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Randomized phase II study of nintedanib with or without pirfenidone in patients with idiopathic pulmonary fibrosis who experienced disease progression during prior pirfenidone administration

Satoshi Ikeda, MD, PhD[a,*], Akimasa Sekine, MD, PhD[a], Tomohisa Baba, MD[a], Terufumi Kato, MD[b], Takuma Katano, MD[a], Erina Tabata, MD[a], Ryota Shintani, MD[a], Hideaki Yamakawa, MD, PhD[a], Tsuneyuki Oda, MD, PhD[a], Ryo Okuda, MD[a], Hideya Kitamura, MD, PhD[a], Tae Iwasawa, MD, PhD[c], Tamiko Takemura, MD, PhD[d], Takashi Ogura, MD[a]

Abstract

Introduction: A subgroup analysis of the CAPACITY and ASCEND trials showed that pirfenidone use beyond disease progression reduced the risk of subsequent forced vital capacity (FVC) decline and death. Our study aimed to compare the efficacy and safety of nintedanib with or without pirfenidone for patients with idiopathic pulmonary fibrosis (IPF) who experienced disease progression during previous pirfenidone therapy.

Methods: In this randomized, open-label, selection design phase II trial, patients with IPF and a ≥5% relative decline in FVC within 6 months of the pirfenidone administration period were randomly assigned to nintedanib (switch group) or nintedanib plus pirfenidone (combination group). The primary endpoint was the incidence of a ≥5% relative decline in FVC or death during the first 6 months.

Results: Only 7 patients were enrolled (4 in the switch group and 3 in the combination group). Although the switch group continued with nintedanib for 1 year or more, 2 patients (66.7%) in the combination group discontinued nintedanib within 6 months due to severe adverse events. Given the slow case registration and safety concerns in the combination group, the trial was terminated without extending the registration. The incidence of a ≥5% relative decline in FVC during the first 6 months was 50.0% in the switch group and 66.7% in the combination group. There were no deaths during the observation period.

Conclusions: Clinical trials verifying the use of pirfenidone after disease progression in IPF may be difficult to enroll patients. Definitive conclusions on both safety and efficacy cannot be drawn from the results of this study alone.

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All data generated or analyzed during this study are included in this published article.

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[a] Kanagawa Cardiovascular and Respiratory Center, Department of Respiratory Medicine, Kanazawa-ku, Yokohama, Japan, [b] Kanagawa Cancer Center, Department of Thoracic Oncology, Asahi-ku, Yokohama, Japan, [c] Kanagawa Cardiovascular and Respiratory Center, Department of Radiology, Kanazawa-ku, Yokohama, Japan, [d] Japanese Red Cross Medical Center, Department of Pathology, shibuya-ku, Tokyo, Japan.

[*] Correspondence: Satoshi Ikeda, Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, 6-16-1 Tomioka-Higashi, Kanazawa-ku, Yokohama, 236-0051, Japan (e-mail: isatoshi0112@gmail.com).

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Abbreviations: AE = adverse event, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BSA = body surface area, BW = body weight, CTCAE = Common Terminology Criteria for Adverse Events, DLco = diffusing capacity for lung carbon monoxide, FVC = forced vital capacity, GGT = gamma glutamyl transpeptidase, IPF = idiopathic pulmonary fibrosis, SGRQ = St. George's Respiratory Questionnaire.

Keywords: anti-fibrotic therapy, forced vital capacity, idiopathic pulmonary fibrosis, nintedanib, pirfenidone

