Composite Physiologic Index, Percent Forced Vital Capacity and Percent Diffusing Capacity for Carbon Monoxide Could Be Predictors of Pirfenidone Tolerability in Patients with Idiopathic Pulmonary Fibrosis

Satoshi Konishi,1,2 Machiko Arita1, Isao Ito2, Hiromasa Tachibana1, Takuya Takaïwa1, Yasushi Fukuda1, Naoki Watanabe1, Kazuya Tsubouchi1, Gen Masuda1, Maki Tanaka1, Youhei Kourogi1, Kei Kunimasa1, Akihiro Nishiyama1, Masahiro Iwasaku1, Akihiro Ito1, Fumiaki Tokioka1, Hiroshige Yoshioka1, Toru Hashimoto1 and Tadashi Ishida1

Abstract

Objective The goals of this study were to assess the efficacy and tolerability of pirfenidone in patients with idiopathic pulmonary fibrosis (IPF) and to identify predictors of tolerability to pirfenidone.

Methods We conducted a retrospective observational study. When the patient showed deterioration in the percent forced vital capacity (%FVC) or experienced acute exacerbations or severe adverse events, treatment of the patient with pirfenidone was discontinued. We classified the patients who did not display progression following six months of pirfenidone treatment as the tolerant group and the patients who did display progression as the intolerant group. We retrospectively analyzed differences between the two groups in terms of baseline characteristics. The efficacy of pirfenidone was evaluated by the changes in vital capacity (VC) and %FVC before and after the start of treatment in the tolerant group.

Patients A total of 20 patients who had been diagnosed with IPF were treated with pirfenidone.

Results In the tolerant group, the baseline %FVC (p=0.01) and the percentage diffusing capacity of the lungs for carbon monoxide (DLco, p=0.02) were significantly higher, and the baseline composite physiologic index (CPI) was significantly lower (p=0.009) than in the intolerant group. In the tolerant group, pirfenidone significantly reduced the decline in VC and %FVC of the patients after treatment. In the intolerant group, five patients discontinued pirfenidone treatment because of anorexia.

Conclusion We found that pirfenidone was better tolerated in patients with milder disease symptoms, as indicated by their baseline CPI, %FVC and %DLco, and that patients in the tolerant group could benefit from the use of pirfenidone.

Key words: interstitial lung disease, idiopathic pulmonary fibrosis, emphysema, pirfenidone, composite physiologic index


Introduction

Idiopathic pulmonary fibrosis (IPF), the most common form of idiopathic interstitial pneumonias (IIPs), is a chronic, progressive, irreversible and often fatal lung disease (1, 2). Therapeutic options for patients with IPF are limited and the course of the disease is difficult to predict, generally involving a progressive deterioration with a median survival time of 2.5 to 3.5 years after diagnosis (3). According to a recent statement from a joint committee of the American Thoracic Society, the European Respiratory...
Society, the Japanese Respiratory Society and the Latin American Thoracic Association, there is insufficient evidence to support the use of any specific pharmacologic therapy for patients with IPF (2).

Pirfenidone [5-methyl-1-phenyl-2-(1H)-pyridone, Shionogi & Co., Ltd., Osaka, Japan; Marnac, Inc., Dallas, USA] (4-7) is a drug developed for the treatment of IPF that shows combined anti-fibrotic, anti-inflammatory and anti-oxidant effects in experimental animal models of pulmonary fibrosis (8-11). Three of the four Phase III randomized controlled trials of pirfenidone in patients with IPF suggested that pirfenidone ameliorated progression of the disease in terms of vital capacity (VC) and forced vital capacity (FVC) in patients with IPF, and one trial showed the improvement of progression-free survival (12-14). Azuma et al. analyzed the Phase III trial data in Japan and reported that pirfenidone was more effective in patients with relatively mild impairment of lung function (percent VC ≥70%) (15). Despite these reports, the subpopulation of patients who most benefit from pirfenidone treatment is unclear, and additional research is needed.

