Marked Improvement with Pirfenidone in a Patient with Idiopathic Pulmonary Fibrosis

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Abstract

A man in his mid-60’s with idiopathic pulmonary fibrosis and hepatitis B-related liver cirrhosis developed exertional dyspnea and a dry cough lasting for three months. High-resolution computed tomography (HRCT) showed increasing bilateral ground-glass opacity superimposed on the usual interstitial pneumonia pattern. Six months after starting pirfenidone therapy, the partial pressure of arterial oxygen at rest increased from 81 to 101 torr, the predicted forced vital capacity (FVC) value increased from 75% to 94% and the ground-glass opacity on HRCT improved. The FVC value was subsequently maintained near or above baseline for 43 months. We concluded that our patient was a super-responder to pirfenidone therapy.

Key words: high-resolution computed tomography, idiopathic pulmonary fibrosis, pirfenidone, pulmonary function test

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Introduction

Idiopathic pulmonary fibrosis (IPF) remains a devastating disease with a poor prognosis, despite emerging evidence-based treatment options (1-3). Pirfenidone is an agent that inhibits abnormal fibrosis by downregulating the transcription of profibrotic growth factors, such as transforming growth factor-beta (4). A phase III trial demonstrated that the decline in vital capacity was reduced with statistical significance in the pirfenidone group compared with the placebo group (5). To our knowledge, however, there are no detailed case reports on increased forced vital capacity (FVC) values associated with pirfenidone therapy. We herein report a case of IPF in which treatment with pirfenidone yielded a remarkable improvement in pulmonary function test results, high-resolution computed tomography (HRCT) findings and exercise capacity, as evaluated by the 6-minute walk test. It is a noteworthy fact that the patient’s FVC value has been maintained near or above baseline for at least 43 months since starting pirfenidone.

Case Report

A 66-year-old man with IPF developed exertional dyspnea and a non-productive cough lasting for three months. The patient had previously undergone a liver biopsy 28 years before starting pirfenidone treatment and was with liver cirrhosis due to hepatitis B virus. His liver function had improved and stabilized after antiviral therapy with interferon-alpha, and the antiviral therapy was discontinued nine years before the pirfenidone treatment. The patient worked as a public servant and was a former smoker of two packs of cigarettes a day for 30 years. There was no history of occupational dust exposure, rearing of birds, drug abuse or drug allergies and no family history of interstitial lung diseases. No underlying conditions were identified that may cause interstitial lung disease, such as collagen vascular disease or hypersensitivity pneumonitis. HRCT performed four months before initiating pirfenidone therapy (Fig. 1A, B) showed findings

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consistent with the typical features of the usual interstitial pneumonia (UIP) pattern, including honeycomb changes with basal and subpleural predominance. HRCT performed at the start of treatment showed superimposed bilateral ground-glass opacity, distributed predominantly adjacent to the honeycomb changes (Fig. 1C, D). The oxygen saturation percutaneous oxygen saturation (SpO₂) level decreased from 94% to 87% during a 6-minute walk test, and pulmonary function test results showed FVC and diffusing capacity of the lung for carbon monoxide (DLco) values of 2.87 L (75% predicted) and 10.9 mL/min/torr (51% predicted), respectively. The serum levels of lactate dehydrogenase (LDH) and C-reactive protein (CRP) were 234 IU/L (normal range: 119-229 IU/L) and 0.2 mg/dL (normal range: 0.0-0.2 mg/dL), while the serum level of Krebs von den Lungen-6 (KL-6) was 1,139 U/mL (normal range <=500 U/mL), respectively. A bacterial culture of the sputum was negative for pathogens. No laboratory tests, vital sign data or physical examinations showed results indicative of infection.

Pirfenidone administration was started at a dose of 600 mg/day. The dose was increased weekly to 1,800 mg/day without adverse events. Two weeks after the initiation of pirfenidone therapy, the lowest SpO₂ value obtained during a 6-minute walk test dramatically increased from 87% to 93%, enabling the discontinuation of supplemental oxygen therapy during exertion. After one month of treatment, the patient’s symptoms, including dyspnea on exertion and a dry cough, greatly improved.