1. Introduction

Idiopathic pulmonary fibrosis (IPF), the most common form of idiopathic interstitial pneumonia, has a chronic and progressive course, resulting in progressive fibrosis and irreversible honeycomb lung formation. The prognosis of IPF has been unfavorable because no effective treatment has been established over the years. However, recently, studies have shown that pirfenidone and nintedanib, two antifibrotic drugs, reduce the decline in the forced vital capacity (FVC) among patients with IPF and have a manageable adverse-effect profile.[1–3] The drugs received a conditional recommendation for use in the current clinical practice guidelines of IPF.[4] Each of these drugs has its own outstanding characteristics. Pirfenidone has been shown to reduce both all-cause and IPF-related mortality in a prespecified pooled analysis of CAPACITY and ASCEND trials.[5] This pooled analysis also showed that pirfenidone use beyond disease progression reduced the risk of subsequent FVC decline and death.[6] On the other hands, nintedanib is considered to restrain acute exacerbation of IPF. In the global, phase-III placebo-controlled INPULSIS trials on the use of nintedanib, a prespecified verification by a central adjudication committee indicated that the risk of acute exacerbation of IPF was significantly lower in the nintedanib group than in the placebo group.[1,7] The open-label extension of these trials (INPULSIS-ON) indicated that the nintedanib's beneficial effect on slowing disease progression was maintained and that the change from baseline FVC was consistent in the long term.[8] However, the optimal treatment strategy for maximising the use of both pirfenidone and nintedanib has not been established.

Given that Japan approved the use of pirfenidone (in 2008) prior to approving the use of nintedanib, a large number of patients were treated with pirfenidone prior to nintedanib. For these patients, nintedanib monotherapy will be usually considered a "second-line therapy" after disease progression during pirfenidone administration. However, the safety and efficacy profile of nintedanib switched from pirfenidone after disease progression were not fully investigated. As mentioned earlier, pirfenidone use beyond disease progression can potentially reduce the risk of subsequent FVC decline and death.[6] Several clinical trials that evaluated the safety and pharmacokinetics of the combined use of pirfenidone and nintedanib have recently been published[9–11] and showed that pirfenidone combined with nintedanib was a promising candidate for second-line therapy beyond disease progression after the prior administration of pirfenidone.

The aim of our study was to compare the efficacy and safety of nintedanib with or without pirfenidone for IPF patients who experienced a clinically meaningful decline in FVC during previous therapy with pirfenidone.

2. Methods

2.1. Study design

This study was a single center, randomized, open-label, selection design, phase II trial conducted at the Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan. Patients with IPF who experienced a 5% or more relative decline in FVC within the last 6 months of the pirfenidone administration period were randomly assigned in a 1:1 ratio to nintedanib (switch group) or nintedanib plus pirfenidone (combination group). In both groups, nintedanib was started at a dosage of 150 mg twice daily. In the combination group, pirfenidone was maintained at the same dosage as was administered prior to the study. The stratification factors were age ($\leq$65 or >65 years) and FVC ($\leq$70% or >70%). The trial start date was October 16, 2015, and the planned registration period was 2 years. Central monitoring has been planned once every year. An independent data and safety monitoring committee regularly reviewed the data, especially the serious adverse events leading to discontinuation of the study drug, and made recommendations concerning the continuation of the trial. This study adhered to the Consolidated Standards of Reporting Trials guidelines, and the clinical trial registry number is UMIN000019436 (date of first registration, 21/10/2015; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000022471).

2.2. Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research issued by the Japanese Ministry of Health, Labour and Welfare. The protocol was approved by the Research Ethics Committee of the Kanagawa Cardiovascular and Respiratory Center (approval date, October 16, 2015; approval number, 27-16). All patients provided their written informed consent.

2.3. Clinically meaningful decline in the forced vital capacity

Although specific criteria for the decline in FVC to assess the effectiveness of pirfenidone have not been developed, Du Bois MR et al reported that the minimum clinically significant difference for FVC is between 2% and 6%. In addition, the 1-year mortality risk was higher ($P < .001$) in patients with a 10% or greater decline in FVC within 6 months and patients with a 5% to 10% decline in FVC within 6 months than in patients with a 5% or lower decline in FVC.[12] Based on this result, a 5% or greater decline in FVC within the last 6 months was regarded as a clinically meaningful decline in FVC in our study.

