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

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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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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,