The Effect of Pirfenidone on the Prescription of Antibiotics and Antitussive Drugs in Patients With Idiopathic Pulmonary Fibrosis

A Post Hoc Exploratory Analysis of Phase III Clinical Trial

To the Editor:

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and devastating fibrotic lung disease. Patients with IPF often experience various symptoms as pulmonary function deteriorates, which are associated with an increase in the prescription of concomitant drugs. Most IPF patients are middle-aged to older adults with various comorbidities, leading to further increase in the use of concomitant drugs. This polypharmacy results in complications related to the drug-drug interactions and increases in medical spending. There is an urgent need to find ways to avoid polypharmacy in the management of IPF.

Pirfenidone is an antifibrotic drug approved in multiple countries for the treatment of IPF. In multinational phase III clinical trials, pirfenidone reduced disease progression as reflected by pulmonary function, exercise tolerance, and progression-free survival in patients with IPF. Studies further demonstrated that pirfenidone reduces respiratory-related hospitalizations and objective cough. Considering these findings, we posited that pirfenidone may reduce the prescription of antibiotics and antitussive drugs and contribute to the avoidance of polypharmacy. The aim of this study was to assess the potential effects of pirfenidone in delaying the prescription of concomitant drugs in patients with IPF.

Methods

This is a post hoc exploratory analysis of a phase III multicenter, randomized, double-blind, placebo-controlled trial, conducted with Japanese IPF patients to determine the efficacy and safety of pirfenidone over 52 weeks. In this phase III clinical trial, 325 patients were screened at 73 centers in Japan, and 275 patients were randomized to one of the three groups: high-dose pirfenidone (1,800 mg/day), low-dose pirfenidone (1,200 mg/day), and placebo. Two hundred sixty-seven patients were deemed eligible for the full analysis set (high-dose pirfenidone, n = 108; low-dose pirfenidone, n = 55; placebo, n = 104). Eight patients were excluded for lack of post-baseline data. The full analysis set population was used in this post hoc exploratory analysis. The clinical trial protocol was approved by the institutional review board at each center, and written informed consent was obtained from all participants. The diagnostic criteria of IPF in the trial was previously described. This clinical trial was registered with the Japan Pharmaceutical Information Center on September 13, 2005 (JapicCTI-050121).

We examined the effect of pirfenidone in delaying new prescriptions of antitussive drugs or antibiotics for respiratory adverse events (respiratory AEs). The first prescription after initiation of trial drugs was recorded in this analysis. Respiratory AEs included upper respiratory tract infection, pneumonia, and acute exacerbations of IPF. In this study, all concomitant drugs including over-the-counter drugs were ascertained.

Using Kaplan-Meier curves and the log-rank test, we compared the time to new concomitant drug use between the pirfenidone and placebo groups. The effects of pirfenidone were also evaluated by univariate Cox proportional hazards model, and the model with vital capacity (VC) as a time-dependent covariate (at baseline and 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 weeks after initiation of trial drugs), and assessed in subgroups defined by the gender-age-physiology (GAP) index.

Analysis was completed using SAS ver. 9.2 or 9.4 (SAS Institute Inc). All tests were performed at a significance level of P < .05, and multiplicity of tests was not adjusted because of post hoc exploratory analysis.

Results

Baseline patient characteristics are shown in Table 1. During the study period of 52 weeks, more than half of IPF patients were newly prescribed antibiotics (n = 144 [54%]) and antitussive drugs (n = 153, [57%]), respectively. Approximately 40% of patients (n = 104 [39%]) were prescribed both drugs during the observational period, and one fifth (n = 56, [21%]) were prescribed them at same time. The median time from initiation of the trial drug to prescription of antibiotics and antitussive drugs was 267 days and 217 days, respectively.

