never	6/15.79%	5/13.16%	0.03
Former	6/15.79%	0/0.00%	
Current	26/68.42%	33/86.84%	
Environmental exposure			
None	25/65.79%	31/81.58%	0.3
Birds	2/5.26%	0/0.00%	
Mold	1/2.63%	0/0.00%	
Dust	5/13.16%	5/13.16%	
Others*	5/13.16%	2/5.26%	
Past medications [†]			
Yes	28/73.68%	26/68.42%	
No	10/26.32%	12/31.58%	0.80
No baseline disease 19/50.00%	18/47.37%	1.00	
Drug allergy			
No	32/84.21%	35/92.11%	0.48
Clinical manifestations			
Cough	34/89.47%	35/92.11%	1.00
Dyspnea	27/71.5%	23/60.53%	0.47
Clubbing	17/44.74%	18/47.37%	1.00
Velcro rales	35/92.11%	37/97.37%	0.61
PFT			
FVC, L	2.85 ± 0.72	3.04 ± 0.68	0.24
FVC (%predicted)	75.55 ± 14.72	79.07 ± 18.25	0.36
TLC, L	4.68 ± 1.19	4.78 ± 1.12	0.70
TLC (%predicted)	75.69 ± 17.66	73.74 ± 17.45	0.63
DLCO, mL/min/mmHg	12.71 ± 4.16	12.81 ± 5.27	0.93
DLCO (%predicted)	47.43 ± 12.73	47.68 ± 13.76	0.93
PO ₂ (mmHg, @room air)	77.89 ± 13.01	78.15 ± 11.56	0.93
6MWT distance, m	459.87 ± 100.86	469.58 ± 81.56	0.65
SPO ₂ (%) changes during 6MWT	-4.55 ± 3.56	-5.58 ± 5.14	0.32
Total SGRQ score [‡]	38.71 ± 19.48	32.18 ± 19.73	0.15
HRCT score	6.00 ± 1.69	5.87 ± 1.47	0.72

BMI = body mass index, DLCO = carbon monoxide diffusing capacity, FVC = forced vital capacity, HRCT = high-resolution computed tomography, IPF = idiopathic pulmonary fibrosis, 6MWT = 6-minute walk test, PFD = pirfenidone, PFT = pulmonary function test, TLC = total lung capacity.

* Including aluminum processing × 1, raising a dog × 2, raising a cat × 2, making carpet more than 10 years × 1 and cotton planting and processing × 1.

[†] Including prednisone, NAC, immunosuppressant, for example, azathioprine, cyclophosphamide, mycophenolate mofetil.

[‡] St. George's Respiratory Questionnaire (SGRQ).

the control group ($P = 0.65$), and the SPO₂ (%) decreased by $4.55\% \pm 3.56\%$ in the PFD group and by $5.58\% \pm 5.14\%$ in the control group ($P = 0.32$). There were no significant differences in the baseline PFT indices, including FVC, TLC, and DLCO, between the PFD and control groups (Table 1).

Primary Efficacy Analysis

The effect of PFD treatment was significant at the 24th week, but this effect did not persist to the 48th week. At the 24th week, the mean decline in both FVC and Δ SPO₂ (%) on the 6MWT in the PFD group was lower than that in the control group (-0.08 ± 0.20 L vs -0.22 ± 0.29 L, $P = 0.02$ and

$-3.44\% \pm 4.51\%$ vs $-6.29\% \pm 6.06\%$, $P = 0.03$, respectively). Although the mean decline in these indices tended to be smaller in the PFD group, there was no evident difference between these 2 groups at the 48th week (-0.15 ± 0.25 L vs -0.25 ± 0.28 L, $P = 0.11$ and $-4.25\% \pm 7.27\%$ vs $-5.31\% \pm 5.49\%$, $P = 0.51$, respectively) (Figure 2A–D). PFD treatment did not result in a maximum distance difference on the 6MWT at either the 24th or the 48th week. However, there was a trend of a smaller decline in the PFD group (Table 2).

