Improvement in Patient-Reported Outcomes and Forced Vital Capacity during Nintedanib Treatment of Idiopathic Pulmonary Fibrosis

Takayuki Takeda,1 Mayumi Takeuchi,1 Masahiko Saitoh1 and Sorou Takeda1

1Department of Respiratory Medicine, Uji-Tokushukai Medical Center, Uji, Kyoto, Japan

Idiopathic pulmonary fibrosis (IPF) is a progressive and incurable disease with limited overall survival. Nintedanib is a multikinase inhibitor, and its efficacy on IPF was demonstrated in phase III trials. However, a discrepancy exists between forced vital capacity (FVC) and patient-reported outcomes during nintedanib treatment. Accordingly, we retrospectively analyzed the effects of nintedanib on FVC and patient-reported outcomes among 25 IPF patients. Patient-reported outcomes were evaluated with modified medical research council (mMRC) grade and COPD assessment test (CAT) score. The changes in mMRC grade, CAT score, and FVC data were obtained 6 months before, at the time of, and 6 and 12 months after nintedanib introduction. Significant difference in the mMRC grade was observed only between the baseline and 6 months after treatment (improvement: p = 0.0429). By contrast, there were significant deterioration (p < 0.001) in the CAT scores between 6 months before and the baseline and significant improvement (p < 0.001) between the baseline and 6 months or 12 months after treatment. Overall, 14 patients were judged as efficient with CAT scores after 6-month treatment. Among these 14 patients, only 4 patients (28.6%) were also judged as efficient with mMRC grade. Thus, the CAT score could be more useful in the subjective assessment of IPF. Moreover, FVC was improved 6 months after nintedanib introduction in 12 out of 24 patients with the complete set of the relevant data. These results indicate that nintedanib exhibits favorable effects in IPF from both subjective and objective evaluations.

Keywords: forced vital capacity; idiopathic pulmonary fibrosis; nintedanib; patient-reported outcomes; quality of life

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic and progressive fibrosis of unknown cause with a median survival period of 2-5 years after diagnosis (Raghu et al. 2011, 2015; du Bois 2012). IPF is the most common form of idiopathic interstitial pneumonias and is characterized by fibrosis of lung parenchyma and loss of lung function. The symptoms of IPF, such as dyspnea and dry cough, may be distressing and are associated with progressive deterioration in lung function and quality of life (QOL). The discrepancy between objective outcomes such as forced vital capacity (FVC) and patient-reported outcomes (PROs) has been focused on in the treatment and research in patients with incurable, morbid and life-shortening disease like IPF (Swigris and Fairclough 2012). In the pursuit of QOL in the treatment of IPF patients, PROs could be as important as the maintenance of FVC. By way of quantitative assessment of subjective symptoms of patients with IPF, the St. George’s Respiratory Questionnaire (SGRQ) score and the modified medical research council (mMRC) grade are usually applied in both usual care settings and clinical trials. However, the SGRQ score is too complicated in the usual care setting, and the mMRC is too simple for the assessment of diverse symptoms of IPF. Since the usefulness of the COPD (chronic obstructive pulmonary disease) assessment test (CAT) score has been reported in patients with IPF (Matsuda et al. 2017), CAT score was also adopted as a PRO in the current study.

Lung function usually deteriorates gradually in patients with IPF (Katoh et al. 1995; Kim et al. 2006) and generally worsens rapidly as IPF advances. Heterogeneity in disease progression has been observed with some patients experiencing rapid disease progression and others who maintain lung function for several years (Kim et al. 2006).

Pirfenidone is the first antifibrotic agent to be approved for the treatment of IPF, which targets several pathways involving factors, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β, interleukin (IL)-12, that functions against IPF (Azuma 2010). Its effect on retarding disease progression has been demonstrated in
2 randomized trials; CAPACITY-004 trial (Noble et al. 2011) and ASCEND trial (King et al. 2014).

The occurrence of acute exacerbation (AE) during IPF (IPF-AE) is associated with high mortality rates (Collard et al. 2007, 2013; Song et al. 2011), and IPF-AE is the most frequent cause of death among patients with IPF (Natsuiizaka et al. 2014). Therefore, the prevention of IPF-AE is also important.