In this study, we ascertained the efficacy of pirfenidone in terms of the change in VC and the percent of FVC (%FVC), and have explored the characteristics of patients who benefit most from pirfenidone treatment in terms of their baseline characteristics using a retrospective single-center observational study performed at our university. To assess the severity of IPF in the patients, we used the indices obtained from the pulmonary function test (%D_{cO2}, %FVC, %VC). However, because smoking is a common risk factor for both emphysema and pulmonary fibrosis, patients with IPF may have combined pulmonary fibrosis and emphysema (CPFE). In the IPF cohort, the prevalence of emphysema is reported to be almost 30% (16), and the presence of emphysema modifies the results of pulmonary function tests and outcomes in patients with IPF (17).

The composite physiologic index (CPI) is an index which quantifies functional impairment specifically due to pulmonary fibrosis, while excluding that due to emphysema. The CPI better correlates with the extent of IPF in computed tomography (CT) and mortality than other pulmonary function variables (18). Because it adjusts for the confounding functional effects of coexistent emphysema (19), CPI offers theoretical advantages over other measures. Thus, we also calculated the CPI based on baseline characteristics.

Overall design

This was a single-center retrospective observational study performed at Kurashiki Central Hospital (Okayama, Japan). We had two objectives. First, we sought to evaluate the efficacy of pirfenidone by assessing changes in VC and %FVC for six months before and after the start of pirfenidone treatment and to assess tolerance to the drug. Second, we aimed to identify baseline patient characteristics that can serve as predictors of patient tolerability to pirfenidone.

After obtaining informed consent, we administered pirfenidone to adult patients diagnosed with IPF at our institution since July 2009 on the basis of the criteria below. The data of patients with interstitial pneumonia were extracted from the database of our hospital, and we confirmed each patient’s prescription history. Thus, all 20 patients who were treated with pirfenidone from July 2009 to November 2011 were registered. The diagnosis of IPF was made on the basis of the consensus statement from the American Thoracic Society and the European Respiratory Society (19). When the study began, we used high-resolution computed tomography (HRCT) to assess each patient for the presence of the usual interstitial pneumonia (UIP) pattern on the basis of the criteria established by Raghu et al. (5). All 20 patients were consistent with the UIP pattern, so none of the screened patients were excluded.

The following pirfenidone dose-titration schedule was used: patients received oral tablets of 200 mg every eight hours (600 mg a day) for the first two weeks; 400 mg every eight hours (1,200 mg a day) for the following two weeks; and 600 mg every eight hours (1,800 mg a day, maximum dose) for the remaining time. The maximum dose was maintained throughout the study in patients who tolerated it. Pulmonary function testing was performed every six months after the initiation of the treatment, and treatment was discontinued when patients showed deterioration of five percent in %FVC within six months [marginal decline, (20)], acute exacerbations or severe adverse events.

Acute exacerbation of IPF was defined as a manifestation of any of the following: worsening or otherwise unexplained clinical features within one month; progression of dyspnea; radiographic or HRCT evidence of new parenchymal abnormalities without pneumothorax; pulmonary edema; apparent pulmonary infection; or a decrease in the PaO2 of 10 or more mmHg (21, 22). We classified the patients who completed six months of treatment as tolerant and those who did not as intolerant to pirfenidone. We retrospectively analyzed the differences between the two groups (tolerant and intolerant) in terms of baseline characteristics. In addition, we determined the efficacy of pirfenidone in the tolerant group by assessing improvement or decline in VC and %FVC for six months before and after the start of treatment.

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*Measurements*

VC, FVC, diffusing capacity of the lungs for carbon monoxide (D_{cO2}), serum KL-6 level, serum surfactant protein-D (SP-D) level, distance and lowest blood oxygen saturation level (SpO2) during a six minute walk test (6MWT), and the partial pressure of oxygen in the blood (PaO2) at rest were measured at the start of treatment and six months after the start of treatment. Changes in the patient’s VC and %FVC were assessed for the six months after initiation of the treatment and compared with changes for the six months before induction of the treatment. The CPI was calculated at the in-
Figure 1. HRCT images: definite UIP pattern. These are the time course HRCT images of one patient whose HRCT images showed definite UIP patterns. HRCT images show basal and peripheral predominant reticular opacity with multiple layers of honeycombing and showed progression with time.

