CASE REPORT

Distinct improvement of pulmonary function, ground-glass opacity, hypoxia and physical findings in an idiopathic pulmonary fibrosis patient after pirfenidone treatment : a case report with a review of the literature

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Abstract : Background : Pirfenidone (PFD), an anti-fibrosis drug for idiopathic pulmonary fibrosis (IPF), suppresses disease progression and delays decline of forced vital capacity. However, this drug rarely makes marked improvement of pulmonary function, chest high-resolution computed tomography (HRCT) findings and hypoxia. Case presentation : A 59 year-old-man, who was a former smoker and had a history of alcoholic liver cirrhosis, developed exertional dyspnea and was referred to our hospital. HRCT showed honeycomb changes with surrounding ground-glass opacity (GGO) in a predominantly basal and subpleural distribution. He was diagnosed with IPF and the treatment with PFD was started. At 16 months after the start of treatment, the predicted forced vital capacity value markedly improved from 82.9% to 98.6%. His resting-state partial pressure of arterial oxygen while breathing room air increased from a minimum of 54.7 mmHg (at 2 months treatment) to 72.5 mmHg. The GGO observed at diagnosis disappeared in HRCT. But after 32 months of treatment, his general condition got worse gradually, and he died from chronic progression of IPF after 48 months of treatment. Conclusion : Our case suggests that a complication of chronic liver disease and the existence of GGO may be characteristics of super-responder to PFD treatment for IPF patients. J. Med. Invest. 67 : 358-361, August, 2020

Keywords **:** *idiopathic pulmonary fibrosis, pirfenidone, chronic liver disease, ground-glass opacity, super-responder*

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrotic lung disease with poor prognosis. The histopathologic and radiological pattern of IPF is defined as usual interstitial pneumonia (UIP) pattern (1). Although it has been reported that smoking and gastro-esophageal reflux can be cause of development of IPF, the detailed etiology of IPF is not known. Recently, it was demonstrated that two anti-fibrotic drugs, pirfenidone (PFD) and nintedanib, suppressed disease progression and delayed the decline of forced vital capacity (FVC) (2-5). PFD exhibits pleiotropic pharmacological effects such as anti-inflammatory, anti-oxidative and anti-fibrotic effects (6). However, the exact target molecule of PFD has not been elucidated. Moreover, PFD, as well as nintedanib, rarely make marked improvement of pulmonary function and chest high-resolution computed tomography (HRCT) findings. To our knowledge, there are only 4 reported cases of so-called "super-responder" to PFD treatment (7-10). In addition, these cases have not been compared in detail. We present herein a case of IPF, in which PFD markedly improved pulmonary function, ground-glass opacity (GGO) and hypoxia, and discuss similar background factors to other super-responders.

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CASE REPORT

A 59 year-old-man who had smoked two packs of cigarettes a day for 30 years (at age 20 to 50) developed exertional dyspnea for one year, and visited his primary care doctor. He had history of alcoholic liver cirrhosis (Child-Pugh score class A) for 9 years and hypopharynx cancer which was treated by chemoradiotherapy two years before. There was no history of occupational dust exposure, keeping birds and drug abuse. His mother suffered as a result of interstitial pneumonia of unknown details. He was suspected of interstitial pneumonia from chest CT images and was referred to our hospital.

On admission, he complained of dyspnea on exertion, with Modified British Medical Research Council (mMRC) grade 3. His blood pressure was 124/69 mmHg, body temperature 36.9°C, percutaneous oxygen saturation (SpO_2) 94% and resting-state partial pressure of arterial oxygen (PaO_2) while breathing room air 71.4 mmHg. The minimum SpO_2 while six-minute walk test was 88%, so disease severity according to Japanese staging