In the overall study population, pirfenidone did not delay new prescription of concomitant antitussive drugs compared with the placebo (hazard ratio [HR], 0.875; 95% CI, 0.635-1.205; P = .4122) (Fig 1). Conversely,
pirfenidone tended to delay new onset of respiratory AEs (HR, 0.751; 95%CI, 0.560-1.007; \( P = .0560 \)), and also to delay new antibiotic use for respiratory AEs compared with the placebo (HR, 0.714; 95%CI, 0.481-1.060; \( P = .0948 \)) (Fig 2). This tendency was maintained in GAP stage 1, but not in GAP stages 2 and 3. Cox proportional hazards model with VC as a time-dependent covariate in the overall population showed a similar trend for the effects of pirfenidone on new antibiotic use for respiratory AEs (vs placebo; HR, 0.721; 95%CI, 0.485-1.070; \( P = .1042 \)), but not for new antitussive drugs use.

**TABLE 1**  Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pirfenidone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>163</td>
<td>104</td>
</tr>
<tr>
<td>Age</td>
<td>64.9 (6.7)</td>
<td>64.7 (7.3)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>132/31</td>
<td>81/23</td>
</tr>
<tr>
<td>BMI</td>
<td>24.1 (2.9)</td>
<td>24.6 (3.2)</td>
</tr>
<tr>
<td>VC, %pred.</td>
<td>76.9 (17.4)</td>
<td>79.1 (17.4)</td>
</tr>
<tr>
<td>DLCO, %pred.</td>
<td>52.6 (17.6)</td>
<td>55.2 (18.2)</td>
</tr>
<tr>
<td>PaO2, torr</td>
<td>80.5 (9.6)</td>
<td>81.0 (9.5)</td>
</tr>
<tr>
<td>Lowest Spo2, %</td>
<td>89.0 (2.3)</td>
<td>89.0 (2.0)</td>
</tr>
<tr>
<td>GAP index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>90 (55%)</td>
<td>63 (61%)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>63 (39%)</td>
<td>36 (35%)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>8 (5%)</td>
<td>4 (4%)</td>
</tr>
</tbody>
</table>

Data are presented as No. (%) or mean (SD). \( P \) value was calculated by Welch’s \( t \) test or Fischer exact test. Lowest Spo2 was measured during 6-minute walking test. DLCO = diffusing capacity of the lung for carbon monoxide; GAP index = gender-age-physiology index; Spo2 = peripheral oxygen saturation; VC = vital capacity

\( ^a \) \( N = 161. \)
\( ^b \) \( N = 162. \)
\( ^c \) \( N = 103. \)

Figure 1 – Kaplan-Meier curves for the new prescription of antitussive drugs.
Discussion

To the best of our knowledge, this is the first study to assess the effect of pirfenidone on the prescription of concomitant drugs in IPF patients. In this exploratory analysis, pirfenidone did not delay new prescription of concomitant antitussive drugs, but it tended to delay respiratory AEs and new prescription of antibiotics. Polypharmacy is reported to be present in more than half of IPF patients.³ Our findings may indicate that pirfenidone has the potential to avoid polypharmacy by delaying the prescription of antibiotics.

Figure 2 – Kaplan-Meier curves for the new onset of respiratory AEs and the new prescription of antibiotics for respiratory AEs.
Pulmonary infection is the most common comorbidity among patients with IPF.10 A recent pooled analysis of phase III clinical trials showed that pirfenidone significantly reduced the risk of nonelective respiratory-related hospitalization, including pneumonia.9 Although the exact mechanisms remain unknown, pirfenidone may delay the need for antibiotics by reducing the incidence or the severity of pulmonary infection.

The strength of our study is that it is a post hoc analysis of a “double-blind” trial. The decisions on concomitant drug prescriptions were not affected by the presence or absence of pirfenidone. The study also has some limitations. FVC is the currently established measure of pulmonary function in IPF, but VC was used as the primary end point in this study. This phase III multicenter, randomized, double-blind trial was conducted between 2004 and 2005, and VC was the standard for pulmonary function measurement at that time. In addition, we could not assess the objective cough and medical spending.

In conclusion, we report initial findings on the potential effect of pirfenidone on the prescription of concomitant drugs in IPF patients. Further studies will be warranted to confirm these findings.

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References


