Predictors of the clinical effects of pirfenidone on idiopathic pulmonary fibrosis

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Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with a poor prognosis. Recently, pirfenidone was reported to slow the rate of decline in vital capacity and improve progression-free survival in IPF. The purpose of this study was to clarify the factors that predicted a good response to pirfenidone, as well as its adverse effects.

Methods: Forty-one IPF cases, treated with pirfenidone from January 2009 to January 2011, were enrolled in this investigation. Disease severity was classified into grades I–IV, as defined by the Japanese Respiratory Society (JRS). Short-term responsiveness to pirfenidone was evaluated by the modified criteria of the JRS. Predictors of nausea, anorexia, or both that represented important adverse effects were examined by multivariate Cox proportional hazards regression analysis.

Results: Eighteen (44%) of the 41 patients showed improvement of respiratory function, according to the modified criteria of the JRS. Predictors of improved respiratory function included: lower age, higher baseline forced expiratory volume in 1 second (FEV1), higher baseline diffusing capacity of carbon monoxide (DLco), lower baseline dyspnea grade, and lower baseline functional class. Nausea was the most frequent adverse effect, occurring in 22 of 41 patients (54%). The commonest adverse events were nausea, anorexia, weight loss, and insomnia. Predictors of nausea included: lower weight at baseline; higher body mass index (BMI); higher baseline DLco; and lower baseline FEV1.

Conclusions: The modified criteria of the JRS for the assessment of short-term responsiveness to pirfenidone were useful in predicting the clinical effects of pirfenidone in IPF. Patients with better baseline lung function and lower dyspnea grades were more likely to show a favorable response to pirfenidone. Nausea was the most frequent adverse effect of pirfenidone, and its occurrence was predicted by lower weight at baseline, higher BMI, higher baseline DLco, and lower baseline FEV1.

Abbreviations: IPF, Idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; SLB, surgical lung biopsy; VC, vital capacity; NHO-KCCMC, National Hospital Organization Kinki-Chuo Chest Medical Center; UIP, usual interstitial pneumonia; HRCT, high-resolution computed tomography; ATS, American Thoracic Society; ERS, European Respiratory Society; TLC, total lung capacity; DLco, diffusing capacity of carbon monoxide; KL-6, Krebs von den Lungen-6; (SP)-D, surfactant protein-D; MRC, Medical Research Council; PaO2, arterial oxygen tension; PPIs, proton pump inhibitors; H2RAs, histamine H2-receptor antagonists

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Anorexia

Acid-secretion inhibitors

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a lung disease with a poor prognosis that includes the progressive deterioration of pulmonary function. Its etiology is unknown, and there is no proven effective therapy [1,2]. The pathophysiology of IPF is not fully understood; however, treatments targeting the fibrotic pathway and epithelial injury are supposed to attenuate IPF progression [3].

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) elicits both antifibrotic and anti-inflammatory effects in experimental pulmonary fibrosis models [4]. Open-label studies have revealed that pirfenidone stabilizes IPF disease progression [5,6]. A phase III clinical trial conducted in Japan showed that vital capacity (VC) declined to a lesser degree in pirfenidone-treated IPF patients than that of placebo-treated patients [7]. A significant difference in the progression-free survival was also observed between the 2 groups. On the basis of these findings, in 2008, pirfenidone was approved for IPF treatment in Japan. However, Noble et al. reported controversial results from 2 concurrent phase III trials in the United States [8].

The adverse effects of pirfenidone have been frequently observed. A phase II trial showed that 98.5% of pirfenidone-treated IPF patients had complications including various adverse effects as compared to that of 88.9% of the placebo group [9]. Photosensitivity, nausea, anorexia, and fatigue were observed in 43.8%, 21.9%, 31.5%, and 21.9%, respectively, of the patients; moreover, a significant increase in the frequency of these side effects was observed in the pirfenidone group than that of the placebo group. Photosensitivity can be controlled by prophylactic sunscreen use, which is recommended in the guideline of Shionogi & Co., Ltd. Gastrointestinal adverse effects are the most important dose-limiting and withdrawal-determining factors of pirfenidone.

