Risk Factors for Dose Reduction of Pirfenidone in Patients With Idiopathic Pulmonary Fibrosis: a Study Based on Real-world Clinical Data

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Abstract

Background Although pirfenidone slows disease progression in patients with idiopathic pulmonary fibrosis (IPF), patients often cannot tolerate the recommended dose of pirfenidone because of several adverse events in clinical practice. This study aimed to investigate adverse events associated with pirfenidone and the risk factors in patients requiring dose reduction.

Methods This single center retrospective cohort study included 156 consecutive patients with IPF who received pirfenidone. Demographic characteristics, pulmonary function, and pirfenidone-related adverse events were investigated. We compared patients who received standard and reduced dose of pirfenidone.

Results The mean age of patients was 69.7 years. The median follow-up duration was 243 days. The low dose group ($n = 99$) comprised older patients (71.0 vs. 67.4 years, $p = 0.012$), fewer smokers (79.8% vs. 96.4%, $p = 0.004$), and patients with lower body mass index (BMI; 24.2 vs. 25.7, $p = 0.020$) compared with the standard dose group ($n = 57$). Multivariate logistic regression analysis revealed that older age (odds ratio = 1.060, $p = 0.014$) was significantly associated with dose reduction of pirfenidone after adjusting for sex, smoking history, and BMI. No significant difference was found in the reduction rate of forced vital capacity ($p = 0.260$) and diffusing capacity for carbon monoxide ($p = 0.186$) between the standard and low dose groups.

Conclusions Although older patients are more likely to undergo dose reduction of pirfenidone, low dose pirfenidone is effective for treating patients with IPF. Low dose pirfenidone can be considered an effective treatment option for older patients with IPF.

Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fibrotic interstitial lung disease [1]. The clinical course of IPF is highly variable and unpredictable, with a median survival of 3–5 years after diagnosis [2, 3].

The antifibrotic drug, pirfenidone, reduces lung function decline in patients with IPF compared with placebo [4, 5] and is used in clinical practice [6, 7]. In addition, several recent studies have reported that pirfenidone might reduce mortality in patients with IPF [8, 9].

However, it is well known that pirfenidone may cause side effects. Gastrointestinal- and skin-related events are common side effects of pirfenidone [4, 5, 10, 11]. In clinical trial in Japan, the efficacy of 1800 mg/day pirfenidone was evaluated, which was lower than that administered (2403 mg/day) in the United States, Europe, Australia, and North America. However, the dose of 1800 mg/day was thought to be comparable to 2403 mg/day on weight-normalized basis [5, 12]. According to a recent post-marketing surveillance (PMS) study in Korea, 86.3% of patients experienced adverse events [13], suggesting that the number of side effects of pirfenidone is likely to be higher in Asia, especially in real-world practice than in randomized controlled trials (RCTs).

Even though some studies have reported that a low dose of pirfenidone group is not inferior to a standard dose [12, 14, 15], there are few reports focused on the side effects associated with pirfenidone and reduced doses. Thus, we aimed to investigate clinical characteristics and risk factors associated with dose reduction of pirfenidone in a real-world setting.

Method

Patients and settings

This single center retrospective cohort study enrolled patients with IPF from the Asan Medical Center, Seoul, Republic of Korea. Patients who started pirfenidone therapy between August 2017 and July 2021 were identified using electronic medical records (EMRs).

Inclusion criteria were as follows: (1) diagnosis of IPF, (2) treatment with pirfenidone, and (3) at least one followed up after taking pirfenidone to assess the occurrence of adverse events. IPF was diagnosed based on the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines published in 2018 [1].

Demographic and clinical data, including age, sex, body mass index (BMI), smoking status, comorbidities, concurrent medication, pulmonary function test (PFT) result, six-minute walk test (6MWT) result, high-resolution computed tomography (HRCT), echocardiogram findings, prescribing information for pirfenidone therapy, reasons for dose reduction, and adverse events, were collected from EMRs. Spirometry was performed and diffusing capacity of the lungs for carbon monoxide (DLCO) was measured. Pulmonary hypertension was diagnosed based on echocardiographic evidence: maximal tricuspid regurgitation velocity (TR Vmax) >3.4 m/s or estimated systolic pulmonary arterial pressure >40 mmHg [16, 17].

The study was conducted in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Asan Medical Center (IRB number: 2021-0787). The requirement for informed consent was waived because of the retrospective nature of the study and use of anonymized clinical data for analysis.