2.4. Study participants

The inclusion criteria for the study participants were as follows:

1. IPF diagnosed based on the official American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association statement of 2011[13];
2. Forty years of age or older;
3. Pirfenidone (600–1800 mg/day) administered for more than 3 months;

4. A 5% or greater relative decline in FVC within the last 6 months;
5. Adequate organ function;
6. An expected survival of 6 or more months; and
7. Written informed consent.

The exclusion criteria were as follows:

1. Aspartate aminotransferase, alanine aminotransferase, and total-bilirubin levels ≥ 2.5-fold the upper limit of normal;
2. Having already taken corticosteroids (>15 mg/day), immunosuppressants, N-acetyl cysteine, pulmonary vasodilators, or other antifibrotic drugs except for pirfenidone;
3. Active infection;
4. Malignant tumour;
5. Other severe complications;
6. Pregnancy or breastfeeding; and
7. Severe drug allergy.

2.5. Outcome measures

The primary endpoint was the incidence of a 5% or greater relative decline in FVC and/or death during the first 6 months. The secondary endpoints were the incidence of a 10% or greater relative decline in FVC and/or death during the first 6 months, the annual rate of decline in FVC, incidence of acute exacerbation, change in the score on the St. George's Respiratory Questionnaire (SGRQ) over 1 year, tolerability, and adverse events, the latter of which were graded using the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0.[14]

2.6. Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

2.7. Statistical analysis

Given that second-line therapy beyond disease progression with the prior administration of pirfenidone has not been established, this randomized phase II trial employed a selection design to establish prioritisation between two promising "experimental" regimens. The results were then ranked, and the arm with the lower incidence of 5% or greater decline in FVC and/or death during the first 6 months was selected for further study. The target sample size was determined by the actual number of patients in our hospital; as of September 2015, there were 110 outpatients with IPF who were administered pirfenidone in our hospital. Approximately 30 to 40 patients start using pirfenidone each year. Assuming that 30% to 40% of these patients were included in the study during the 2-year registration period, the target sample size would be 60 patients. We included all treated patients in the safety and efficacy analyses and employed the Fisher's exact test to compare the categorical data and the Mann–Whitney *U* test to compare the continuous data. A P value $< .05$ was considered statistically significant.

3. Results

3.1. Patient population and disposition

From October 16, 2015 to October 15, 2017, 27 patients with IPF who were administered pirfenidone and considered switching to nintedanib were screened (Fig. 1). Sixteen patients (59.3%) were excluded based on the inclusion and exclusion criteria; 9 patients considered a switch due to adverse events without a clinically meaningful FVC decline, and 7 patients had not undergone a lung function test within the past 6 months. Four of the 11 patients who met the study criteria did not wish to participate in this trial, 3 over concerns regarding the gastrointestinal adverse events of pirfenidone and one whose attending physician did not want them to participate.

Ultimately, only 7 patients were enrolled within the planned registration period; 4 patients in the switch group and 3 patients in the combination group. All 4 patients of the switch group continued taking nintedanib for 1 year or more, while 66.7% (2 of 3 patients) of the combination group discontinued nintedanib within 6 months due to severe adverse events (one due to acute exacerbation of IPF, and one due to diarrhoea and anorexia accompanied by weight loss) (Table 1). Due to the slow registration of cases and safety concerns for the combination group, an independent data and safety monitoring committee recommended the study to be discontinued. Based on this recommendation, we terminated the trial without extending the registration period. The patients undergoing treatment were allowed to continue. The data cut-off was applied on July 4, 2018.

3.2. Patient characteristics

The patient characteristics are summarised in Table 2. All 7 patients were men whose median weight, body surface area estimated using the Du Bois formula, and body mass index were 64.8 kg, 1.71 m^2, and 21.1, respectively. The median %FVC and %diffusing capacity for lung carbon monoxide (DLco) at baseline were 54.3% and 47.9%, respectively. There were no significant differences in the characteristics including the factors related to physique, lung function test, and treatment status of prior pirfenidone use between the switch and combination groups.