Thus, if we can predict the responsiveness and adverse effects of pirfenidone treatment in IPF patients, treatment regimens could be better managed. In this study, we examined the predictors of responsiveness and adverse effects of pirfenidone in IPF patients treated in our institute.

2. Materials and methods

2.1. Subjects

From January 1, 2009 to January 1, 2011, 41 patients with IPF were prospectively enrolled and treated with pirfenidone (Shionogi & Co., Ltd., Osaka, Japan) in National Hospital Organization Kinki-Chuo Chest Medical Center (NHO-KCCMC). Informed consent was obtained from all subjects. The institutional review board at NHO-KCCMC approved this study (approval number: Jutaku-20-22; approval date: January 16, 2009). Twenty-three patients were clinically diagnosed with IPF with an usual interstitial pneumonia (UIP) pattern using high-resolution computed tomography (HRCT), while 18 patients were histologically diagnosed as IPF/UIP by surgical lung biopsy (SLB) specimens under the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society guidelines for IPF [10]. HRCT patterns (e.g., UIP pattern or possible UIP pattern) upon pirfenidone initiation were also evaluated in IPF/UIP cases. The patients’ demographics are summarized in Table 1.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Frequency or median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n)</td>
<td>41 cases</td>
</tr>
<tr>
<td>Gender, male (n)/female (n)</td>
<td>34/7</td>
</tr>
<tr>
<td>Age, (years)</td>
<td>70 (65.5–75.5)</td>
</tr>
<tr>
<td>Smoking status (n), CS/ES/NS</td>
<td>6/24/11</td>
</tr>
<tr>
<td>Diagnosis (n), Clinical/SLB</td>
<td>23/18</td>
</tr>
<tr>
<td>Modified MRC scale (n), grade 0/1/2/3/4</td>
<td>2/6/18/12/3</td>
</tr>
<tr>
<td>VC, % predicted (%)</td>
<td>66.7 (54.8–77.8)</td>
</tr>
<tr>
<td>Severity grade of IPF (n), I/II/III/IV</td>
<td>9/5/9/18</td>
</tr>
<tr>
<td>Serum KL-6 (U/mL)</td>
<td>858 (1600–687)</td>
</tr>
<tr>
<td>Serum SP-D (ng/mL)</td>
<td>187 (138–299)</td>
</tr>
<tr>
<td>Serum cholinesterase (U/L)</td>
<td>270 (216–327)</td>
</tr>
<tr>
<td>Long term oxygen therapy (n), Yes/No</td>
<td>22/19</td>
</tr>
<tr>
<td>Treatment before pirfenidone</td>
<td></td>
</tr>
<tr>
<td>Corticosteroid alone (n)</td>
<td>3</td>
</tr>
<tr>
<td>Corticosteroid and azathioprine (n)</td>
<td>4</td>
</tr>
<tr>
<td>Corticosteroid and cyclosporine (n)</td>
<td>1</td>
</tr>
<tr>
<td>Inhalation of N-acetyl-cysteine (n)</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; CS, current smokers; ES, ex-smokers; NS, non-smokers; SLB, surgical lung biopsy; MRC scale, Medical Research Council score for shortness of breath upon exertion; VC, vital capacity; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D.
2.2. **Clinical parameter measurement**

Pulmonary function tests, including VC, total lung capacity (TLC), and diffusing capacity of carbon monoxide (DLCO), were performed using CHESTAC-8800 (Chest M.I., Inc., Tokyo, Japan). A 6-min walk test was performed in accordance with ATS guidelines [11]. Serum Krebs von den Lungen-6 (KL-6), surfactant protein-D (SP)-D were measured by the enzyme-linked immunosorbent assay using commercially available kits [12]. Dyspnea was assessed by the modified Medical Research Council (MRC) scale from the ATS/ERS [13].

2.3. **IPF severity grade**

The IPF severity grade was classified per the JRS criteria [7] using the arterial oxygen tension (PaO2) at rest and minimum SpO2 during a 6-min walk test performed before pirfenidone initiation. Patients with a PaO2 $\geq$ 80 Torr were classified as grade I; $\geq$ 70 Torr and $<$ 80 Torr as grade II; $\geq$ 60 Torr and $<$ 70 Torr as grade III; and $<$ 60 Torr as grade IV. For patients with $\geq$ grade II, if the SpO2 during a 6-min walk test was $<90\%$, then the severity grade was increased by one grade.