Pirfenidone dose

Patients diagnosed with IPF were initially prescribed 600 mg/day pirfenidone. The dose was increased every 1–2 weeks until 1800 mg/day. The patients were divided into the following two groups: treated with pirfenidone at a standard dose (1800 mg/day) and treated with at a low dose (<1800 mg/day). The standard dose group comprised patients who continued taking the standard dose of pirfenidone (1800 mg/day) after dose escalation. The low dose group comprised patients who did not receive higher doses of the drug (maximum: standard dose [1800 mg/day]), who reduced the dose of the drug, and who discontinued the drug.

Statistical analysis

The baseline characteristics of all patients are presented as number (percentage; categorical variables) or mean $\pm$ standard deviation (continuous variables). Continuous and categorical variables were compared between the groups using an independent t test and the Fisher’s exact test or Pearson’s chi-square test, respectively. Univariate and multivariate logistic regression analysis were performed to evaluate the risk factors for the dose reduction of pirfenidone.

In addition, a linear mixed model was used to compare the treatment effect according to the dose of pirfenidone. Forced vital capacity (FVC) and DLCO data of patients who underwent at least two PFTs after receiving pirfenidone were used for analysis.

Statistical analysis was performed using SPSS version 26. A p value of <0.05 was considered statistically significant.

Results

Characteristics

This study included 156 patients who received pirfenidone treatment for IPF. The median follow-up period was 243 days (interquartile range [IQR]: 84–385 days). The mean age of patients was 69.7 years. A total of 90.4% patients were male and 85.8% were ever-smokers (Table 1). Study population classification by pirfenidone dose and maintenance is summarized in Figure 1. A total of 26 (28.8%) patients discontinued pirfenidone treatment during the follow-up period and 99 (63.5%) patients did not receive higher than initial dose or received a reduced pirfenidone dose were classified into the low dose group.

The low dose group ($n = 99$) comprised older age patients (71.0 vs. 67.4 years, $p = 0.012$), fewer smokers (79.8% vs. 96.4%, $p = 0.004$), and patients with lower BMI (24.2 vs. 25.7, $p = 0.020$) compared with the standard dose group ($n = 57$) (Table 1). No significant difference was found in baseline PFT, exercise capacity, and cancer history between the two groups. In addition, no significant difference was found in the rate of pulmonary hypertension between the two groups; however, patients in the standard dose group had emphysema ($p = 0.091$), unlike those in the low dose group. Data regarding emphysema and pulmonary hypertension in patients who underwent serial PFT are presented in Supplementary Table 1.

Table 1. Baseline characteristics of patients

	Total (n = 156)	Standard dose group (n = 57)	Low dose group (n = 99)	<i>P</i> value
Age, years	69.7 ± 8.5	67.4 ± 9.6	71.0 ± 7.6	0.012
Male, n (%)	141 (90.4)	55 (96.5)	86 (86.9)	0.050
Ever smoker, n (%)	133 (85.8)	54 (96.4)	79 (79.8)	0.004
BMI, kg/m ²	24.7 ± 4.0	25.7 ± 4.9	24.2 ± 3.3	0.020
Diagnosis				0.223
Biopsy proven, n (%)	23 (14.7)	11 (19.3)	12 (12.1)	
Clinical, n (%)	133 (85.3)	46 (80.7)	87 (87.9)	
Pulmonary function test				
%FVC, %	70.9 ± 15.1	73.0 ± 15.1	69.7 ± 15.0	0.204
%FEV ₁ , %	80.5 ± 15.7	81.2 ± 13.3	80.0 ± 16.9	0.646
%DLCO, %	54.2 ± 18.8	54.3 ± 19.0	54.1 ± 18.8	0.953
6MWT, m	418.5 ± 101.8	428.1 ± 106.5	413.6 ± 99.5	0.439
6MWT, the lowest SpO ₂ , %	91.7 ± 4.7	91.0 ± 5.5	92.0 ± 4.2	0.229
*Pulmonary hypertension, n (%)	17 (10.9)	6 (11.1)	11 (10.5)	0.910
Emphysema, n (%)	71 (45.5)	31 (54.4)	40 (40.4)	0.091
Co-existing cancer, n (%)	62 (39.7)	20 (35.1)	42 (42.4)	0.367
Chemotherapy, n (%)	14 (9.0)	5 (8.8)	9 (9.1)	0.946

Data presented as mean ± standard deviation or number (percentage), unless otherwise indicated.