3.3. Efficacy

The chronological change in FVC is shown in Figure 2 and Supplemental Table 1, http://links.lww.com/MD2/A992. In both groups, nintedanib suppressed the decline in FVC, even if slightly and/or temporally, compared with that during the prior pirfenidone administration period. The incidence of 5% or greater FVC decline or death during the first 6 months (the primary endpoint of this trial) was similar for the two groups: 50.0% in the switch group (2 of 4 patients) and 66.7% in the combination group (2 of 3 patients). There were no deaths during the observation period.

Figure 3 shows the chronological change in the SGRQ scores. Nintedanib did not improve the SGRQ scores for the switch group. In case 5 of the combination group, a lung function test and SGRQ were performed for the 6-month efficacy assessment on day 167, which showed a temporary improvement in the SGRQ score and a slight increase in FVC. However, the patient developed acute exacerbation IPF soon afterwards and discontinued nintedanib on day 172 before the 6-month check-up. In case 6, the lung function test and SGRQ were performed on the same day the patient discontinued taking nintedanib (day 168).

3.4. Tolerability and safety

Table 1 shows the treatment status for both groups. All four patients of the switch group continued taking nintedanib for 1

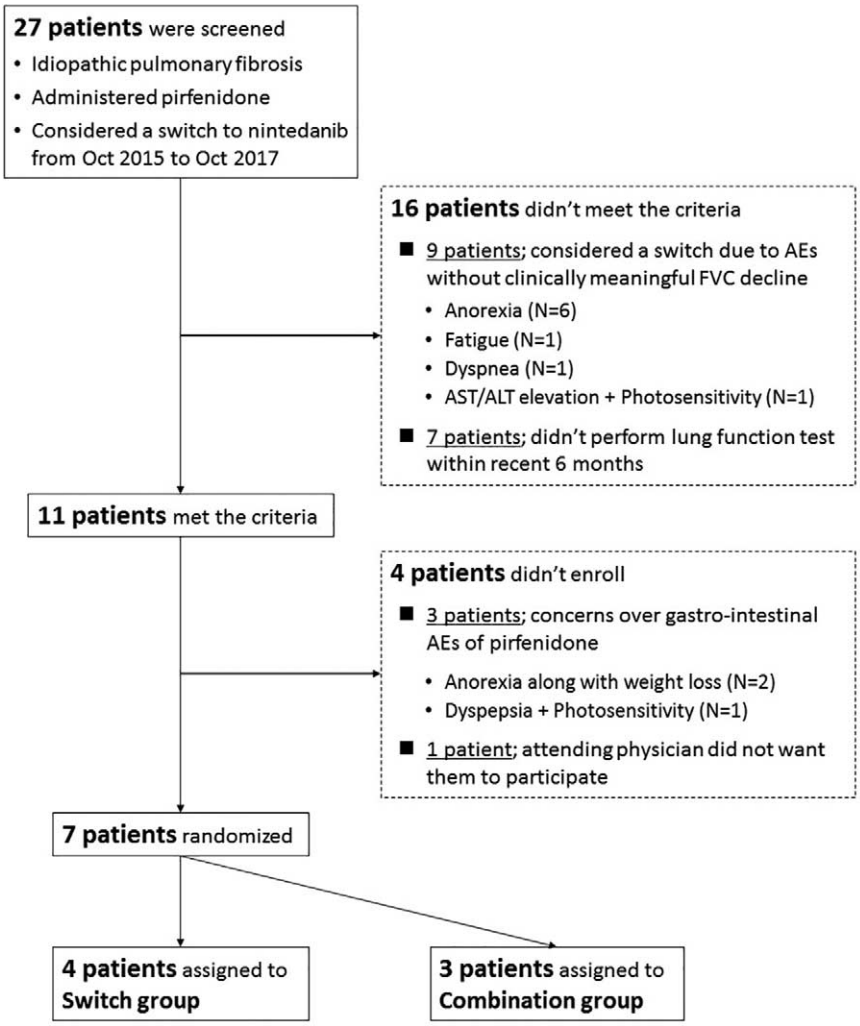

Figure 1. Consort flow diagram.