2.4. **Pirfenidone administration**

Pirfenidone daily dosing was increased in a stepwise manner from 600 to 1800 mg every 2 weeks [7]. The median maximum dose was 1800 mg (range, 600–1800 mg), and the median final dose in the treatment period was 1200 mg (range, 600–1800 mg). The dose was decreased in accordance with the occurrence of adverse events. The median observation period for each IPF patient administered pirfenidone was 400 days (range, 12–885 days).

2.5. **Pirfenidone response**

A comprehensive evaluation of the patients was performed regarding short-term responsiveness at 3–6 months after pirfenidone initiation to classify the patients as experiencing either an improvement (good response) or a deterioration of at least 2 of the 3 parameters (clinical symptoms, radiological findings, and physiological findings) according to modified criteria [14] of JRS, as well as King et al. [15] on the basis of a prior ATS/ERS consensus statement on IPF that was published in 2000 [16]. Stable state was defined as neither improvement nor deterioration. Evaluation of each parameter is defined in the online supplement (Table S1 in the online supplementary data).

The effects of pirfenidone in 10 IPF cases could not be evaluated because of death (n = 1; pirfenidone treatment, 12 days), transfer to other hospitals (n = 1; pirfenidone treatment, 88 days), or pirfenidone withdrawal because of adverse effects (n = 8; pirfenidone treatment range, 10–65 days) within 3 months of initiation. Thus, short-term responsiveness was evaluated in 31 cases. One patient who died within 3–6 months of pirfenidone initiation was evaluated as deteriorated.

2.6. **Evaluation and treatment of adverse effects, including anorexia, nausea, or both**

Adverse effects in all cases were evaluated using the Common Terminology Criteria for Adverse Events (v. 4). Acute exacerbation of IPF was defined according to the criteria in Japan [7,14]. Of all adverse effects, we evaluated nausea or anorexia that would be classified as $\geq$ grade 2. In grade 2, oral ingestion decreased without significant weight loss; in grade 3, hospitalization was necessary because of significant weight loss secondary to inadequate oral ingestion. Drugs to protect the gastric mucosa and activate gastric motility, including proton pump inhibitors (PPIs) and histamine H2-receptor antagonists (H2RAs), were administered before IPF treatment because of comorbidities that included chronic gastritis, gastric/duodenal ulcers, and gastroesophageal reflux disease. The PPIs, including omeprazole, lansoprazole, and rabeprazole, were administered to 2, 5, and 9 cases, respectively. Cimetidine (H2RA) was administered to 3 cases. Each patient was additionally prescribed several types of drugs for gastrointestinal symptoms if nausea, anorexia, or both occurred.

2.7. **Statistical analyses**

Patient demographics data are presented as frequency (%) or median with a range. Correlation between pirfenidone response and IPF severity grade was examined by Fisher’s exact test and Spearman rank correlation. Univariate and multivariate logistic regression analyses were performed to clarify the predictors of pirfenidone responsiveness. Each numerical parameter was divided into 2 groups by the median. For grades $\geq$ 2, the Kaplan–Meier method was used to assess the occurrence of nausea, anorexia, or both as adverse effects according to Time without nausea/anorexia for IPF patients taking pirfenidone. Clinical parameters determining the occurrence of anorexia, nausea, or both were examined by univariate and multivariate Cox proportional hazard regression analyses. A P-value of $<0.05$ was considered statistically significant.

All statistical analyses were performed using SPSS software (v.19) (Chicago, IL, USA).

3. **Results**

3.1. **Short-term pirfenidone response and IPF severity stage**

Physiological and radiological improvements were observed in 4 cases and 2 cases, respectively. Symptoms improved in 11 cases (cough, 8 cases; shortness of breath, 6 cases). A comprehensive assessment revealed that 6 cases improved 3–6 months after pirfenidone initiation. The patients’ pirfenidone response was found to be significantly associated with the IPF severity grade using the Fisher’s exact test ($P=0.025$) and Spearman rank correlation ($\rho=0.5039$; $P=0.0039$) (Table 2).