After six months of treatment with pirfenidone, pulmonary function tests and a blood gas analysis were repeated to evaluate the treatment efficacy. The FVC value markedly improved from 2.87 L to 3.53 L (from 75% to 94% pre-
The changes in the serum KL-6 and SP-D values are displayed in Fig. 3. The alteration of the serum KL-6 level seemed to be bimodal. Since pirfenidone treatment was started, the elevation of the serum KL-6 level noted in the first and second year (11th and 23rd months) might be related to the winter season; however, no elevation was observed in the third year (35th month). Furthermore, there were no correlations with the severity of symptoms. A gradual decrement in the serum SP-D level was observed.

Forty-five months after starting the therapy, new consolidation refractory to antibacterial agents developed in the left upper lobe. A positive result for serum antibodies against Aspergillus resulted in a clinical diagnosis of chronic pulmonary aspergillosis, although fungal culture results for the endobronchial washing material were negative. It became difficult to obtain a pure evaluation of the respiratory status related to IPF using pulmonary function tests and the 6-minute walking test. However, 72 months after starting this therapy, pirfenidone remains tolerable for the patient. In addition, no acute exacerbation of IPF has been observed during the patient’s clinical course, although his respiratory status gradually and chronically declined. We believe that pirfenidone helped to slow down the progression of IPF in this patient.

Discussion

In this report, we described a case in which an improvement of the FVC, PaO₂ and lowest SpO₂ during the 6-minute walking test values and ground-glass opacity on HRCT was obtained as a treatment effect of pirfenidone. The %FVC value improved only three months after starting pirfenidone and was maintained for at least 43 months above baseline.

According to the findings of a Japanese phase III trial of pirfenidone, the mean change in vital capacity over 52 weeks was -0.16 L in the placebo group and -0.09 L in the high-dose pirfenidone (1,800 mg/day) group (5). In our patient, the FVC value substantially increased by +0.66 L (+19% predicted) from baseline, and the CT findings improved after six months of pirfenidone administration. The patient has been stable for more than two years under pirfenidone treatment at a dose of 1,800 mg daily.

We propose two explanations for the dramatic effects of pirfenidone observed in this patient. First, our patient had liver cirrhosis. Pirfenidone is mostly metabolized by CYP1A2 in the liver (6), and liver cirrhosis might have resulted in higher serum pirfenidone concentrations than normally expected because of an impaired metabolic function. The onset of hepatopulmonary syndrome in patients with
liver cirrhosis may be another factor accounting for the progression of initial subacute symptoms in this case, including dyspnea on exertion and coughing (7). Liver cirrhosis is a potential target for pirfenidone treatment (8). In addition, hepatopulmonary syndrome develops in patients with severe decompensated liver cirrhosis associated with portal hypertension. It is possible that pirfenidone is effective for treating the features of hepatopulmonary syndrome; however, the current case involved no findings or signs of hepatopulmonary syndrome associated with portal hypertension, such as esophageal varices.

Second, the data for this patient at administration, including the difference in oxygen desaturation between the resting SpO2 and the lowest SpO2 during the 6-minute walk test, matched the inclusion criteria for a Japanese randomized trial (5). That randomized trial excluded patients with so-called subclinical (too mild) disease (9) or end-stage (too severe) disease. In addition, a stratified analysis of the data obtained from a Japanese phase III randomized controlled trial (10) showed that IPF patients with a predicted vital capacity of more than 70% and lowest SpO2 during the 6-minute walking test of less than 90% at baseline are the most likely to benefit from pirfenidone therapy. Our patient can be categorized into the group of subjects who are highly expected to obtain the best treatment efficacy with pirfenidone.