*Pulmonary hypertension was assessed based on echocardiography.

Abbreviations: 6MWT, 6-minute walking test; BMI, body mass index; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; FEV₁, forced expiratory volume in one second; SpO₂, Peripheral oxygen saturation.

Adverse events

A total of 109 (69.9%) patients of the total population experienced adverse events. The most frequent adverse events were dyspepsia (19.9%), urticaria (19.9%), anorexia (12.8%), and general weakness (7.7%).

The incidence of anorexia (3.5% vs. 18.2%, $p = 0.008$), urticaria (10.5% vs. 25.3%, $p = 0.026$), and general weakness (0.0% vs. 12.1%, $p = 0.004$) was higher in the standard dose group than in the low dose group. No significant difference was found in the incidence of dyspepsia, nausea, diarrhea, rash, and photosensitivity between the two groups. However, after categorization of patients by symptoms, more GI-related adverse events ($p < 0.01$), skin-related adverse events ($p = 0.006$), and uncategorized adverse events ($p = 0.001$) were found in the standard dose group than in the low dose group (Table 2).

Table 2. Adverse events in enrolled patients

Adverse events, n (%)	Total (n = 156)	Standard dose group (n = 57)	Low dose group (n = 99)	<i>P</i> value
Gastrointestinal	60 (38.5)	9 (15.8)	51 (51.5)	<0.001
Dyspepsia	31 (19.9)	7 (12.3)	24 (24.2)	0.071
Anorexia	20 (12.8)	2 (3.5)	18 (18.2)	0.008
Nausea	6 (3.8)	0 (0.0)	6 (6.1)	0.087
Diarrhea	3 (1.9)	0 (0.0)	3 (3.0)	0.300
Skin	42 (26.9)	8 (14.0)	34 (34.4)	0.006
Urticaria	31 (19.9)	6 (10.5)	25 (25.3)	0.026
Rash	6 (3.8)	2 (3.5)	4 (4.0)	>0.999
Photosensitivity	5 (3.2)	0 (0.0)	5 (5.1)	0.159
Others	17 (10.9)	1 (1.8)	16 (16.2)	0.005
General weakness	12 (7.7)	0 (0.0)	12 (12.1)	0.004
AST/ALT elevation	4 (2.6)	0 (0.0)	4 (4.0)	0.297
Azotemia	1 (0.6)	0 (0.0)	1 (1.0)	>0.999
Weight loss	2 (1.3)	1 (1.8)	1 (1.0)	>0.999
Myalgia	1 (0.6)	0 (0.0)	1 (1.0)	>0.999

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Factors associated with dose reduction of pirfenidone

Logistic regression analysis was performed to evaluate the risk factors associated with dose reduction of pirfenidone. In univariate analysis, older age (odds ratio [OR] = 1.052, $p = 0.014$), male (OR = 0.241, $p = 0.067$), ever smoking status (OR = 0.146, $p = 0.012$), and lower BMI (OR = 0.903, $p = 0.030$) were associated with dose reduction of pirfenidone. In multivariate logistic regression analysis, older age (OR =

1.060, $p = 0.014$) was significantly associated with dose reduction of pirfenidone after adjusting for sex, ever smoking status, and BMI (Table 3).

Table 3. Risk factors for dose reduction of pirfenidone

Parameters	Odds ratio	95% confidence interval	P value
Univariate analysis			
Patients, n			
Age, years	1.052	1.010-1.096	0.014
Male sex	0.241	0.052-1.107	0.067
Ever-smokers	0.146	0.033-0.652	0.012
BMI, kg/m ²	0.903	0.823-0.990	0.030
FVC, % predicted	0.986	0.964-1.008	0.204
FEV ₁ , % predicted	0.995	0.974-1.016	0.643
DLCO, % predicted	0.999	0.982-1.017	0.953
6MWT, m	0.999	0.995-1.002	0.436
6MWT, %	1.047	0.971-1.130	0.229
*Pulmonary hypertension	1.062	0.371-3.045	0.910
Emphysema	0.569	0.295-1.098	0.093
Co-existing cancer	1.363	0.695-2.676	0.368
Chemotherapy	1.040	0.331-3.269	0.946
Multivariate analysis			
Age, years	1.060	1.012-1.110	0.014
Male sex	1.905	0.138-26.365	0.631
Ever-smokers	0.093	0.007-1.157	0.065
BMI, kg/m ²	0.920	0.834-1.015	0.095

*Pulmonary hypertension was assessed based on echocardiography.