3.2. **Predictors of short-term pirfenidone response**

Using the 2 significant parameters as determined by the univariate analysis (Table S2 in the online supplementary data), the multivariate analyses (Table 3) showed that diagnosis with
SLB specimens was a significant predictor, in addition to an IPF severity grade of I/II. Similar results were found in the evaluable short-term response cases after the addition of 1 deceased case that had died 12 days after pirfenidone initiation. No difference was observed between clinical IPF and IPF/UIP at pirfenidone initiation, except for age, gender, and HRCT patterns (Table S3 in the online supplementary data).

3.3. VC change before and after pirfenidone initiation

A change (L/year) in VC could be compared between 3 and 12 months before and 3 and 6 months after pirfenidone initiation by the Wilcoxon signed-rank test in 21 cases. In patients with severity grade I/II, the change in VC significantly decreased after pirfenidone initiation ($p=0.0039$) (A). However, the change in VC did not significantly decline in severity grade III/IV patients ($p=0.1748$) (B). The change in VC before pirfenidone administration in severity grade I/II patients was significantly smaller than that of severity grade III/IV patients with Wilcoxon rank-sum test ($p=0.0290$).

3.4. Pirfenidone adverse effects

Adverse effects were observed in 31 of the 41 IPF patients (75.6%) following pirfenidone initiation. Anorexia, nausea, or both were observed in 24 of the 41 (58.5%) IPF patients. Other adverse effects were photosensitivity (5 cases, 12.2%), allergic skin reaction (2 cases, 4.9%), sleepiness (2 cases, 4.9%), photophobia (1 case, 2.4%), vertigo (1 case, 2.4%), diarrhea (1 case, 2.4%), and acute exacerbation (4 cases, 9.8%). Pirfenidone was ceased in 15 cases (34.1%) because of anorexia, nausea, or both (6 cases, 14.6%); disease progression including acute exacerbation (7 cases, 17.1%); and transfer to other hospitals (2 cases, 4.9%). Six cases (14.6%) died from disease progression.

3.5. Pirfenidone induced anorexia, nausea, or both

Nineteen IPF cases (acid-secretion inhibitor group) were taking PPIs or H2RAs before pirfenidone initiation as treatment for

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**Table 2 – Short-term response to pirfenidone.**

<table>
<thead>
<tr>
<th>Severity grade of IPF</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>3</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>VC, %predicted (IQR) (%)</td>
<td>76.6 (69.7–83.2)</td>
<td>87.6 (86.0–88.9)</td>
<td>64.8 (57.7–71.7)</td>
<td>58.9 (47.7–64.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response to pirfenidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement (n)</td>
</tr>
<tr>
<td>Stable (n)</td>
</tr>
<tr>
<td>Deterioration (n)</td>
</tr>
</tbody>
</table>

Abbreviations: IPF, idiopathic pulmonary fibrosis; VC, vital capacity; IQR, interquartile range. Significant correlation between response to pirfenidone and severity grade of IPF was observed by Fisher’s exact test ($p=0.0255$). Definition of severity grade and response of pirfenidone was described in Section 2 and Table S1 in the online supplementary data.

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**Table 3 – Predictors of short-term good response to pirfenidone.**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity grade (I/II)</td>
<td>32.988</td>
<td>1.813–600.319</td>
<td>0.018</td>
</tr>
<tr>
<td>Diagnosis (SLB)</td>
<td>23.651</td>
<td>1.265–442.125</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; SLB, surgical lung biopsy; IPF, idiopathic pulmonary fibrosis.

* Univariate logistic regression analysis was performed using age ($\leq 70$ years), smoking status (non-smoker), diagnosis by SLB, severity grade (I/II), Modified Medical Research Council scale for shortness of breath upon exertion (0–1), cholinesterase ($>270$ U/L), Krebs von den Lungen-6 ($>858$ U/mL), surfactant protein-D ($>187$ ng/mL) and usage of proton pump inhibitor (Table S2 in the online supplementary data). Multivariate logistic regression analysis was performed using significant parameters by univariate analysis (e.g. diagnosis with SLB and severity grade of IPF) (Table S2).