classification system was Ⅲ. Chest radiography showed reticular shadow in both of middle and lower lung fields. HRCT showed honeycomb changes with surrounding GGO in a predominantly basal and subpleural distribution, that was consistent with UIP pattern (Figure 1A). Pulmonary function test results were as followed : vital capacity (VC) of 2.91 L (82.9% predicted), FVC of 2.91 L (82.9% predicted), forced expiratory volume in 1 second (FEV_1) of 2.6 L, FEV1/FVC ratio of 89.4% and diffusion capacity of carbon monoxide (DL_{CO}) of 4.41 ml/min/mmHg (24.1% predicted). VC had declined by 0.58 L for 16 months ; no further data of pulmonary function test except for VC. The serum test showed elevated levels of Krebs von den Lungen-6 (1560 U/mL), surfactant protein D (171 ng/mL), surfactant protein A (101 ng/mL) and lactate dehydrogenase (296 U/L). Regardless of the fact that there were elevated levels of rheumatoid factor (44 IU/mL) and anti-nuclear antibody (×40), he did not meet the criteria for the diagnoses of any connective tissue diseases. Laboratory tests or physical examinations did not show specific results indicative of pulmonary infection and hypersensitivity pneumonia. He was diagnosed with IPF according to the 2011 international consensus criteria (1).

PFD administration was started at a dose of 600 mg/day and we increased the dosage of it every two weeks up to 1800 mg/day. At 2 months of PFD treatment, his resting-state PaO_2 level decreased to 54.7 mmHg and long-term oxygen therapy via nasal cannula was initiated. He used 1 L/min at rest, but needed 3 L/min with exertion. After that, his pulmonary function improved gradually. At 16 months of treatment, the FVC and predicted FVC (%FVC) value markedly improved from 2.91 L to 3.44 L and 82.9% to 98.6% respectively, and the predicted DL_{CO} ($\%DL_{CO}$) value also improved from 24.1% to 33.0%. His resting-state PaO_2 level while breathing room air increased to 72.5 mmHg. As a result, he became free from oxygen therapy at rest. Honeycomb changes worsened, but GGO observed at diagnosis disappeared in HRCT (Figure 1B). There was no severe adverse effect and no acute exacerbation during the PFD treatment, but then, his pulmonary function and dyspnea got worse gradually. At 24 months of treatment, he needed oxygen therapy at rest again and the amount of oxygen supplied by a nasal cannula was 2 L/min. At 32 months of treatment, honeycombs changes increased in chest HRCT images (Figure 1C). The FVC, %FVC and $\%DL_{CO}$ value declined to 3.05 L, 89.2% and 15.5% respectively. At 38 months treatment, the FVC, %FVC and $\%DL_{CO}$ value was 2.93 L, 85.7% and 13.6% respectively, and his resting-state PaO_2 level when oxygen was supplied at 2 L/min decreased to 58.0 mmHg. Inhaled N-acetylcysteine was added to his treatment, but we could not stop his disease activity of IPF. His general condition got worse still and died from chronic progression of IPF, after 48 months of treatment (Figure 2).

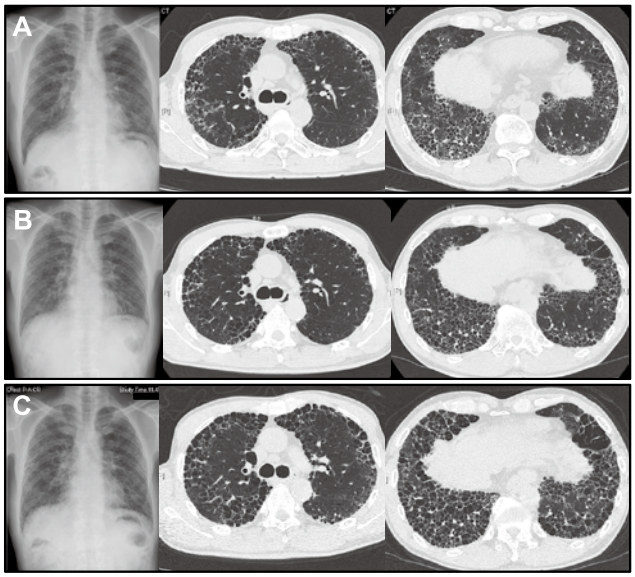

Figure 1. Time course of chest X-ray and HRCT
A) On starting pirfenidone. B) At sixteen months of PFD treatment. C) At thirty-five months of PFD treatment.
HRCT, high-resolution chest tomography ; PFD, pirfenidone