Based on subgroup analysis, we found that 4 cases (3 cases in the PFD group and 1 case in the control group) had a significant AE-associated decline in the PFT results during

the second 24 weeks. In the PFD group, 1 case suffered from an aggravated dry cough after a cold during the 28th week, and this event influenced the PFT procedure; 1 case caught an upper respiratory infection that was complicated by acute bronchiolitis on the 47th week and completed the end-of-treatment (EOT) follow-up on the 48th week; and 1 case suffered from AE-IPF on the 46th week and completed the EOT follow-up on the 48th week 3 days after discharge. In the control group, one case suffered from AE-IPF on the 44th week and completed the EOT follow-up on the 48th week, 8 days after discharge. If we excluded these 4 cases, there was a significant difference in FVC between the PFD group and the control group at both the 24th (-0.08 ± 0.20 vs -0.22 ± 0.29 , 38 vs 38 cases, $P = 0.018$) and 48th weeks (-0.11 ± 0.25 vs -0.24 ± 0.28 , 35 vs 37 cases, $P = 0.048$).

Secondary Efficacy Analysis

For the PFT indices, the mean decline in FVC% and DLCO at the 24th week in the PFD group was lower than that in the control group ($0.68\% \pm 7.66\%$ vs $6.11\% \pm 7.70\%$, $P = 0.004$ and $0.73\% \pm 9.36\%$ vs $5.29\% \pm 9.62\%$, $P = 0.048$, respectively). Although the difference between the PFD group and the control group disappeared at the 48th week, there smaller declines were observed in the PFD group. There were no significant differences in the other PFT indices included as secondary endpoints between the 2 groups (Table 3).

TABLE 2. Changes of Indexes in the 6MWT During the Study

Indexes	PFD Group	Control Group	P Value
Maximum distance, m			
Baseline	459.87 ± 100.86	469.58 ± 81.56	0.65
24th week	469.71 ± 93.44	459.71 ± 94.95	0.64
48th week	473.68 ± 128.78	464.45 ± 92.62	0.72
Δ24th week	9.84 ± 74.05	-9.87 ± 76.14	0.25
Δ48th week	13.82 ± 125.19	-5.13 ± 85.48	0.43
SPO ₂ , %			
Δ24th week	-3.44 ± 4.51	-6.29 ± 6.06	0.03
Δ48th week	-4.25 ± 7.27	-5.31 ± 5.49	0.51

6MWT = 6-minute walk test, PFD = pirfenidone.

No significant differences were observed in the percent change in the ABG (PaCO₂, PaO₂, and SaO₂) levels, the dyspnea score, the HRCT findings, the SGRQ score, or the number of AE-IPF episodes between the PFD and placebo groups (Table 3).

However, PFD treatment prolonged the PFS duration of the IPF patients (hazard ratio = 1.88, 95% confidence interval: 1.092–3.242, $P = 0.02$) (Figure 3).

