Respiratory Medicine (2013) **107**, 1431–1437

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Safety and efficacy of pirfenidone in idiopathic pulmonary fibrosis in clinical practice

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Received 10 February 2013; accepted 13 June 2013
Available online 9 July 2013

KEYWORDS
Diffusion capacity of the lung for carbon monoxide;
Forced vital capacity;
Idiopathic pulmonary fibrosis;
Interstitial pneumonia;
Lung function test;
Pirfenidone

Summary
Backgroud: Previous pirfenidone trials have only involved patients with mild-to-moderate idiopathic pulmonary fibrosis (IPF). The aim of this study was to investigate the safety and efficacy of pirfenidone in patients with mild-to-severe IPF in clinical practice.
Methods: The clinical records of 76 patients who were diagnosed with IPF and received pirfenidone were reviewed.
Results: The most frequent adverse event was anorexia, although the grade of anorexia in most patients was mild. Dose reduction of pirfenidone improved anorexia in 84% affected patients, which resulted in a high medication compliance rate. The mean forced vital capacity (FVC) at the initiation of pirfenidone therapy in this study was approximately 10% lower than that in previous clinical trials. The mean change in FVC during the 6-month period prior to the therapy initiation was −188 mL, which improved to −19 mL during the 6-month period after therapy. Significant attenuation in percentage predicted diffusion capacity of the lung for carbon monoxide decline was also achieved after pirfenidone therapy initiation. The efficacy of pirfenidone in attenuating the degree of FVC decline was higher in the group with FVC decline of ≥150 mL during the 6-month period prior to therapy initiation. The levels of serum markers, such as KL-6 and SP-D, were also lowered by the therapy.
Conclusions: These results showed that pirfenidone was well-tolerated and had beneficial effects in patients with mild-to-severe and/or progressive IPF. The degree of disease progression prior to the initiation of pirfenidone therapy had an impact on the response to the therapy.

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http://dx.doi.org/10.1016/j.rmed.2013.06.011

Introduction

Idiopathic pulmonary fibrosis (IPF) is an entity of interstitial pneumonia that has an unfavorable prognosis; approximately 50% patients die within 2–5 years from diagnosis [1]. No effective drugs were available for treating IPF until 2008, when a phase III trial conducted in Japan demonstrated that pirfenidone attenuated the decline in vital capacity (VC) and prolonged the progression-free survival in patients with mild-to-moderate IPF [2]. In the CAPACITY 2 study conducted in 13 countries, pirfenidone was shown to significantly attenuate the decline in the percent change of forced vital capacity (FVC) in patients with mild-to-moderate IPF [3]. Pirfenidone was approved for the treatment of IPF in Japan in 2008 and for the treatment of adult patients with mild-to-moderate IPF in the EU in 2011. Although the statement issued by the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society and the Latin American Thoracic Association in 2011 [4] gave a weak recommendation on the use of pirfenidone for treating IPF, pirfenidone is one of the drugs expected to be a useful therapeutic agent for IPF because clinical trials with the three-drug regimen of prednisolone + azathioprine + N-acetylcysteine and those with warfarin have shown negative results [5].

The study cohorts in previous pirfenidone trials only involved patients with mild-to-moderate IPF; therefore the efficacy of pirfenidone in patients with severe IPF remains unclear. However, in Japan it is not uncommon to treat severe IPF patients with pirfenidone in the clinical setting. The present study attempted to assess the safety and efficacy of pirfenidone therapy in IPF patients, including those with severe disease.

Methods

Subjects

The study was designed and conducted at a single institution in Yokohama, Japan. The clinical records of patients who were diagnosed with IPF and who were administered pirfenidone between December 1, 2008 and March 31, 2011 were retrospectively investigated in this study. The diagnosis of IPF was established in every case in accordance with the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society and the Latin American Thoracic Association statement issued in 2011 [4]. The pirfenidone dose was escalated over 28 days to the full dose of 1800 mg per day. All patients were included in the safety analysis; only those who underwent all three respiratory function tests 6 months before, at the initiation of pirfenidone therapy and 6 months after were included in the efficacy evaluation set. This study was approved by institutional review board of Kanagawa Cardiovascular and Respiratory Center.