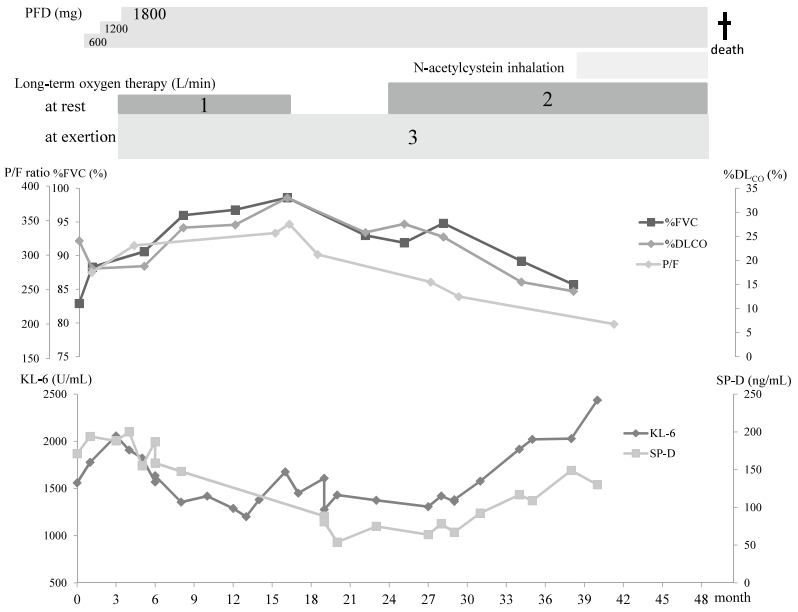

Figure 2. Clinical course of the patient.
PFD, pirfenidone ; %FVC, predicted forced vital capacity value ; $\%DL_{CO}$, predicted diffusion capacity of carbon monoxide ; P/F ratio, PaO_2/FiO_2 ratio ; KL-6, Krebs von den Lungen-6 ; SP-D, surfactant protein D.

DISCUSSION

In our case, the %FVC value increased by 15.7% at the maximum and kept above the baseline for at least 38 months, and the oxygen therapy at rest temporarily became unnecessary. Ogawa *et al*. revealed that %FVC < 60% was a predictor of the inability to receive PFD for over 1 year (11). %FVC of our case was 82.9% (> 60%) and the patient could receive PFD for a long time. Bando *et al*. reported in a retrospective observational study that 22.1% (111 cases) of the 502 IPF patients administered with PFD were treated for more than 2 years (12). In the cases where pulmonary function test information was available, 6.4% of patients showed an increase in %FVC of 10% or more at 2 years, and 6.3% of patients showed an increase of 5% or more at 3 years. It suggested that in only few percentages of all IPF patients treated with PFD, improvement of %FVC was sustained for a long period. Therefore, our case was very rare entity and regarded as a so-called "super-responder" to PFD treatment.

To our knowledge, there were only 4 reported cases in which PFD improved %FVC for 18 months or more. This manuscript is the fifth report of super-responder to PFD treatment (7-10) (Table 1). In general, it is thought that PFD treatment should be started in the early stages of IPF patients (2, 11). However, pretreatment disease severity of two super-responders was IV according to Japanese staging classification system and their %FVC was below 60% (Table 1) (13). Therefore, analysis of background factors of super-responders seems to be important.