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**Fig. 1 –** A change in vital capacity (VC; L/year) was compared with the Wilcoxon signed-rank test between 3 and 12 months before and 3 and 6 months after pirfenidone initiation with (A) severity grade I/II ($n=10$) and (B) severity grade III/IV ($n=11$). In severity grade I/II patients, the change in VC significantly decreased after pirfenidone initiation ($p=0.0039$) (A). However, the change in VC did not significantly decline in severity grade III/IV patients ($p=0.1748$) (B). The change in VC before pirfenidone administration in severity grade I/II patients was significantly smaller than that of severity grade III/IV patients with Wilcoxon rank-sum test ($p=0.0290$).
other comorbidities (Table 4). The other 22 cases (no acid-secretion inhibitor group) were not administered acid-secretion inhibitors but administered drugs to protect the gastric mucosa. No significant difference in frequency of coadministration of gastrointestinal drugs was observed between the 2 groups (Table S4 in the online supplementary data). One case was administered drugs to activate gastrointestinal motility. There was no difference in pirfenidone dose between the 2 groups.

In the no acid-secretion inhibitor group, 16 cases (72.7%) complained of anorexia, nausea, or both, and 5 cases (22.7%) ceased taking pirfenidone; however, 7 cases continued to take pirfenidone because of additional PPI usage. In the acid-secretion inhibitor group, anorexia, nausea, or both occurred in only 8 cases (42.1%), and almost all cases remained on pirfenidone because of other adverse events, other than anorexia, nausea, or both, were treated as censored cases.

### Table 4 – Prophylactic effects of acid-secretion inhibitors on anorexia and/or nausea due to pirfenidone.

<table>
<thead>
<tr>
<th>Drugs at the introduction of pirfenidine</th>
<th>No. of cases</th>
<th>Anorexia and/or nausea</th>
<th>Dose reduction of pirfenidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid-secretion inhibitors(^a) (n)</td>
<td>19</td>
<td>8</td>
<td>None</td>
</tr>
<tr>
<td>No acid-secretion inhibitors(^b) (n)</td>
<td>22</td>
<td>16</td>
<td>Reduction</td>
</tr>
</tbody>
</table>

Frequency of anorexia and/or nausea was significantly less in the acid-secretion inhibitors group than that in the no acid-secretion inhibitors group as determined by the chi-square test \((p<0.05)\).

\(^a\) Proton pump inhibitors (PPIs) or histamine H2-receptor antagonists (H2RA) were administered. The PPIs, omeprazole, lansoprazole, and rabeprazole, were administered to two, five, and nine cases, respectively. The H2RA, cimetidine, was administered in three cases.

\(^b\) Acid-secretion inhibitors were not administered, but drugs for gastritis, drugs to protect gastric mucosa or to activate motility of the gastrointestinal tract were administered. Gastrointestinal drugs in detail were shown in Table S4 in the online supplementary data.

\(^c\) Anorexia and/or nausea improved after the additional use of PPIs after the onset of the adverse effects.

Fig. 2 – Kaplan–Meier plots of anorexia/nausea-free time in IPF patients administered pirfenidone and acid-secretion inhibitors (solid line) or pirfenidone alone (dotted line). The median anorexia/nausea-free time from pirfenidone initiation to the onset of anorexia/nausea in patients with grade 2 was significantly shorter in cases with no acid-secretion inhibitors (34 days) than in cases with acid-secretion inhibitors (324 days), as determined by log-rank test \((p=0.0211)\). Cases that continued pirfenidone treatment and then stopped because of other adverse events, other than anorexia, nausea, or both, were treated as censored cases.

### Table 5 – Predictors of nausea and/or anorexia caused by pirfenidone\(^a\)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Risk ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid-secretion inhibitors (No)(^b)</td>
<td>2.346</td>
<td>1.053–5.591</td>
<td>0.037</td>
</tr>
<tr>
<td>Age (&gt;70 years)</td>
<td>1.910</td>
<td>0.868–4.410</td>
<td>0.1083</td>
</tr>
</tbody>
</table>

Abbreviations: PPI, proton pump inhibitor; CI, confidence interval.