Data analysis

For evaluation of safety, adverse events that occurred from the initiation to 13 months of pirfenidone therapy (or until 4 weeks after completion of the therapy) were assessed according to the system organ class and grading specified in the Common Terminology Criteria for Adverse Events ver. 4.0 by reviewing medical records. The time of onset was counted from the initiation of treatment. Efficacy evaluation was performed on the basis of the degree of FVC decline during the 6-month period after initiation of pirfenidone therapy as an assessment parameter, which was similar to the CAPACITY 1 and 2 studies. Other assessment parameters included the changes in percentage predicted diffusion capacity of the lung for carbon monoxide (%DLco), serum levels of interstitial pneumonia markers (KL-6 and SP-D), arterial oxygen tension, and the distance in the 6-min walk test (6MWT). The frequency of acute exacerbations of IPF during the 1-year period after the initiation of pirfenidone therapy was also evaluated. Acute exacerbation of IPF was diagnosed as per the Japanese guideline on the basis of the presence of the following criteria: increased severity of dyspnea, presence of honeycomb lung features and newly-appearing ground-glass opacities and infiltrates on high-resolution CT and a decrease in arterial oxygen tension by $\geq$10 mmHg, after exclusion of other disorders such as overt infection and cardiac failure. Disease severity of IPF was determined as per the Japanese guideline. Patients having PaO_2 $\geq$80 Torr were classified as stage I, $\geq$70 Torr and $<$80 Torr as stage II, $\geq$60 Torr and $<$70 Torr as stage III, and $<$60 Torr as stage IV. For patients with stage II or more, if the SpO_2 during the 6MWT was less than 90%, the disease severity should be increased by one stage. The patients were categorized by the disease severity using criteria of the USA as defined by the features of baseline %VC ($<$65%), SpO_2 on 6MWT ($\leq$88%), and %DLco ($<$50%); the patients had no feature were stratified in mild, one feature in moderate, and two or more in severe disease.

Statistical analysis

Data are presented as mean $\pm$ standard deviation, unless otherwise stated. An unpaired *t*-test, a paired *t*-test or Chi-square test was used to compare numerical variables, and *p*-values $<$0.05 were considered statistically significance. Statistical analyses were carried out using GraphPad Prism 5J (MDF CO., Ltd.).

Results

Patient background characteristics

The background characteristics of the 76 patients with IPF are summarized in Table 1. The patients comprised 60 males and 16 females, with a mean age of 70.5 years. Surgical lung biopsy was performed in 36 cases (47%). According to the severity grading criteria currently used in Japan, the severity of IPF was classified as grade I in 20 patients, grade II in 11 patients, grade III in 15 patients, grade IV in 27 patients and unmeasurable because of missing test data in three patients. The mean values of the respiratory function parameters in the study population were as follows: FVC, 2.04 L; %FVC, 65.3% and %DLco,

Table 1 Baseline clinical characteristics and laboratory data.