Abbreviations: 6MWT, 6-minute walking test; BMI, body mass index; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; FEV₁ forced expiratory volume in one second.

Adverse events in old age group and young age group

We compared the differences between patients aged ≥ 70 years (old age group) and those aged < 70 years (young age group). No significant difference in sex ratio, smoking history, and BMI was found between the two groups. Among adverse events, anorexia ($p = 0.042$) occurred more frequently in the old age group than in the young age group (Table 4).

Table 4. Comparison of baseline characteristics and adverse events according to age

	Total (n = 156)	Age ≥ 70 years (n = 84)	Age < 70 years (n = 72)	P value
Male, n (%)	141 (90.4)	77 (91.7)	64 (88.9)	0.557
Ever-smoker, n (%)	133 (85.8)	72 (86.7)	61 (84.7)	0.719
BMI, kg/m ²	24.7 $\pm$ 4.0	24.4 $\pm$ 4.4	25.1 $\pm$ 3.5	0.256
Gastrointestinal	60 (38.5)	34 (40.5)	26 (36.1)	0.576
Dyspepsia	31 (19.9)	14 (16.7)	17 (23.6)	0.279
Anorexia	20 (12.8)	15 (17.9)	5 (6.9)	0.042
Nausea	6 (3.8)	5 (6.0)	1 (1.4)	0.218
Diarrhea	3 (1.9)	0 (0.0)	3 (4.2)	0.096
Skin	42 (26.9)	22 (26.2)	20 (27.8)	0.824
Urticaria	31 (19.9)	16 (19.0)	15 (20.8)	0.781
Rash	6 (3.8)	3 (3.6)	3 (4.2)	>0.999
Photosensitivity	5 (3.2)	3 (3.6)	2 (2.8)	>0.999
Others	17 (10.9)	10 (11.9)	7 (9.7)	0.663
General weakness	12 (7.7)	9 (10.7)	3 (4.2)	0.126
AST/ALT elevation	4 (2.6)	1 (1.2)	3 (4.2)	0.336
Azotemia	1 (0.6)	1 (1.2)	0 (0.0)	>0.999
Weight loss	2 (1.3)	1 (1.2)	1 (1.4)	>0.999
Myalgia	1 (0.6)	1 (1.2)	0 (0.0)	>0.999

Results presented as means $\pm$ standard deviations or number of patients (%), unless otherwise indicated.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index.

Factors associated with discontinuation of pirfenidone

A total of 26 (16.7%) patients discontinued pirfenidone and 130 (83.3%) patients continued pirfenidone. No significant differences in baseline characteristics were found between patients who discontinued pirfenidone and those who continued pirfenidone. Considering adverse events, general weakness ($p = 0.030$) was significantly higher in patients who discontinued pirfenidone than in those who continued pirfenidone. After classification of adverse events according to symptoms, skin-related ($p = 0.053$) adverse events and uncategorized ($p = 0.040$) adverse events occurred more frequently in patients who discontinued the drug than in patients who continued the drug (Table 5). Logistic regression analysis was performed to evaluate the risk factors for discontinuation of pirfenidone. Skin-related adverse events ($p = 0.033$) and uncategorized adverse events ($p = 0.025$) were significantly associated with discontinuation of pirfenidone after adjusting for ever smoking status (Supplementary Table 2).

Table 5. Comparison of baseline characteristics and adverse events between patients who continued and discontinued pirfenidone

	Total (n = 156)	Continued pirfenidone (n = 130)	Discontinued pirfenidone (n = 26)	P value
Age, years	69.7 ± 8.5	69.4 ± 8.6	70.8 ± 8.5	0.449
Male, n (%)	141 (90.4)	117 (90.0)	24 (92.3)	>0.999
Ever-smoker, n (%)	133 (85.8)	113 (85.0)	20 (76.9)	0.213
BMI, kg/m ²	24.7 ± 4.0	24.8 ± 4.2	24.5 ± 2.9	0.698
Gastrointestinal	60 (38.5)	49 (37.7)	11 (42.3)	0.659
Dyspepsia	31 (19.9)	26 (20.0)	5 (19.2)	0.929
Anorexia	20 (12.8)	17 (13.1)	3 (11.5)	>0.999
Nausea	6 (3.8)	4 (3.1)	2 (7.7)	0.262
Diarrhea	3 (1.9)	2 (1.5)	1 (3.8)	0.424
Skin	42 (26.9)	31 (23.8)	11 (42.3)	0.053
Urticaria	31 (19.9)	24 (18.5)	7 (26.9)	0.324
Rash	6 (3.8)	4 (3.1)	2 (7.7)	0.262
Photosensitivity	5 (3.2)	3 (2.3)	2 (7.7)	0.194
Others	17 (10.9)	11 (8.5)	6 (23.1)	0.040
General weakness	12 (7.7)	7 (5.4)	5 (19.2)	0.030
AST/ALT elevation	4 (2.6)	2 (1.5)	2 (7.7)	0.130
Azotemia	1 (0.6)	0 (0.0)	1 (3.8)	0.167
Weight loss	2 (1.3)	1 (0.8)	1 (3.8)	0.306
Myalgia	1 (0.6)	1 (0.8)	0 (0.0)	>0.999