\(^a\) Multivariate Cox proportional Hazard analysis was performed using two parameters with \(p\)-value less than 0.10 by univariate Cox proportional Hazard analysis using age (>70 years), smoking status (non-smoker), diagnosis (clinical), severity grade (IV), Modified Medical Research Council scale for shortness of breath upon exertion (0–2), serum cholinesterase (>270 U/L), no administration of acid-secretion inhibitors and administration of prednisolone described in Table S5 in the online supplementary data.

\(^b\) PPIs and histamine H2-receptor antagonists was not administered at the commencement of pirfenidone.

Patients administered pirfenidone in the acid-secretion inhibitor group was 324 days (Kaplan–Meier method), and this was significantly longer than that of the no acid-secretion inhibitor group (34 days) (Fig. 2).

### 3.6. Predictors of anorexia, nausea, or both with pirfenidone administration

A univariate analysis (Table S5 in the online supplementary data) using the Cox proportional hazard regression analyses revealed that the lack of acid-secretion inhibitors was the only significant factor. Prednisolone administration did not affect the onset of nausea, anorexia, or both. The multivariate analyses using factors with a \(p\)-value of <0.10 (Table 5) showed that the lack of acid-secretion inhibitors was a significant predictor of anorexia, nausea, or both.

### 4. Discussion

Our investigation demonstrated that the IPF severity grade (I/II) was a significant predictor of a short-term, good response to pirfenidone. Azuma et al. [17] performed an exploratory analysis in a phase III pirfenidone trial and reported that pirfenidone was effective in IPF patients with a %VC \(\geq 70\%\) or PaO\(_2\) \(\geq 70\) Torr and...
a SpO2 <90% during a 6-min walk test at baseline, as compared to that of the placebo group. Their criteria for good responders corresponded to IPF cases with mild-to-moderate lung function impairment, although it was not necessarily similar to stage I/II per the JRS criteria. IPF cases with severity grade I/II also had a significant decrease in VC change after pirfenidone initiation. Thus, pirfenidone might have some effects in the unimproved grade I/II cases.

Another important predictor of a good response to pirfenidone was diagnosis by SLB specimens. Five of the 6 IPF cases with a good, short-term response to pirfenidone were diagnosed by an SLB. Similar results were reported in a bosentan clinical trial for IPF [18]. These results might be explained by the hypothesis that the beneficial effect was greater in IPF cases with a possible UIP pattern on HRCT. It is true that all the IPF/UIP cases in our study demonstrated a possible UIP pattern at diagnosis; however, the HRCT pattern in 8 of the 13 IPF/UIP cases was a definite UIP pattern upon pirfenidone initiation, and 3 of the 5 IPF/UIP cases that had a good response to pirfenidone exhibited a definite UIP pattern. Thus, other factors supposedly have an effect on a good response, although the HRCT pattern might be partially associated with a good response. A detailed reevaluation of the pathological and radiological findings may be warranted to determine the features associated with a good response to pirfenidone.

We performed a multidisciplinary evaluation of a pirfenidone response using radiological and symptomatic parameters, in addition to physiological parameters. Iwashita et al. reported that the radiological findings have improved in only 3 of the 38 cases 1 year after pirfenidone initiation [19], which is consistent to our result. However, our investigation showed that radiologic improvement could be observed in shorter treatment periods, 3–6 months after pirfenidone initiation. The degree of cough had not been evaluated in previous reports. We observed a cough improvement in some cases, although it remains unclear if this was because of a direct effect of pirfenidone. Acute exacerbation of IPF was not inhibited by pirfenidone in the phase III trials [7]. However, the incidence of acute exacerbation in our population (9.8%) was high, as compared with that of the previous clinical trials [7,9]. This may have occurred because severe cases were included in this study.