Statistical analysis

Differences in the baseline characteristics between tolerant and intolerant groups were analyzed using a 2-sided Fisher’s exact test, Mann-Whitney U test or Student’s t-test, depending on the distribution of the data. An analysis of the changes in VC and %FVC for six months was performed using a paired t-test, based on the results of the Shapiro-Wilk test (p>0.05). A p value less than 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves of %FVC, %Dco and CPI were used to assess which patients benefited from pirfenidone treatment. Areas under the ROC curves (AUC) were compared with a nonparametric approach as described by DeLong et al. (23). Sensitivities, specificities and positive and negative predictive values for the different prediction models were determined. We used the IBM SPSS Statistics software version 19 (SPSS, Inc., Cary, USA) for all analyses.

Results

A total of 20 patients with IPF (median age: 71.8±8.2) were treated with pirfenidone and evaluated. Radiologically, 12 patients were diagnosed with a definite UIP pattern and eight with a possible UIP pattern, based on official criteria (5) (Fig. 1). Most patients (n=15) had a history of smoking, and HRCT scans showed concomitant emphysema in all of these subjects. Eleven patients tolerated the treatment for six months (tolerant group), while the medication was discontinued prematurely in nine patients (intolerant group) because of disease progression (two patients), acute exacerbations (two patients) or severe adverse events (five patients). In the tolerant group, five patients tolerated 1,200 mg/day of pirfenidone, and six patients tolerated the maximum dose of 1,800 mg/day. In the intolerant group, two patients tolerated 600 mg/day, six patients tolerated 1,200 mg/day, and one patient tolerated 1,800 mg/day during the dose-titration schedule. Statistical analysis of the baseline characteristics showed that the tolerant and intolerant groups did not differ significantly in HRCT pattern, VC, PaO2 at rest, lowest SpO2 during 6MWT, serum KL-6 level, serum SP-D level, and alveolar-arterial O2 (A-a) gradient at rest. However, the
Table 1. Baseline Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Total (n=20)</th>
<th>Tolerant (n=11)</th>
<th>Intolerant (n=9)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71.8 (± 8.2)</td>
<td>71.8 (± 6.9)</td>
<td>71.8 (± 9.9)</td>
<td>0.99</td>
</tr>
<tr>
<td>Men</td>
<td>15 (75%)</td>
<td>9 (82%)</td>
<td>6 (67%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Brinkman Index</td>
<td>671 (±612)</td>
<td>683 (±594)</td>
<td>655 (±670)</td>
<td>0.09</td>
</tr>
<tr>
<td>Smoking status</td>
<td>3/12/5</td>
<td>1/8/2</td>
<td>2/4/3</td>
<td>0.55</td>
</tr>
<tr>
<td>Definite UIP/Possible UIP (HRCT)</td>
<td>12/8</td>
<td>6/5</td>
<td>6/3</td>
<td>0.67</td>
</tr>
<tr>
<td>Surgical lung biopsy</td>
<td>3 (15%)</td>
<td>2 (18%)</td>
<td>1 (11%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Maintenance dose(600/1,200/1,800)</td>
<td>2/11/7</td>
<td>0/5/6</td>
<td>2/6/1</td>
<td>0.050</td>
</tr>
<tr>
<td>MMRC-DS (0/1/2/3/4)</td>
<td>0/9/1/10</td>
<td>0/8/0/3/0</td>
<td>0/1/1/7/0</td>
<td>0.012</td>
</tr>
<tr>
<td>Risk stratification (0, 1, 2, 3)</td>
<td>2/6/6/6</td>
<td>2/5/2/2</td>
<td>0/1/4/4</td>
<td>0.21</td>
</tr>
<tr>
<td>PaO₂ at rest (Torr)</td>
<td>80.1 [69.1–84.5]</td>
<td>80.9 [79.1 – 85.7]</td>
<td>73.5 [65.3 – 80.3]</td>
<td>0.15</td>
</tr>
<tr>
<td>Lowest SpO₂ (6MWT) (%)</td>
<td>86.5±5.4</td>
<td>88.3±5.3</td>
<td>84.3±5.0</td>
<td>0.11</td>
</tr>
<tr>
<td>VC (mL)</td>
<td>1,907.6 (±452.59)</td>
<td>2,175.5 (±410.13)</td>
<td>1,598.9 (±266.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>%FVC (%)</td>
<td>64.7 (±13.6)</td>
<td>71.4 (±13.9)</td>
<td>56.0 (±7.7)</td>
<td>0.010</td>
</tr>
<tr>
<td>%DLCO (%)</td>
<td>43.1 (±15.0)</td>
<td>49.8 (±14.6)</td>
<td>34.7 (±11.3)</td>
<td>0.021</td>
</tr>
<tr>
<td>KL-6 (U/mL)</td>
<td>1,266 [784-1,520]</td>
<td>815 [641 – 1,168]</td>
<td>1,251 [1061 – 1,983]</td>
<td>0.075</td>
</tr>
<tr>
<td>SP-D (ng/mL)</td>
<td>236 [159-294]</td>
<td>167 [140 - 261]</td>
<td>242 [216 - 297]</td>
<td>0.18</td>
</tr>
<tr>
<td>CPI</td>
<td>53.6 (±11.6)</td>
<td>47.9 (±11.3)</td>
<td>60.5 (±7.8)</td>
<td>0.0089</td>
</tr>
<tr>
<td>A-a gradient (mmHg)</td>
<td>24.2 (±14.6-26.4)</td>
<td>16.4 (±14.3 - 22.0)</td>
<td>24.7 (±19.0 - 32.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>294 (±105)</td>
<td>339 (±86)</td>
<td>238 (±103)</td>
<td>0.028</td>
</tr>
<tr>
<td>Use of supplemental oxygen</td>
<td>5 (25.0%)</td>
<td>1 (0.0%)</td>
<td>4 (44.4%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Use of immunosuppressant</td>
<td>4 (20.0%)</td>
<td>1 (9%)</td>
<td>3 (33.3%)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Data are shown number (%) or mean (± SD) or median [Interquartile range]. p values are two-sided Fisher’s exact test or Mann-Whitney U test or Student’s t test.