Data are presented as mean ± standard deviation or number of patients (%), unless otherwise indicated.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index.

Efficacy of low dose pirfenidone in IPF

To evaluate the efficacy of low-dose pirfenidone on disease progression, we compared the changes in lung function using FVC and DLCO changes between the standard and low dose groups. FVC and DLCO changes after treatment were investigated in patients with data of at least two PFTs, at baseline and after treatment. No significant difference was found in the reduction rate of FVC ($p = 0.260$) and DLCO ($p = 0.186$) between the two groups (Figure 2).

Discussion

In the present real-world study, 109 (69.9%) patients experienced side effects and 99 (63.5%) patients did not receive higher doses of pirfenidone up to 1800 mg/day or decreased dosage during the follow-up period. Old age was an independent risk factor for dose reduction of pirfenidone; however, no significant difference was found in lung function change between the standard and low dose groups.

In previous prospective clinical studies (CAPACITY trials), 98% patients reported treatment-related adverse events. The most common adverse events were nausea (36%), rash (32%), and dyspepsia (19%) [4]. Similarly, in the pirfenidone use group in the ASCEND trial, 36% of patients experienced nausea and 28.1% developed a rash. In that study, adverse events occurred more frequently in the pirfenidone use group than in the placebo group, in which 13.4% of patients experienced nausea and 8.7% developed rash [5]. However, Taniguchi et al. reported that photosensitivity was the most common adverse event in the study population of 267 Japanese patients with IPF, which was 51% in the high-dose group and 53% in the low dose group [12]. Oltmannus et al. reported that 52 (85%) of patients experienced adverse events, including fatigue (54%), weight loss (30%), and skin reaction (28%), in real-world practice in Germany [18]. A PMS study in Japan reported that 64.6% of patients experienced side effects [19]. In a single-center study in China, 43.6% of patients with IPF experienced adverse events, which included GI related (35%) and skin related (20.5%) adverse events [20]. In the current study, 109 (69.9%) patients experienced adverse events, 60 (38.5%) of whom experienced GI-related adverse events and 42 (26.9%) experienced skin-related adverse events. Hence, there is a possibility that the side effects of pirfenidone may differ between races and may occur at a higher frequency in real world practice than in RCTs.

Based on real-world data, dose reduction of pirfenidone is common [21-25]. Salih et al. reported that of 113 patients with IPF who were treated with pirfenidone, 51 (45.2%) required dose adjustment and 18 (16%) discontinued the treatment [21]. In addition, Dbooria et al. reported that of 115 patients with IPF who were treated with pirfenidone, only 49 (42.6%) patients tolerated the full dose (2400 mg/day) and 51 (44.3%) patients tolerated the reduced dose [22]. Although the maximal dose of pirfenidone in Asia is 1800 mg, it has been reported that few patients are actually taking the maximal dose [14, 19]. Indeed, in our study, 99 (63.5%) patients belonged to the low dose group, which is comparable to that reported in previous studies. Although dose adjustment of pirfenidone is known as a method to reduce the occurrence of drug-related adverse events and risk of drug discontinuation [23, 24], few studies have investigated the requirements of dose adjustment and risk factors for dose reduction. However, Uehara et al. suggested that an adjusted dose of pirfenidone for body surface area or body weight could reduce adverse events and promote continued treatment of pirfenidone based on the data of a small number of patients [25]. In the current study, old age was an independent risk factor for pirfenidone dose reduction. Considering the findings of previous reports that elderly patients usually experience drug side effects [26, 27], it may be necessary to carefully monitor adverse events, especially in elderly patients with IPF who receive pirfenidone.