Three cases of these 5 cases were complicated with chronic liver disease (CLD) such as chronic hepatitis C, hepatitis B-related cirrhosis and alcoholic liver cirrhosis (Table 1). A history of severe hepatic impairment or end-stage liver disease was generally one of the medical exclusions from clinical studies of PFD (4). Considering five cases, average maximum Δ%FVC was +14.1% in the CLD group and +9.7% in the non-CLD group. Duration of FVC improvement is 37 months in the CLD group and 21 months in the non-CLD group. Miyamoto *et al*. reported a case of super-responder to PFD treatment similar to our patient, who had liver cirrhosis (9). They pointed out the possibility that impaired metabolic function might result in higher serum PFD level, because PFD is mostly metabolized by CYP1A2 in liver. In Japan, the therapeutic effect of PFD at doses higher than 1800 mg/day has not been verified, but in overseas clinical studies, dose-effect relationships have been observed between the 1197 mg/day and 2403 mg/day groups (14). However, in all of super-responders with CLD including this case, the blood concentrations of PFD were not measured, and dose-dependent side effects of PFD, such as anorexia and nausea, were not observed. Miyamoto *et al*. also described another possibility that PFD had been effective for hepatopulmonary syndrome (HPS), a complication of CLD, because liver fibrosis is a promising target for PFD treatment (15, 16). HPS is defined as an arterial oxygenation defect induced by intrapulmonary vascular dilatations (IPVD) associated with hepatic disease, but contrast-enhanced echocardiography or perfusion lung scanning for the detection of IPVD was also not performed in super-responders with CLD (17).

The characteristic HRCT features of UIP are honeycomb changes and reticular shadows, but occasionally accompanied by atypical findings such as GGO and consolidations (18). In 5 cases of super-responders, 4 cases were accompanied by GGO and 1 case by consolidations, which were improved by PFD treatment (Table 1). These clinical courses are noteworthy, because GGO and consolidation have not been reported to be predictors of PFD

Table 1. Summary of the patient with the four super-responders to pirfenidone reported in the literature.

Case of Study (reference)	Age	Sex	Medical history	Maintenance pirfenidone dose (mg/day)	Disease severity	%FVC before treatment (%)	Pathological diagnosis	Main HRCT findings
Okuda *et al*. (7)	61	F	type2 DM	1800	IV	58	UIP pattern (VATS before treatment)	reticular pattern, GGO, traction bronchiectasis
Shintani *et al*. (8)	72	M	pulmonary tuberculosis chronic hepatitis C	1800	IV	40	Not obtained	honeycombing, reticular pattern, GGO
Miyamoto *et al*. (9)	66	M	hepatitis B-related cirrhosis	1800	III	45	Not obtained	honeycombing, GGO
Varone *et al*. (10)	70	M	rectal adenocarcinoma	2403	III	108	UIP pattern (cryobiopsy after 2 years of PFD treatment)	thickening of the interlobular and intralobular septa, consolidation
present case	59	M	alcoholic liver cirrhosis hypopharynx cancer	1800	III	83	Not obtained	honeycombing, GGO

Case of Study (reference)	maximum ΔFVC (mL)	maximum Δ%FVC (%)	maximum ΔKL-6 (U/mL)	maximum ΔSP-D (ng/mL)	duration of FVC improvement (months)
Okuda *et al*. (7)	+140	+6.4	-453	-263	18
Shintani *et al*. (8)	+170	+5.5	not evaluated	not evaluated	36
Miyamoto *et al*. (9)	+690	+21	-735	-307	37
Varone *et al*. (10)	+340	+13	not evaluated	not evaluated	24
present case	+530	15.7	-1114	-128	38

%FVC, predicted forced vital capacity value ; UIP, usual interstitial pneumonia ; VATS, Video Assisted Thoracic Surgery ; GGO, ground-glass opacity ; PFD, Pirfenidone.

efficacy in past clinical trials. In addition, reductions in the areas of GGO and consolidation were reported in a super-responder to nintedanib (IPF stage III) (19). On the other hand, the possibility of the coexistence of UIP and nonspecific interstitial pneumonia (NSIP) at the same time cannot be denied, although efficacy of PFD for NSIP pattern is unknown (18, 20).

In the series of case studies, characteristics of super-responders to PFD treatment were 1) relatively advanced patient, 2) atypical HRCT findings such as GGO and consolidation, and 3) complication of chronic liver disease. However, prior to the initiation of PFD treatment, a surgical lung biopsy was performed on only one patient (Table 1), and pharmacokinetic study of PFD or molecular biological analysis using patient specimens was not performed. It is desirable to prospectively accumulate detailed background factors in IPF cases with the above characteristics. In-depth studies on the pathophysiology of super-responders seem to be important for elucidating the exact target molecule of PFD.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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