year or longer, whereas 66.7% (2 of 3 patients) of the combination group discontinued nintedanib within 6 months (172 days and 168 days, respectively). Case 5 discontinued due to acute exacerbation of IPF, and case 6 discontinued due to diarrhoea and anorexia accompanied by body weight loss. Moreover, 75.0% of the switch group and 66.7% of the combination group required a dose reduction of nintedanib.

The details of the adverse events are summarised in Table 3. In the switch group, all four patients developed diarrhoea (50% of which were grade ≥ 2). In the combination group, the incidence of diarrhoea and weight loss was relatively low, which was probably due to the short administration period for nintedanib. Although increased hepatobiliary enzyme levels was also common, all were grade 1 in both groups. A patient in the combination group developed acute exacerbation of IPF, and therefore stopped the nintedanib treatment.

4. Discussion

The clinical trial was terminated with a poor patient accrual rate due to the fact that as many as 74.1% of the patients (20/27) could not participate in the trial (Fig. 1). Of the 27 screened patients, 16 patients did not meet the criteria, nine of whom considered a switch from pirfenidone to nintedanib due to adverse events without a clinically meaningful decline in FVC. Moreover, three of the remaining 11 patients who met the criteria did not wish to participate due to concerns over gastrointestinal adverse events from continuous pirfenidone use. These three patients had experienced pirfenidone-induced anorexia or dyspepsia with a CTCAE grade ≥ 2. Since the substantial number of patients had to cease pirfenidone treatment due to adverse events, the enrollment in clinical trials which verify the pirfenidone use beyond disease progression may be difficult.

The critical limitation of this study was that it was a single-center phase II trial with a small number of patients and was terminated prematurely. Therefore, we cannot draw any definitive conclusions about both safety and efficacy from the results of this study. This study has been discontinued as per the recommendation of an independent data and safety monitoring committee, and no more patients can be enrolled. However, it remains an important clinical unmet need to determine what is the optimal treatment for patients whose lung function has deteriorated despite being on pirfenidone, which is the subject of this study. Nevertheless, no prospective clinical trials have been reported in the past, and none are currently underway, that

Table 1

Treatment status.

		Switch group (N = 4)	Combination group (N = 3)
Nintedanib			
Dose reduction (%)		3 (75.0%)	2 (66.7%)
Discontinuation (%)		0	2 (66.7%)
Time to discontinuation	-	Case 5; 172 days Case 6; 168 days	
Reason for discontinuation	-	Case 5; acute exacerbation Case 6; diarrhoea + anorexia	
Pirfenidone			
Dosage at registration	1200 mg/day	2 (50.0%)*	2 (66.7%)
	1800 mg/day	2 (50.0%)*	1 (33.3%)
Dose reduction (%)		-	1 (33.3%)
Discontinuation		-	0

Categorical data are presented as numbers (percentages).
* In the switch group, pirfenidone was discontinued before starting nintedanib.

would answer this clinical question. No matter how small the number of cases, the data obtained from the patients enrolled in this study are rare and meaningful, and the following two points suggested by the limited case experience of this study may provide some insight into the planning of future clinical trials and daily clinical practice.