%FVC (p=0.01) and %DLCO (p=0.02) were significantly higher, walking distance during 6MWT was significantly longer (p=0.03) and CPI (p=0.009) was significantly lower in the tolerant group than in the intolerant group (Table 1).

In the tolerant group, we measured the VC and %FVC for the six months before the start of pirfenidone treatment in nine of the 11 tolerant patients. These nine patients showed deterioration in the VC and %FVC during the six months, and five of the nine patients showed a decline of more than five percent in %FVC. Two patients were not evaluated for changes in the VC and %FVC for the six months before treatment. These two patients showed a significant deterioration in their symptoms, CT images and pulmonary function tests over several years prior to their first visit to our hospital, and treatment was started immediately without pulmonary function testing. Six months after initiation of treatment, pirfenidone treatment reduced the decline in the VC and %FVC in eight of the nine tolerant patients. The remaining patient showed a continuous decline in the VC and %FVC, but the 6-month decline in %FVC was less than five percent. Five of the nine patients showed improvement in the VC and %FVC over six months (Fig. 2).

Collectively, in the tolerant group, pirfenidone treatment significantly reduced the decline in the VC (p=0.01) and %FVC (p=0.002) in the six months before the start of treatment, as seen when comparing the pre-treatment decline with the results after the start of the treatment (Fig. 2). Therefore, we concluded that patients in the tolerant group benefited from the pirfenidone treatment.

We analyzed the CPI by ROC curve analysis (AUC: 0.82; 95% CI: 0.63-1.00) and determined the cut-off point of the CPI for assessment of the tolerability of pirfenidone to be 51, based on the sensitivity and specificity suitable for diagnostic use (sensitivity: 1.000, specificity: 0.636). Thus, our data suggest that IPF patients with CPI levels under 51 could especially benefit from pirfenidone treatment. In fact, the distribution chart of CPI levels shows that the CPI values of the intolerant group patients were over 51 (Fig. 3). We also analyzed the %FVC (AUC: 0.82; 95% CI: 0.64-1.00) and %DLCO by ROC curve analysis (AUC: 0.81; 95% CI: 0.62-1.00). Unfortunately, the number of patients was insufficient to analyze the ROC curve; thus, at present, analytic data of the ROC curve is of limited use.

A total of 15 (75%) patients experienced an adverse event. The adverse events observed were gastrointestinal events (anorexia, nausea), skin events (photosensitivity) and psychological events (depression, vertigo). In the intolerant group, five patients discontinued pirfenidone treatment because of anorexia (Table 2).
Results

Table 2. Results: Adverse Events.