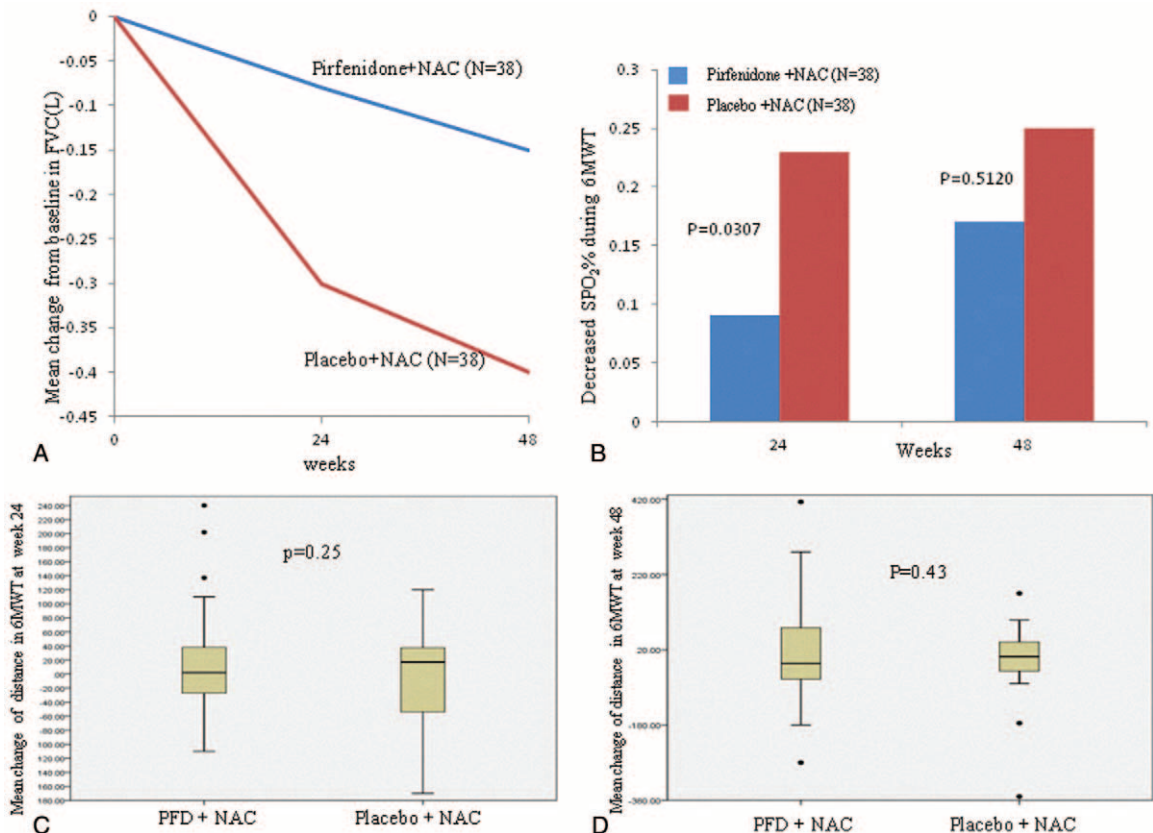


FIGURE 2. (A) Shows the mean change in FVC from baseline to the 24th week ($P = 0.02$) and the 48th week in the PFD and placebo groups ($P = 0.11$). (B) Shows the mean decline in Δ SPO₂ (%) during the 6MWT. (C) Shows the mean change in the maximum walk distance on the 6MWT from baseline to the 24th week. (D) Shows the mean change in the maximum walk distance on the 6MWT from baseline to the 48th week. FVC = forced vital capacity, 6MWT = 6-minute walk test, PFD = pirfenidone.

TABLE 3. Summary of the Secondary Endpoints

	PFD Group	Control	P Value
PFT indexes			
ΔFVC%	-1.95 ± 9.99	-5.40 ± 6.56	0.10
ΔFEV1, L	-0.17 ± 0.22	-0.16 ± 0.19	0.83
ΔFEV1%	-3.09 ± 12.54	-4.66 ± 7.01	0.53
ΔTLC, L	-0.47 ± 0.81	-0.29 ± 0.72	0.36
ΔTLC%	-7.32 ± 14.30	-5.22 ± 11.22	0.52
ΔDLCO, mL/min/mmHg	-1.15 ± 3.49	-1.61 ± 4.42	0.65
ΔDLCO%	-2.83 ± 9.95	-4.44 ± 10.68	0.53
ΔPO ₂ , mmHg	-0.15 ± 11.90	-2.61 ± 11.89	0.40
ΔHRCT score	5.84 ± 1.63	5.74 ± 1.38	0.77
ΔSGRQ score	-6.19 ± 20.99	0.18 ± 21.48	0.23
ΔDyspnea score	0.69 ± 2.99	1.65 ± 2.76	0.26
AE-IPF, %	5.26	13.2	0.43

AE-IPF=acute exacerbation of idiopathic pulmonary fibrosis, DLCO=diffusing capacity of the lung for carbon monoxide, FEV1=forced expiratory volume in one second, FVC=forced vital capacity, HRCT=high-resolution computed tomography, PFD=pirfenidone, PO₂=partial pressure of oxygen, SGRQ=St. George hospital respiratory questionnaire, TLC=total lung capacity.