First, the use of pirfenidone in combination with nintedanib beyond disease progression might be burdensome for IPF patients, causing difficulty in continued administration. In fact, 66.7% of the patients (two of three) in the combination group discontinued taking nintedanib within 6 months due to adverse events. Although there have been two clinical trials on pirfenidone and add-on nintedanib, these trials only evaluated the short-term tolerability and safety of combination therapy and included numerous stable patients.[9,11] In the phase IV trial, the enrolled patients showed only slight decreases in FVC and DLco within the past 6 months before registration.[11] We believe that patients with IPF who undergo pirfenidone treatment but experience apparent disease progression are in fragile condition, which would result in second-line combination treatment failure due to adverse events. According to our previous retrospective study evaluating the safety and tolerability of nintedanib switched from pirfenidone, as many as 53.3% of the patients exhibited anorexia with a CTCAE grade of ≥2, and 56.7% presented a weight loss of ≥5% from baseline during the prior pirfenidone administration period.[15] In this retrospective study, the incidence of early nintedanib termination within 6 months was high when switched from pirfenidone (53.3%). Patients who continue taking pirfenidone until the apparent disease progression can experience persistent gastrointestinal adverse events during the pirfenidone administration period, which can affect the subsequent treatment. Since nintedanib is also associated with gastrointestinal adverse events, the use of pirfenidone with add-on nintedanib beyond disease progression would cause distress and become a burden for patients with IPF.

Second, although the number of patients studied was still small, it was suggested that nintedanib monotherapy might be relatively well tolerated and could be continued even after disease progression during pirfenidone administration. In fact, the incidence of a 5% or greater relative decline in FVC or death during the first 6 months was similar for the two groups, and the chronological change in FVC and SGRQ scores was generally the same regardless of the beyond use of pirfenidone. It is also noteworthy that, even in the switch group, as many as 75.0% (3 of 4) of the patients required a dose reduction. Second-line therapy switched from pirfenidone demands delicate dose modifications and symptomatic therapy.

In addition to the small number of cases, there are many other limitations to this study. It is possible that the speed of disease progression and the duration of pirfenidone treatment were not equivalent in the switch and combination groups, possibly due to the small number of cases. It may not be appropriate to evaluate the progression of IPF only by the absolute change in FVC. It would have been better to take into account the decline in FVC due to aging and the accompanying worsening of respiratory symptoms. Statistical analysis (and results depicting as percen-

Table 2

Patient characteristics.

					Physical characteristics				Lung function test			Prior pirfenidone	
Group	Case number	Age	Sex	Smoking (pack-years)	Height (cm)	BW (kg)	BSA (m^2)	BMI	FVC (L)	FVC (%)	DLco (%)	Duration (days)	Dosage (mg/day)
Switch	1	78	Male	18	175	74.1	1.89	24.2	2.73	74.4	49.8	111	1800
Switch	2	77	Male	40	176.1	64.8	1.80	20.9	1.99	53.2	77.1	98	1800
Switch	4	65	Male	12.8	163.3	55.8	1.60	20.9	1.16	33.0	40.9	115	1200
Switch	7	67	Male	0	167.2	59.1	1.66	21.1	1.97	54.3	41.4	586	1200
Combination	3	59	Male	4	172.2	67.5	1.80	22.8	2.80	69.7	47.9	814	1200
Combination	5	68	Male	45	163.8	65.1	1.71	24.3	2.24	64.7	37.6	140	1800
Combination	6	75	Male	0	164.6	50.8	1.54	18.8	1.74	51.9	50.6	756	1800

BMI = body mass index, BSA = body surface area, BW = body weight, DLco = diffusing capacity for lung carbon monoxide, FVC = forced vital capacity.