Characteristics	
Subjects	76
Male	60
Female	16
Age (yrs)	70.5 ± 8.3
Smoking history	
Never smoker	16
Ex- and current smokers	60
Brinkman index	849 ± 637
Surgical lung biopsy	
Yes	36
No	40
IPF ATS/ERS statement	
IPF	66
Probable IPF	2
Possible IPF	8
Treatment period (day)	282 ± 113
Prior treatment received	
No	59
Yes	17
Steroids only	7
Steroids + immunosuppressant	10
Immunosuppressant only	0
Average dose of prednisolone (mg/day)	7.8 ± 2.5
Combined treatment received with pirfenidone	
No	44
Yes	32
Steroids only	19
Steroids + immunosuppressant	13
Immunosuppressant only	0
Average dose of prednisolone (mg/day)	9.6 ± 3.4
Disease severity	
(criteria of the Japanese Respiratory Society)	
I/II/III/IV/unmeasurable	20/11/15/27/3
(criteria of the USA)	
Mild/moderate/severe/unmeasurable	11/38/11/17
Blood tests	
KL-6 (U/ml)	1428 ± 1129
SP-D (ng/ml)	323 ± 280
PaO_2 (Torr)	76.0 ± 11.9
Pulmonary function	
VC (L)	2.05 ± 0.61
VC % pred	66.5 ± 15.8
FVC (L)	2.04 ± 0.61
FVC % pred	65.3 ± 16.1
FEV_1 (L)	1.67 ± 0.48
DLco % pred	55.9 ± 17.8
6MWT	
Distance (m)	313 ± 105
Lowest SpO_2 (%)	86.0 ± 5.5

Data are presented as *n*, *n*(%) or mean ± standard deviation, unless otherwise stated. VC: vital capacity; %pred: % predicted; FVC: forced vital capacity; DLco: diffusion capacity of the lung for carbon monoxide; KL-6: Kerb von den Lungen-6; SP-D: surfactant protein D; PaO_2: arterial oxygen tension; 6MWT: 6-min walk test; SpO_2: oxygen saturation measured by pulse oximetry. Brinkman index: daily number of cigarettes × years.

55.9%; thus, the patients had restrictive ventilatory defect and impaired diffusing capacity. The mean levels of both interstitial pneumonia markers were elevated: KL-6, 1428 U/mL (reference range:152—400 U/mL) and SP-D, 323 ng/mL (reference range : 0—109.9 ng/mL).

Safety

Pirfenidone therapy was discontinued in 34.2% patients; of these, 18.4% patients discontinued therapy because of the occurrence of adverse events. Another major reason for discontinuation was poor general condition that made oral intake of the medication difficult.

Table 2 shows the incidence of adverse events and their time of occurrence. Anorexia occurred at an incidence as high as 42%; however, it was mild (grade $\leq$2) in almost all cases. Anorexia improved following dose reduction of pirfenidone in 84% affected patients, which resulted in a high medication compliance rate. The mean time of anorexia onset was approximately 90 days. There was no correlation between anorexia and age of IPF onset ($p = 0.273$) or disease severity; there was also no correlation between anorexia and use of steroid and/or immunosuppressive drugs (Table 3).

In contrast, the incidence of photosensitivity was 18%, which was lower than that reported in a phase III trial in Japan (Table 2). The incidences of other adverse events were generally comparable with those reported from a phase III trial conducted in Japan. All the reported adverse events were reversible and left no sequelae.

Effects on the assessment parameters

The mean change ± standard error in FVC from baseline value during 6 months prior to the pirfenidone therapy was −188 ± 34 mL, which was a significant decrease from the

Table 2 Summary of adverse events.

	Grade					
	Total	1	2	3	4—5	Onset of events
Adverse events	64 (84.2)					(days)
Photosensitivity	14 (18.4)	9	5	0	0	116 ± 63
Anorexia	32 (42.1)	23	7	2	0	96 ± 97
Nausea	9 (11.8)	7	2	0	0	145 ± 135
Gastric distress	9 (11.8)	9	0	0	0	83 ± 95
Fatigue	11 (14.5)	6	5	0	0	114 ± 107
Drowsiness	5 (6.6)	5	0	0	0	80 ± 94
Rash	5 (6.6)	5	0	0	0	134 ± 75
Hepatic dysfunction						
γ-GTP elevation	17 (22.4)	13	4	0	0	128 ± 83
AST elevation	13 (17.1)	12	0	1	0	93 ± 80
ALT elevation	14 (18.4)	13	0	1	0	119 ± 96
Others	4 (5.3)	4	0	0	0	

Data are presented as *n*, *n*(%) or mean ± standard deviation. The time of onset was counted from the initiation of treatment. AST: aspartate aminotransferase; ALT: alanine aminotransferase; γ-GTP: γ - glutamyl transpeptidase. Others included dry eye, dry month, vomiting and allergic reaction.