Adverse Effects

The AEs that occurred during the study period are summarized in Table 4. In the PFD group, the AE rate was 52.63% higher than in the control group (26.3%, $P=0.03$). Rash was more common in the PFD group (39.5% vs 13.2%, $P=0.02$). Rash, pruritus, and allergic dermatitis were the skin-related AEs. All of these events were mild to moderate in severity, reversible, and without clinical sequelae. There were no significant differences in the occurrence of other AEs, including gastrointestinal-related events, weight loss, back pain, and changes in hepatic function, between the groups (Table 4). Three cases withdrew from the study because of back pain (1 case), rash (1 case), or an elevation in the alanine aminotransferase and aspartate aminotransferase levels (1 case). After they stopped taking the trial medications, these AEs disappeared.

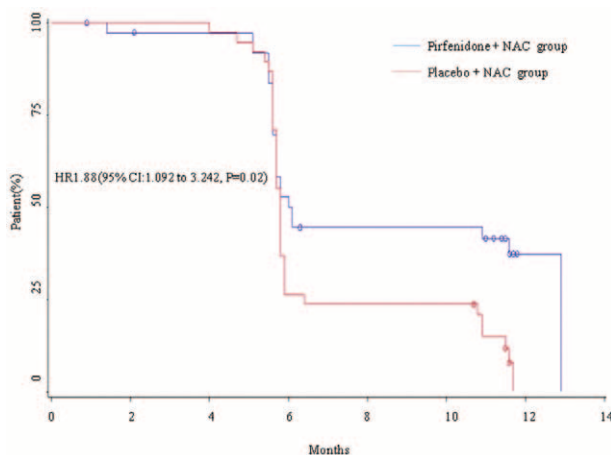


FIGURE 3. Kaplan–Meier curves for the duration of PFS in the PFD and placebo groups. PFD=pirfenidone, PFS=progression-free survival.

No cases in the control group withdrew from the trial because of AEs.

Serious AEs occurred in 4 cases (10.53%), 2 each in the PFD and control groups. In the PFD group, 2 cases (5.26%) died of AE-IPF, 1 case (2.63%) was admitted because of a respiratory infection, and 1 case (2.63%) was hospitalized for ischemic heart disease. In the control group, 2 cases (5.26%) died of AE-IPF, 1 case (2.63%) was hospitalized for dizziness, and 1 case (2.63%) was hospitalized for coronary artery disease.

DISCUSSION

PFD, a new and promising antifibrotic agent,⁸ has been approved due to its efficacy in the treatment of patients with mild to moderate IPF in Japan,^{13,14,23} the European Union,^{15,24} and the United States²⁵ based on an open-label phase II study.¹² It had never been used in a Chinese clinical trial of IPF cases. This double-blind, placebo-controlled, randomized phase II trial is the first study in China to evaluate the efficacy and safety of PFD in IPF patients. A summary of these 4 RCT studies is shown in Table 5.

In our study, although no significant difference in the primary endpoints was observed between the PFD and control groups, significant PFD efficacy was shown based on the decline in FVC at the 24th week between these 2 groups. We also showed that PFD treatment prolonged the PFS duration of IPF patients. Somewhat similar results were observed in one of the CAPACITY studies (ie, study 006), in which no significant difference in the primary endpoint (ie, percentage predicted FVC at the 72nd week [the EOT point]) was shown between the PFD and control groups. However, a significant PFD treatment effect on the percentage-predicted FVC (the primary endpoint) was observed between week 12 and week 48.¹⁵ In contrast, the pooled data from the CAPACITY study supported a PFD effect on the percentage predicted FVC, the PFS time, and the distance on the 6MWT. Furthermore, this PFD effect on the percentage-predicted FVC and the PFS time was verified in the ASCEND study.²⁵ We performed a further analysis of all of the data, and we found that 4 cases, 3 cases in the PFD group and 1 case in the control group, showed a substantial decline in the PFT parameters, including FVC, TLC, and DLCO, because of AEs within 4 weeks of the EOT timepoint. After we reevaluated the data excluding these 4 cases, a significant PFD treatment effect on FVC was observed at both 24 and 48 weeks. Larger sample sizes or long-term similar study is expected to verify the results.