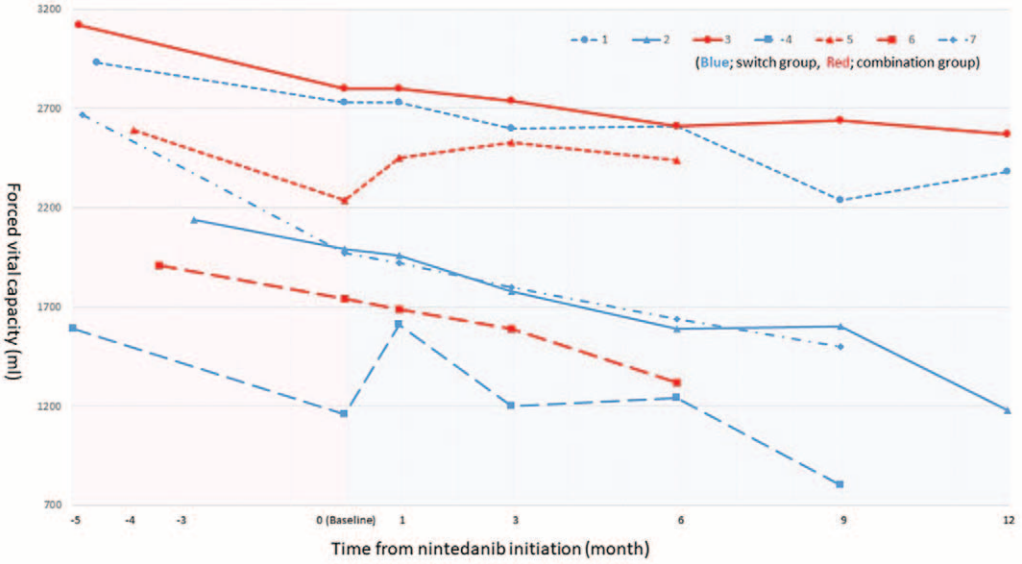

Figure 2. Change in FVC. In both groups, nintedanib suppressed the decline in FVC compared with that during the administration period for pirfenidone. * In case 5, a lung function test was performed at day 167 for the 6-month efficacy assessment. However, the patient developed acute exacerbation of IPF soon after and discontinued taking nintedanib at day 172 before the 6-month follow-up. ☆ In case 6, a lung function test was performed on the same day the patient discontinued taking nintedanib (day 167). FVC = forced vital capacity.

tages) are not inherently applicable given the small number of patients. The overall incidence of adverse events was rather low in the combination group, but this may be due to early discontinuation and short treatment period.

5. Conclusions

Since the substantial number of patients had to cease pirfenidone treatment due to adverse events, clinical trials verifying the use of pirfenidone after disease progression in IPF may be difficult to