<table>
<thead>
<tr>
<th>EVENT</th>
<th>Tolerant</th>
<th>Intolerant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,200mg (n=5)</td>
<td>1,800mg (n=6)</td>
</tr>
<tr>
<td>Event leading to</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any event</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vertigo</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Discussion

In this study, we made two important clinical observations. First, pirfenidone was better tolerated in patients with milder disease symptoms as indicated by their baseline CPI, %FVC and %DLCO measurements. Second, in the tolerant group, pirfenidone significantly reduced the decline in the VC and %FVC of IPF patients who were examined six months before and after the start of treatment. In previous studies, two of the three Phase III randomized controlled trials showed that pirfenidone made disease progression milder than the placebo in terms of VC and FVC in IPF patients (1, 2). IPF is usually a progressive disease, but its clinical course is variable and difficult to predict. Therefore, when evaluating the effectiveness of pirfenidone and the validity of long-term treatment in individual patients, it may be important to compare changes in the VC and %FVC before and after the start of pirfenidone treatment. In our study, in the tolerant group, one patient showed a continuous decline in the VC and %FVC after the initiation of treatment, but the decline in %FVC was less than five percent over six months. Therapeutic options for patients with IPF are limited and the course of the disease generally involves progressive deterioration. Our objective while treating IPF patients was to slow disease progression. Therefore, it is
important to know the disease course before and after the treatment. Physicians are advised to collect as much data as possible before and after initiation of pirfenidone treatment.

We found that pirfenidone was better tolerated in patients with milder disease symptoms, as indicated by their baseline CPI, %FVC, and %DLCO values, and that patients in the tolerant group could benefit from pirfenidone treatment. In an exploratory analysis of a Japanese Phase III study, Azuma et al. reported that a significant efficacy of pirfenidone in reducing the decline in the VC could be seen in a subpopulation of patients with a percent VC ≥70% and an SpO2 <90% at baseline (15). In our study, we showed that the CPI value may also be a reliable predictor of the efficacy of pirfenidone treatment.

In IPF, the indices of pulmonary function, especially FVC and DlCO are considered important for clinical evaluation, and declines in FVC and DlCO are regarded as valuable prognostic factors. Recently, there has been increasing clinical, radiologic and pathologic recognition of the coexistence of emphysema and pulmonary fibrosis, known as CPFE (17). The presence of emphysema modifies the results of pulmonary function tests and outcomes in patients with IPF (17). Moreover, whether patients with CPFE have a worse survival rate than patients with IPF without emphysema is unclear. Mejia et al. reported a lower survival rate in patients with both emphysema and IPF than in patients with isolated IPF (16). In contrast to their results, other studies have found a comparable or better survival rate in CPFE cohorts than in groups with isolated pulmonary fibrosis (24-26). These results raise important questions about whether patients with the characteristics of CPFE can be assessed using a single isolated parameter of pulmonary function such as VC or %FVC in clinical trials of IPF therapies.

In light of questions about pulmonary assessment in CPFE patients, the CPI value offers theoretical advantages because it adjusts for the confounding functional effects of concurrent emphysema (18). Furthermore, the CPI value provides additional advantages over other composite indices of IPF because it is generated only by pulmonary function testing without radiologic or clinical components, and because it is likely to be easier to validate in routine practice, making it more attractive to clinicians. Our findings therefore suggest that CPI could be an important predictor of patient tolerability of pirfenidone, and may be a predictor of the efficacy of pirfenidone treatment. Additional longitudinal studies of CPI in IPF patients should be informative.

There are a few limitations associated with this study. Our study was a retrospective study, and we made inter-subjective comparisons. Therefore, our findings may be influenced by various biases. In addition, the sample size was small, necessitating caution when extending our conclusions to other IPF patients. Additional prospective research including a larger number of patients can address these limitations.

## Conclusion

We found that pirfenidone was better tolerated in patients with milder disease symptoms as indicated by their baseline CPI, %FVC and %DLCO measurements. Patients in the tolerant group benefited from pirfenidone treatment. We propose that the baseline CPI value be considered as a parameter for predicting tolerability of pirfenidone in IPF patients.

The authors state that they have no Conflict of Interest (COI).

## References

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