The diagnosis of IPF was confirmed four months before pirfenidone therapy was started based on findings of typical HRCT features of the UIP pattern (Fig. 1A, B) and the clinical exclusion of alternative causes of interstitial pneumonia. Regarding the development of new ground-glass opacity on HRCT (Fig. 1C, D) and worsening of dyspnea with a subacute process within three months before treatment, there is some possibility that this patient might enter the acute phase. However, our patient did not fulfill the clinical criteria for acute exacerbation of IPF (11) at the time of initiation of therapy. We considered that the development and improvement in the ground-glass opacity on HRCT were part of the clinical course and the result of the treatment efficacy of pirfenidone. Ohkubo et al. reported a case of acute exacerbation that developed after surgical resection in a patient with lung cancer associated with IPF (12). After starting initial high-dose steroid therapy, pirfenidone was administered from day 23 postoperatively with a combination of daily moderate-dose (40-50 mg) prednisolone. The background is different from our case; however, this case report indicates the possibility that pirfenidone may enable stabilization of the respiratory status in patients in the acute phase.

It is important that clearly identifiable elevation of the % FVC value was confirmed in the third month and that the % FVC value improved, with a maximum of 21% in the 19th month after pirfenidone was started. This is a dramatic response in this period for the current patient, and the rapid elevation in the %FVC value within three months corresponds to the results of a randomized controlled trial in the US (2). Randomized controlled trials have demonstrated the efficacy of pirfenidone by evaluating the pace of reduction in the annual decrement of %FVC compared with a placebo, with statistical significance (2, 5). Importantly, these randomized trials did not show whether some proportion of patients might exhibit elevated %FVC values; however, a stratified analysis of a Japanese randomized controlled trial showed the predicted vital capacity improved more than 10% from baseline in a few percent of cases (10). In addition to this report, our case supports the observation that there are super-responders to pirfenidone treatment among patients with IPF.

During the latter 23 months (from the 20th to 43rd month) in this case, the %FVC value was maintained near and above the baseline. A Japanese randomized trial provided data showing that high-dose pirfenidone improves the
progression-free survival compared with a placebo, with statistical significance (5), although the progression-free survival is a surrogate outcome indicating that the prognosis of patients with IPF might improve. Disease progression was defined as a more than 10% decline in the predicted vital capacity from baseline or death as the secondary endpoint of that study. Recently, King et al. reported similar results in the US (2). Comparing the HRCT findings four months before treatment (Fig. 1A, B) with those noted 43 months after treatment (Fig. 1G, H), the fibrotic changes in our case were consistent with relatively typical chronic progression of IPF (13). Sequential changes on HRCT have not been sufficiently evaluated with respect to the efficacy of pirfenidone in most past trials (14). Presently, FVC is the most widely adopted index for assessing disease progression in cases of IPF. Based on the alterations in the %FVC value observed in this case, we considered that the pirfenidone therapy was effective for 43 months, whereas the HRCT findings of fibrotic changes progressed.

The prognosis of patients with IPF has been reported to be worse than that of some malignant tumors (15). Recently, a retrospective large epidemiologic survey of Japanese patients with IPF was published in which the results of the multivariate analysis showed age, %VC and %DLco to be significant predictors (16). A large prospective survey of idiopathic interstitial pneumonia in Japan was also recently documented (17). The median survival time from the time of the initial visit in that study was reported to be 69 months. Furthermore, it was reported that the prognosis from the initial visit was significantly worse in symptomatic patients than in asymptomatic patients. Although it is difficult simply to combine the findings of these large Japanese prospective and retrospective studies with this case, a dramatic improvement in the %FVC induced by pirfenidone therapy might improve the prognosis. In addition, pirfenidone remains tolerable for our patient 72 months after starting the therapy. Overall, we believe that pirfenidone improved the prognosis in this case.

We herein described a patient with IPF and liver cirrhosis who was considered to be a super-responder to pirfenidone therapy, especially related to improvements in pulmonary function test results and symptoms. Identifying predictive factors of the pirfenidone response is important for selecting the appropriate treatment for individual patients with IPF.

This case report was approved by the Toranomon Hospital Institutional Review Board (protocol #795).

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

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