Taniguchi et al. reported that the short-term effects could predict the long-term effects of pirfenidone, using data from a Japanese phase III clinical trial [20]. They evaluated pirfenidone-treated IPF patients for 3 months and categorized them into 2 groups: a “worsening” group with a relative VC decline of ≥5% and a “no worsening” group with no such decline. For 71.7% of the pirfenidone-treated cases in the “no worsening” group, no deterioration occurred 1 year posttreatment, while 87.1% of the pirfenidone-treated cases in the “worsening” group deteriorated 1 year posttreatment. In our examination, 5 of the 6 short-term improvement cases remained on pirfenidone for >1 year, and 4 of the 5 cases were evaluated as stable (data not shown). Although our investigation of the long-term effects was not sufficient, evaluation of the short-term effects may be useful for predicting long-term responsiveness.

Pirfenidone is a promising drug for IPF; however, adverse effects (photosensitivity and anorexia and/or nausea) frequently occurred in several clinical trials [5–7,9]. Gastrointestinal adverse effects are the most important dose-limiting and withdrawal-determining factors of pirfenidone. Our investigation showed the possible preventive effects of PPIs and H2RA against nausea, anorexia, or both.

The pathophysiology of anorexia and nausea with pirfenidone administration has not been fully elucidated; however, it might be associated with the suppression of gastrointestinal motility [21]. Although gastroscopy was not performed on any of our cases, we do not believe anorexia occurred from gastroduodenal ulcers, as it spontaneously resolved after pirfenidone discontinuation. PPIs and H2RAs do not directly activate gastric motility; however, they are known to improve postprandial fullness and early satiation observed in functional dyspepsia without organic disease [22] through attenuating duodenal hypersensitivity to acids [23]. It is reported that PPI monotherapy improves dysmotility-like symptoms significantly better than that of H2RAs plus mosapride in functional dyspepsia [24].

The effect of PPIs on the pharmacokinetics of pirfenidone is an important problem. Although neutralizing acid does not affect pirfenidone absorption or its plasma concentration [25], drug interactions between PPIs and pirfenidone should be considered. In vitro metabolism studies revealed that approximately 48% of pirfenidone is metabolized via cytochrome P450 (CYP) 1A2, while <13% is done so by each of CYP2C9, 2C19, 2D6, and 2E1 [26]. PPIs inhibit some CYP reactions; however, all the CYPs associated with pirfenidone metabolism are not simultaneously inhibited [27], and we postulate that the inhibitory effects of pirfenidone may be clinically limited.

In vitro evaluations using hepatoma cell-lines showed that CYP1A2, the most important metabolizer of pirfenidone, was induced by omeprazole and lansoprazole, but not by rabeprazole [28]. Thus, omeprazole and lansoprazole may accelerate pirfenidone metabolism and theoretically decrease its serum concentration and clinical effects; however, in vitro studies are not always consistent with in vivo studies. In vivo interactions of theophylline and caffeine, which are metabolized by CYP1A2, with omeprazole could be clinically negligible in accordance to pharmacokinetic studies [29]. Although the coadministration of pirfenidone and PPIs might not affect the in vivo clinical effects, rabeprazole is better than omeprazole and lansoprazole from the standpoint of CYP1A2 induction. Rabeprazole was administered to 2 of the 6 improved cases in our examination (data not shown). Esomeprazole may be another important PPI, as it does not interact with drugs metabolized by CYP1A2 [30].

As for H2RAs, cimetidine is known to interfere with the metabolism of many drugs by inhibiting CYP3A4, CYP1A2, and CYP2D6 [31]. Thus, cimetidine and pirfenidone coadministration might lead to elevated serum pirfenidone levels and deteriorating gastrointestinal symptoms in some cases. Interactions of ranitidine and famotidine with CYP isoenzymes are weak and negligible [32,33].

Our study had several limitations. First, this was not a randomized trial, and PPIs were used for comorbidities. Second, the number of patients was small. Future randomized, controlled trials are necessary to assess the effects of PPIs on nausea, anorexia, or both caused by pirfenidone.
5. Conclusion

IPF patients with a mild disease, diagnosis by SLB, or both showed indications of a good response to pirfenidone. In addition, acid-secretion inhibitors may reduce the frequency of nausea, anorexia, or both from pirfenidone.

Conflict of interest

The authors have no conflicts of interest.

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Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.resinv.2013.09.002.

REFERENCES