Treatment with 600 mg of NAC 3 times daily was used as the baseline treatment for both the PFD and control groups. Although a recent trial of NAC in IPF showed that high-dose NAC did not help to preserve FVC in IPF patients who had mild to moderate impairment in pulmonary function at baseline,²¹ some basic research has shown that NAC displays antioxidant activity, which helps suppress oxidative stress in pulmonary fibrosis,^{18,26} inhibits the epithelial-mesenchymal transition in alveoli,²⁰ and inhibits TGF-β1 release into the lung.²⁷ Although in the new treatment guideline conditional recommendation against the use of NAC monotherapy for IPF was suggested, the ATS committee still does recommend to keep patients on NAC if they are tolerating well.¹⁶ All that means is that the overall evidence for or against the use of NAC is still not very clear. We cannot totally exclude the NAC effect on IPF cases. As high-dose NAC was administered to both the PFD and control groups, NAC might have added noise to the results of our trial.

TABLE 4. Treatment-Emergent Adverse Effects

Adverse Effects	PFD Group (n/%)	Control Group (n/%)	P Value
Skin-related			
Rashes	15/39.5%	5/13.2%	0.02
Itching	1/2.63%	0/0.00%	1
Allergic dermatitis	0/0.00%	1/2.63%	1
Gastrointestinal-related			
Nausea	2/5.26%	2/5.26%	1
Anorexia	1/2.63%	1/2.63%	1
Diarrhea	3/7.89%	0/0.00%	0.24
Heart burn	2/5.26%	0/0.00%	0.49
Acid regurgitation	3/7.89%	0/0.00%	0.24
Stomachache	1/2.63%	1/2.63%	1
Epigastric discomfort	2/5.26%	1/2.63%	1
Abdominal distension	1/2.63%	0/0.00%	1
Dyspnea worsening	2/5.26%	2/5.26%	1
Fever	2/5.26%	0/0.00%	0.49
Dry mouth	1/2.63%	0/0.00%	1
Blurred vision	1/2.63%	0/0.00%	1
Chest pain	1/2.63%	1/2.63%	1
Back pain	1/2.63%	0/0.00%	1
Body weight loss	1/2.63%	0/0.00%	1
Laboratory abnormalities			
Hypokalemia	1/2.63%	0/0.00%	1
Hyponatremia	1/2.63%	0/0.00%	1
Aminotransferase elevations	2/5.26%	0/0.00%	0.49
Abnormal ECG	1/2.63%	0/0.00%	1

ECG = electrocardiograph, PFD = pirfenidone.

In Oltmann study,²⁸ 12 cases (19%) used NAC during PFD treatment, and these combination therapy patients had a higher rate of disease progression than their patients with PFD monotherapy. However, the cases receiving NAC and PFD combination therapy exhibited worse baseline pulmonary function. Our clinical trial might be the first study to administer PFD and NAC combination therapy to IPF cases. Larger sample sizes and long-term studies are needed in China to confirm the efficacy of PFD and NAC on Chinese IPF patients.

Similar to 4 RCT studies,^{13–15,25} AEs occurred more frequently in the PFD group than in the control group, and skin- and gastrointestinal-related AEs were the primary AEs in the PFD group. Sixteen cases (42.11%) had skin-related AEs in the PFD group. All of these skin-related events were mild to moderate in severity, reversible, and without clinical sequelae. Only 1 case discontinued the trial because of a severe rash. Similar to previous PFD trials,^{13–15,25} elevation of the aminotransferase levels occurred more frequently in the PFD group. However, all these events in our study were mild to moderate in severity, reversible, and without clinical sequelae. The long-term safety evaluation of PFD showed that the adjusted incidence of aminotransferase level elevation was 1.7 per 100 person exposure years, and the elevations in the alanine aminotransferase or aspartate aminotransferase levels were more than 3-fold above the upper limit of normal (3 × ULN), which only occurred in 2.7% of patients.²⁴ Based on an analysis of cases with a median PFD exposure duration of 2.6 years, Valeyre et al²⁴ suggested that long-term treatment with PFD was safe and generally well tolerated.