Table 3 Correlation between anorexia and disease severity or use of drugs.

Criteria of the Japanese Respiratory Society		
Disease severity	Anorexia (+)	Anorexia (−)
I	7	13
II	4	7
III	7	8
IV	14	13
Criteria of the USA		
Disease severity	Anorexia (+)	Anorexia (−)
I	4	7
II	17	21
III	5	6
Use of drugs		
	Anorexia (+)	Anorexia (−)
Pirfenidone only	20	24
Combined treatment	12	20

[1)]p = 0.875, [2)]p = 0.651, [3)]p = 0.488. Data are presented as n.

baseline ($P < 0.001$). The mean change ± standard error in FVC from baseline value during 12 months prior to the pirfenidone therapy was −207 ± 32 mL. Significant attenuation in degree of FVC decline was observed after 6 months of pirfenidone therapy (Fig. 1).

The mean change ± standard error in %DLco from baseline value during 6 months prior to the pirfenidone therapy was −8.5 ± 3.0%, which was a significant decrease from the baseline ($P = 0.01$). The mean change ± standard error in %DLco from baseline value during 12 months prior to the pirfenidone therapy was −7.9 ± 3.4%, which meant 0.6% increase from initiation (Fig. 2). Significant attenuation in the degree of decline in %DLco was achieved after pirfenidone therapy initiation.

In an attempt to account for the influence of concomitantly administered drugs, the observed changes in FVC were compared between a group that received pirfenidone alone and one that received concomitant corticosteroid and/or immunosuppressant therapy with pirfenidone. The comparison revealed no significant intergroup differences in the effects of pirfenidone.

Analysis of the data stratified by %FVC at the initiation of pirfenidone therapy revealed that pirfenidone tended to attenuate the degree of decline in FVC, particularly in the subgroup of patients with %FVC <60% (Table 4). When the patients were classified into two groups according to the degree of decline in FVC (≥150 mL vs. <150 mL) during the 6-month period before therapy initiation, pirfenidone showed greater efficacy in attenuating FVC decline in the ≥150-mL group than in the <150-mL group (Table 4). It divided by 150 mL so that two groups might become the almost same number of patients. The reported mean decline in FVC during 6-month period was 75−100 mL in placebo groups [2]. When the patients were classified into two groups according to the degree of decline in FVC (≥100 mL vs. <100 mL) during the 6-month period before

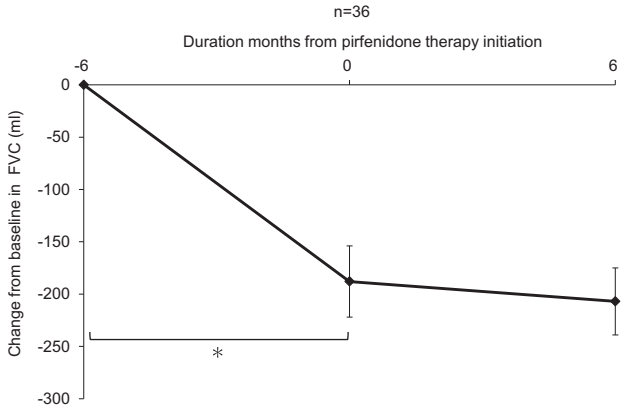

Figure 1 Change from 6 months before therapy in forced vital capacity (FVC). The change in FVC from the baseline value (6 months before initiation of pirfenidone therapy) was −188 mL at initiation of therapy and −207 mL after 6 months of therapy. Paired *t*-test was used. Data are presented as mean ± standard error. *: *p*-value <0.05.

therapy initiation, pirfenidone showed greater efficacy in attenuating FVC decline in the ≥100-mL group than in the <100-mL group.