In the current study, 26 (16.7%) patients discontinued pirfenidone. The rate of discontinuation of the drug was comparable to that reported in previous studies. In a prospective study by Dhooria et al., 22 (19.1%) patients discontinued the treatment [22]. A study assessing the real-world data of pirfenidone in Germany reported that 18 (15.4%) patients discontinued pirfenidone. In a study in Greece, 9 (20.9%) patients discontinued the treatment [28]. However, the risk factors for discontinuation of pirfenidone are not well known. A study reported that low BMI is a predictor for drug discontinuation because of adverse events [22]. Another study reported that older age, use of steroids prior to the study, and female sex are associated with early termination of the treatment [29]. In our study, patients who experienced skin-related or uncategorized adverse events were significantly more likely to discontinue the drug. However, few patients discontinued pirfenidone in our study. Further large-scale studies investigating the risk factors for discontinuation are warranted.

In a pooled analysis of multinational phase III trials, efficacy of pirfenidone was compared between patients according to dose intensity ($>90\%$ and $\leq 90\%$). The study reported that regardless of dose intensity, the pirfenidone group had significantly lower annual rate of FVC decline than the placebo group [23]. Another phase III trial in Japan reported a significant difference in vital capacity (approximately 0.07 L) between the high-dose (1800 mg/day) and placebo groups ($p = 0.0416$) and significant difference in vital capacity (approximately 0.09 L) between the low dose (1200 mg/day) and placebo groups ($p = 0.0394$), suggesting that low-dose pirfenidone is effective [12]. A study assessing the real-world data of pirfenidone in South Korea reported that relatively a low dose of pirfenidone (≤ 1200 mg/day) can have an effect on pulmonary function decline [14, 15]. In our study, we compared FVC and DLCO changes between the standard and low dose groups and found no significant difference in efficacy with dose, which is comparable to that reported in previous studies. Unexpectedly, the change in DLCO at 12 months was not statistically significantly higher, but tended to be higher in the low dose group than in the standard-dose group. This is because emphysema was more common in the standard dose group, which may result in lower DLCO. Based on the results of our study, low-dose pirfenidone treatment might be an effective treatment strategy, especially in elderly patients.

This study has several limitations. First, this study was a single center retrospective study. Second, because patients visited the hospital intermittently and self-reported adverse events, recall bias may exist. Third, not all patients underwent follow-up PFTs, limiting the evaluation of pirfenidone efficacy. Fourth, the follow-up period was relatively short. In a previous post-hoc analysis, the median time to the first adverse event leading to dose modification was 62 days [30]. Therefore, a short follow-up period did not significantly affect the evaluation of adverse events; however, it may have affected the evaluation of disease progression.

Conclusion

The present study revealed that older patients are more likely than younger patients to undergo dose reduction of pirfenidone. Thus, monitoring whether older people experience side effects and show poor compliance is essential. No difference was found in the effect of pirfenidone between the standard and

low dose groups; hence, low dose pirfenidone can be considered effective, especially for the treatment of older patients with IPF.

List Of Abbreviations

alanine aminotransferase (ALT)

aspartate aminotransferase (AST)

body mass index (BMI)

diffusing capacity of the lungs for carbon monoxide (DLCO)

electronic medical record (EMR)

forced expiratory volume in one second (FEV1)

Forced vital capacity (FVC)

high-resolution computed tomography (HRCT)

idiopathic pulmonary fibrosis (IPF)

interquartile range (IQR)

Institutional Review Board (IRB)

maximal tricuspid regurgitation velocity (TR Vmax)

odds ratio (OR)

pulmonary function test (PFT)

post-marketing surveillance (PMS)

Peripheral oxygen saturation (SpO₂)

randomized controlled trial (RCT)

six-minute walk test (6MWT)

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Asan Medical Center (approval number: 2021-0787), and the requirement for written informed consent was waived owing to the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

KJ, CC, and KHC were involved in developing the concept and design of the study. KJ, CC, and CHS were involved in data acquisition, analysis, and interpretation. KJ and KHC drafted the manuscript. All authors read revised and approved the final manuscript.

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Figures

Figure 1

Patient disposition

Figure 2

Changes in FVC and DLCO according to pirfenidone dose: (a) %FVC ($p = 0.260$); (b) %DLCO ($p = 0.186$)

Abbreviations: DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity.

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