To decrease drug-related AEs, the expert panel discussed the management of PFD-related AEs. They supplied detailed recommendations for the prevention and management of PFD-related AEs, including education, general approaches, and additional measures.²⁹ During our trial, education was provided by physicians and the PFD dispenser at the same time as the patients were enrolled. A dose titration schedule, suggestion to administer the medications with food, and recommendation to avoid exposure to direct sunlight were provided to all patients.

There were some limitations to our trial. First, all of our enrolled cases were prescribed high-dose NAC as the baseline treatment, and there was no placebo-only group. Although recent clinical trials have shown that NAC has no significant benefit to the preservation of FVC in IPF patients with mild to moderate impairment in lung function,²¹ the interaction between NAC and PFD is unclear. Because the IFIGENIA study showed the role of high-dose NAC in the preservation of FVC and DLCO in IPF patients, we cannot exclude the influence of high-dose NAC on our results. Second, there was some selection bias in our study. Although our cases were from different provinces, all cases were from China, and almost all were Han Chinese (73 cases, 96.1%). All of our cases had limited function based on the PFT results, and all were able to finish the 6MWT. Third, because all of the cases were from China, only 76 cases were enrolled, which is a smaller sample size than the CAPACITY study¹⁵ and the ASCEND study.²⁵

However, our study is the first randomized, double blind, modified-placebo controlled clinical trial examining the

TABLE 5. Comparison of RCT Researches About Pirfenidone for IPF Cases

	Azuma et al ¹³	Taniguchi et al ¹⁴	Noble et al ¹⁵	King et al ²⁵	Ours
Phase	II	III	III	III	II
Name of the trial	SP2	SP3	CAPACITY	ASCEND	–
Trial no	–	JAPICCTCI-050121	NCT00287729 NCT00287716	NCT1366209	NCT
Published year	2005	2010	2011	2014	–
Enrolled cases (PFD/ placebo)	107 (72/35)	275 (166/109)	779 (432/347)	555 (278/277)	76 (38/38)
Involved sites	25	73	110	127	5
Involved country	1 (Japan)	1 (Japan)	13	9	1 (China)
Duration	9 months	52 weeks	72 weeks	52 weeks	48 weeks
Primary end-point	Changes in the lowest SPO ₂ during the 6MWT	Changes in VC	Changes in FVC (%predicted)	Changes in FVC (%predicted)	Changes in FVC, maximal distance and lowest SPO ₂ during the 6MWT
Reached the primary end-point	No	Yes	Part of the enrolled cases reached	Yes	No
Main AE	Photosensitivity, stomach discomfort, anorexia, nausea, fatigue, and elevation of γ -GT	Photosensitivity	Nausea, dyspepsia, vomiting, anorexia, photosensitivity, rash, and dizziness	Gastrointestinal and skin-related AE	Gastrointestinal and skin-related AE

AE = adverse effect, FVC = forced vital capacity, γ -GT = gamma-glutamyl transferase, IPF = idiopathic pulmonary fibrosis, 6MWT = 6-minute walk test, PFD = pirfenidone, RCT = randomized controlled trial, SPO₂ = sensor oxygen saturation, VC = vital capacity.

efficacy and safety of PFD combined with high-dose NAC in IPF patients with mild to moderate impairment of pulmonary function. This trial is also the first multicenter study investigating PFD treatment in Chinese IPF patients.

CONCLUSIONS

In conclusion, we found that PFD combined with high-dose NAC compared to placebo combined with high-dose NAC prolonged the PFS time in Chinese IPF patients with mild to moderate impairment of pulmonary function. The percent-changes in FVC and SPO₂ on the 6MWT were significantly different at the 24th week, but these effects did not persist to the 48th week. Although AEs were common in the PFD group, they were mild to moderate in severity, reversible, and without clinical sequelae. Further studies including a larger sample size and a longer study duration are needed to confirm these encouraging results regarding the treatment of IPF patients with PFD.

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