There were no other factors, including gender, smoking, age, and PaO_2 that affected the efficacy of pirfenidone (Table 5).

The absolute serum level of KL-6 increased significantly during the 6-month period before treatment ($P = 0.016$). The absolute serum levels of KL-6 ($P = 0.016$) and SP-D ($P = 0.039$) decreased significantly after therapy initiation (Fig. 3), whereas no significant improvement was noted in the minimum oxygen saturation measured by pulse oximetry or the distance in the 6MWT (Table 6).

Acute exacerbation of IPF occurred in four of the 76 patients (5.3%), two patients (50%) died because of acute exacerbation.

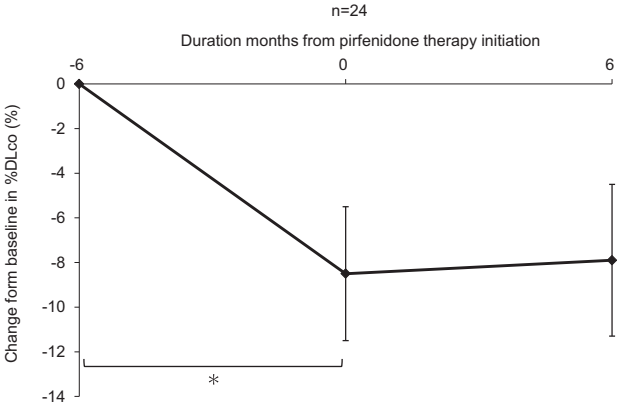

Figure 2 Change in percentage predicted diffusion capacity of the lung for carbon monoxide (%DLco). Change in %DLco from the baseline value (6 months before initiation of pirfenidone therapy) was −8.5% at initiation of therapy and −7.9% after 6 months of pirfenidone therapy. Paired *t*-test was used. Data are presented as mean ± standard error. *: *p*-value <0.05.

Table 4 FVC decline in subpopulations characterized by %FVC and by change in FVC before therapy.

%FVC at initiation of therapy	*n*	Mean change in FVC for 6 months before therapy (ml)	Mean change in FVC for 6 months after therapy (ml)	*p*-Value
%FVC ≥80	4	−60 ± 96	−80 ± 69	0.840
80> %FVC ≥70	11	−130 ± 58	20 ± 70	0.282
70> %FVC ≥60	10	−210 ± 44	−60 ± 63	0.156
60> %FVC	11	−280 ± 72	−80 ± 55	0.074
Decline in FVC for 6 months before therapy	***n***	**Mean change in FVC for 6 months before therapy (ml)**	**Mean change in FVC for 6 months after therapy (ml)**	***p*-Value**
≥150 ml	16	−350 ± 48	30 ± 58	<0.001
<150 mL	20	−60 ± 20	−100 ± 31	0.274

Paired *t*-test was performed. Values are given as mean ± standard error.

Discussion

This study demonstrated that pirfenidone was well-tolerated and significantly attenuated the degree of FVC decline in patients with mild-to-severe IPF, especially in those with progressive disease in clinical practice.

The rate of discontinuation of the drug because of adverse events in this study (18.4%) was essentially similar to those in a phase III clinical trial in Japan (19%) and the CAPACITY 1 and 2 studies (14.8%). The incidence of anorexia in the present study was relatively higher than that in patients treated in the Japanese clinical trial (23%; $n = 265$) and in the CAPACITY 1 and 2 studies (11%). However, the incidence of nausea in the CAPACITY 1 and 2 studies was as high as 36%, and the incidence of all gastrointestinal symptoms was almost comparable between the present study and the CAPACITY 1 and 2 studies. Often, in this study, the gastrointestinal symptoms improved following dose reduction of pirfenidone, and it has been reported that the effect of the drug in attenuating the degree of decline in VC was evident even at a low-dose level of 1200 mg/day [2]. Continuation of pirfenidone therapy by dose reduction rather than cessation of pirfenidone therapy should be considered. The mean time of anorexia onset in this study was almost identical to that reported in the Japanese clinical trials.