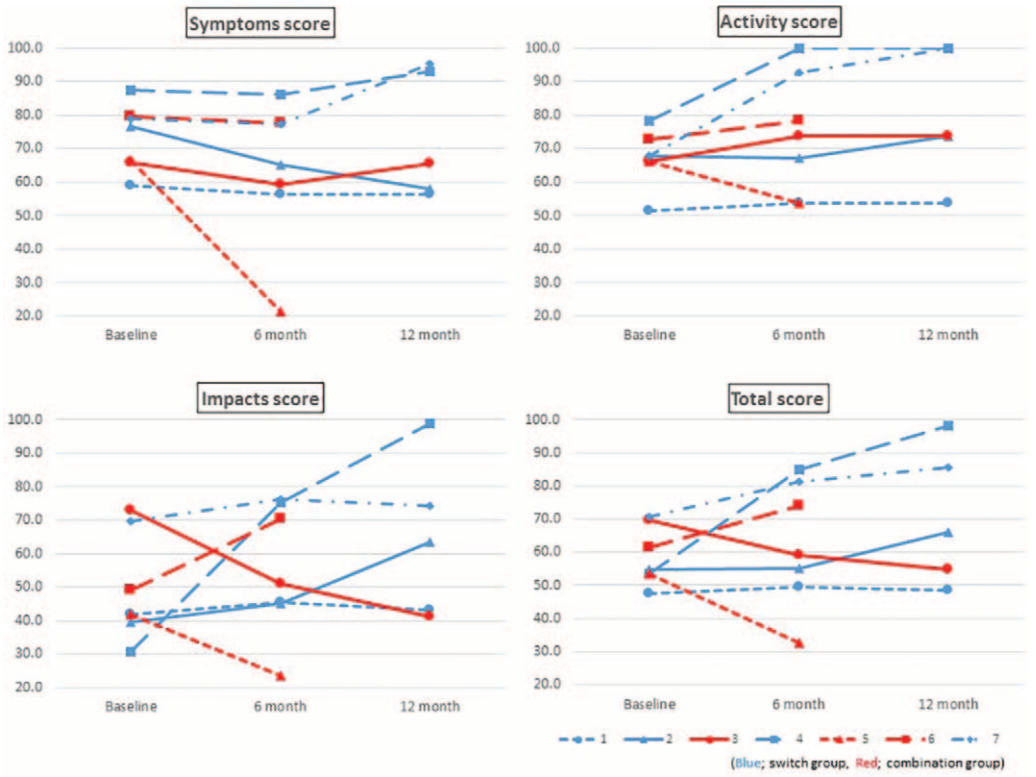

Figure 3. Change in SGRQ score. * In case 5, an SGRQ was performed on day 167 for the 6-month efficacy assessment. However, the patient developed acute exacerbation of IPF soon after and discontinued taking nintedanib on day 172 before the 6-month follow-up. ☆ In case 6, an SGRQ was performed on the same day the patient discontinued taking nintedanib (day 168).

Table 3

Adverse events.

	Switch group (N = 4)				Combination group (N = 3)			
		Grade				Grade		
	All (%)	1	2	3	All (%)	1	2	3
Gastrointestinal								
Diarrhoea	4 (100%)	2	2	0	1 (33.0%)	0	1	0
Weight loss	2 (50.0%)	0	1	1	1 (33.0%)	0	1	0
Anorexia	0	0	0	0	1 (33.0%)	0	1	0
Nausea	0	0	0	0	1 (33.0%)	0	1	0
Hepatobiliary enzymes								
AST elevation	2 (50.0%)	2	0	0	1 (33.0%)	1	0	0
ALT elevation	1 (25.0%)	1	0	0	1 (33.0%)	1	0	0
ALP elevation	3 (75.0%)	3	0	0	1 (33.0%)	1	0	0
GGT elevation	1 (25.0%)	1	0	0	1 (33.0%)	1	0	0
Other								
Acute exacerbation	0	-	-	-	1 (33.0%)	-	-	-
Epilepsy	0	0	0	1	0	0	0	0

Categorical data are presented as numbers (percentages).

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events, GGT = gamma glutamyl transpeptidase.

enroll patients. Definitive conclusions on both safety and efficacy cannot be drawn from the results of this study alone. After reconsidering the patient selection criteria based on the lessons learned from this trial, new clinical trials including a larger number of patients are required to be planned.

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Author contributions

Satoshi Ikeda: conceptualization, methodology, investigation, visualization, project administration, and writing (original draft). Akimasa Sekine and Tomohisa Baba: investigation and writing (review and editing). Terufumi Kato: conceptualization, methodology, and writing (review and editing). Takuma Katano, Erina Tabata, Ryota Shintani, Hideaki Yamakawa, Tsuneyuki Oda, Ryo Okuda, Hideya Kitamura, Tae Iwasawa, and Tamiko Takemura: investigation and writing (review and editing). Takashi Ogura: conceptualization, methodology, and writing (review and editing).

Conceptualization: Satoshi Ikeda, Takashi Ogura, Terufumi Kato

Investigation: Akimasa Sekine, Erina Tabata, Hideaki Yamakawa, Hideya Kitamyura, Ryo Okuda, Ryota Shintani, Tae Iwasawa, Takuma Katano, Tamiko Takemura, Tomohisa Baba, Tsuneyuki Oda

Investigation: Satoshi Ikeda

Methodology: Satoshi Ikeda, Takashi Ogura, Terufumi Kato

Project administration: Satoshi Ikeda

Visualization: Satoshi Ikeda

Writing – review & editing: Akimasa Sekine, Erina Tabata, Hideaki Yamakawa, Hideya Kitamyura, Ryo Okuda, Ryota Shintani, Tae Iwasawa, Takuma Katano, Tamiko Takemura, Tomohisa Baba, Tsuneyuki Oda, Satoshi Ikeda, Takashi Ogura, Terufumi Kato

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