In this study, the incidence of photosensitivity was lower compared than the 51% rate reported in the Japanese clinical trials. The lower incidence of photosensitivity was possibly as a result of our effort in improving the frequency of use of sunscreens and long-sleeved shirt- and hat-wearing, based on the results of the clinical trials. It was thought that the photosensitivity could be suppressed if sun exposure was avoided. Other adverse events were also mild, indicating general satisfactory safety and tolerability of the drug.

Currently, it is extremely difficult to use death as a primary endpoint for evaluation of the therapeutic responses of IPF patients in clinical trials and clinical studies, because of the low prevalence of IPF. It has been reported that the degrees of change in VC or FVC over a 6—12-month period may serve as potent predictors of death in the following year [6—8], and changes in VC or FVC currently represent highly reliable endpoints in the treatment of IPF.

Table 5 Effects of the five variables.

Parameters	*p*-Value
Male vs. female	0.801
Smoker vs. never-smoker	0.137
Age: <70 vs. ≥70	0.849
ΔFVC: <150 mL vs. ≥150 mL	>0.001
PaO_2: <70 Torr vs. ≥70 Torr	0.340

The difference of FVC decline during the 6-month period before the initiation of pirfenidone therapy and during the 6-month period after the initiation of pirfenidone therapy, was used as the efficacy parameter. The effects of the five variables (gender, smoking, age, the FVC decline during the 6-month period before the initiation of pirfenidone therapy and PaO_2) were evaluated with Mann—Whitney's *U*-test.

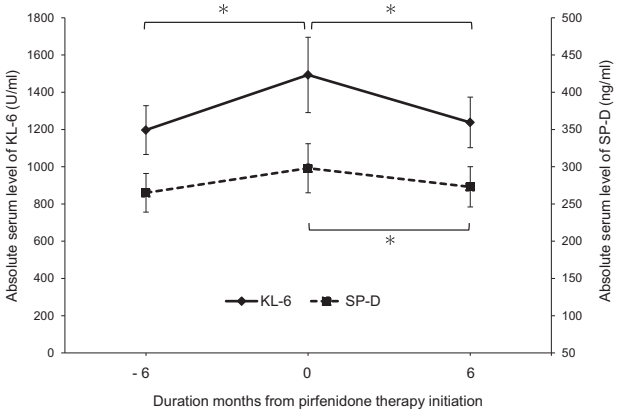

Figure 3 Paired *t*-test was performed for the cases which conducted the blood tests all 3 times (43 cases in KL-6, 41 cases in SP-D). The absolute serum levels of KL-6 and SP-D were shown and improved significantly after initiation of pirfenidone therapy. Data are presented as mean ± standard error. KL-6: Kerb von den Lungen-6; SP-D: surfactant protein D. *: *p*-value <0.05.

Table 6 Comparison of 6-min walk test results.

6MWT					
	n	Initiation of therapy	*n*	6 months after therapy	*p*-Value
Mini SpO_2 (%)	33	86 ± 1	20	88 ± 1	0.399
Distance (m)	29	342 ± 21	13	383 ± 32	0.143

6MWT: 6-min walk test; SpO_2: oxygen saturation measured by pulse oximetry. Data are presented as mean ± standard error.

The present study population included a considerable proportion of patients with severe disease, as indicated by the mean baseline FVC that was approximately 10% lower than that in the patient groups of the aforementioned clinical trials reported in Japan and other countries. Although there are few reports documenting the effectiveness of pirfenidone in cases of severe IPF [9,10], the results of our present study suggest that pirfenidone would also be effective in patients with severe IPF. One of the reasons why there were more than a few cases of severe IPF at the start of pirfenidone therapy in this study is that under the present circumstances in Japan, medical expenses are paid by the public for patients with severe IPF, who thus are in a better situation to receive expensive pirfenidone therapy.

Compared with a decline in FVC by approximately 0.15—0.2 L over a 1-year period in the placebo group reported from a clinical trial conducted on mild-to-moderate disease cases, FVC decreased by as much as 0.19 L during the 6-month period before initiation of pirfenidone therapy in the present study. One reason for this trend may be attributable to the higher likeliness of starting pirfenidone therapy in patients with symptomatic exacerbation or worsening of their laboratory values.

The effect of the therapy was more pronounced in the group with a greater decline of FVC during the 6-month period prior to the initiation of therapy in this study. Therefore, it was inferred that the pre-therapy rate of disease progression also influenced the efficacy of pirfenidone. There might be relatively moderate-to-severe components of interstitial inflammation and fibrosis of lung in the group with a greater decline of FVC during the 6-month period prior to the initiation of therapy; pirfenidone compound with antifibrotic and anti-inflammatory effects might be more effective in moderate-to-severe interstitial inflammation and fibrosis.

Furthermore, it has been documented from a stratified analysis of the data from a phase III clinical trial that pirfenidone exerted greater efficacy in patients with a baseline %VC of $\geq$70% and a baseline minimum oxygen saturation measured by pulse oximetry of $<$90% in the 6MWT [11]. Pirfenidone was effective even in patients with baseline values of $<$60% in the present study. It would be reasonable to infer that in the group with a %FVC of $<$60% in this study, the patients were more responsive to the effect of pirfenidone because of the greater degree of FVC decline during the 6-month pre-therapy period in this group.

There have been sporadic reports of improvement in the serum levels of interstitial pneumonia markers following treatment with pirfenidone, and statistically significant improvements were noted in this study. One study demonstrated that KL-6 served as a predictor of the disease activity in cases of IPF [12], and these interstitial pneumonia markers may serve as useful indicators of the therapeutic responses, because their assay is procedurally simple, unlike respiratory function testing. Although this study did not examine the change in radiological images, computed tomography has been reported to be useful to assess the efficacy of pirfenidone [13].

Acute exacerbation of IPF reportedly occurs at an approximate yearly incidence of 5%—15% [14,15] and is associated with a mortality rate of 60% [16]. The incidence of acute exacerbation in this study was approximately 5%, similar to that reported for the placebo group and the pirfenidone-treated group in the phase III clinical trial; therefore, no evidence was found regarding a suppressive effect of pirfenidone on the development of acute exacerbations of IPF.

This investigation had some limitations. The efficacy of pirfenidone was retrospectively examined, and it is possible that the number of patients in this study was not sufficient for reliable evaluation. There were a substantial number of patients who did not undergo respiratory function testing in both before therapy and on therapy and were therefore excluded from the efficacy evaluation. The possibility of bias related to the selection of patients with mild disease for 6MWT in this study cannot be ruled out because the data were compared solely among patients who underwent 6MWT in room air.

Furthermore, 42% patients were concomitantly receiving corticosteroids or immunosuppressants, and there was no significant difference in the therapeutic response between the pirfenidone monotherapy group and the combined drug regimen group; however, the possibility that the concomitant medication may have affected the respiratory function parameters and/or the risk of occurrence of adverse reactions remains to be explored.

In conclusion, our results showed that pirfenidone was well-tolerated and dose reduction of pirfenidone resulted in a high medication compliance rate. Pirfenidone proved effective in attenuating the degree of FVC decline in clinical settings. Baseline decline of FVC had been confirmed in the patients subjected to the efficacy evaluation in this study, and pirfenidone was more beneficial in patients with a greater FVC decline during the 6-month period before initiation of the therapy.

Conflict of interest statement

Ryo Okuda has no conflicts of interest. Eri Hagiwara has no conflicts of interest. Tomohisa Baba has no conflicts of interest. Hideya Kitamura has no conflicts of interest. Terufumi Kato has no conflicts of interest. Takashi Ogura has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of Shionogi & CO., Ltd.

Acknowledgments

The authors would like to thank Enago (www.enago.jp) for the professional English language review.

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