Nintedanib is a small-molecule multikinase inhibitor that was originally designed to inhibit fibroblast growth factor receptor (FGFR)-1 and vascular endothelial growth factor receptor (VEGFR)-2 (Wollin et al. 2015). Nintedanib has also been shown to inhibit PDGF receptor (PDGFR)-α and β (Cottin 2015; Wollin et al. 2015), an important target for the treatment of IPF. In INPULSIS-1 and -2 trials (Richeldi et al. 2014), the adjusted annual rate of change in FVC at week 52 was significantly lower in the nintedanib group compared to the placebo group. Furthermore, the time to the first IPF-AE was significantly delayed in the nintedanib group compared to the placebo group in INPULSIS-2.

The effect of nintedanib on slowing the FVC decline in a real-world clinical setting in comparison to INPULSIS-1 and -2 trials has not been well elucidated. Furthermore, since the effectiveness of nintedanib on subjective symptoms evaluated with mMRC grade and CAT score has never been reported, the relationships between these PROs and the changes in FVC under nintedanib treatment are also of scientific interest.

**Materials and Methods**

**Patients**

A retrospective study was performed on patients treated with nintedanib at our hospital. Twenty-five patients with IPF who were newly treated with nintedanib at a dose of 150 mg or 100 mg twice daily from November 2015 to April 2016 were consecutively enrolled. The diagnosis of IPF was based on the ATS/ERS/JRS/ALAT clinical practice guideline from 2015 in general (Raghu et al. 2015). Patients with possible usual interstitial pneumonia (UIP) pattern (Raghu et al. 2015) without honeycomb cysts based on chest high-resolution computed tomography (HRCT) were clinically diagnosed as IPF/UIP who met the INPULSIS trial eligibility criteria (Richeldi et al. 2014): the presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance, and the absence of atypical features for UIP. In such cases, the findings that suggested temporal and/or spatial heterogeneity (Gruden et al. 2013) were also regarded as important and taken into account. These HRCT findings were confirmed by more than 2 radiologists. Patients who had been previously treated with nintedanib were excluded. Concomitant therapy with prednisolone up to 10 mg per day was permitted; however, patients receiving other agents including pirfenidone, azathioprine, cyclosporine, cyclophosphamide, and N-acetylcysteine were excluded. This study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Uji-Tokushukai Medical Center (approval date: April 21, 2017; approval number: 2017-04). Written informed consent was omitted since the study was retrospective, and patient anonymity was assured.

The indication criteria for nintedanib at our hospital are as follows: FVC deterioration of more than 10% over 6 months, FVC deterioration of more than 5% over 6 months accompanied by symptoms, FVC deterioration of less than 5% but the patient requests nintedanib to prevent IPF-AEs, and the presence of pulmonary fibrosis that is difficult to suppress by corticosteroids and/or immunosuppressant drugs.

The patients were numbered sequentially from 1 to 25, and individual data sets were managed according to the allocated number.

**Subjective assessments**

Subjective symptoms and activities of daily living were monitored at every visit and were quantitatively assessed with the mMRC grade and the CAT score. The CAT is one of the PROs which consists of 8 items; “cough”, “phlegm”, “chest tightness”, “breathlessness”, “activities”, “confidence”, “sleep”, and “energy” (Jones et al. 2009). Each item is allocated 0 to 5 scores and the total score of 8 items ranges from 0 to 40, which is in good correlation with SGRQ. The treatment was evaluated as “efficient” with subjective symptoms when the mMRC grade or the CAT score improved by 1 or 3 points, respectively.

**Physiological assessments**

Lung function tests were performed in order to obtain objective FVC (ml) data every 6 months starting 6 months prior to nintedanib introduction when possible.

The semiannual rate of change in FVC (%/6 months) prior to nintedanib introduction was calculated by the difference between the FVC at the time of nintedanib introduction and the FVC 6 months prior (defined as ΔFVC−6M) multiplied by 100 and divided by the FVC at the time of nintedanib introduction, which was defined as ΔFVC−6M%. The semiannual (%/6 months) and annual (%/12 months) rates of change in FVC after nintedanib introduction were calculated by the difference between the FVC 6 or 12 months after the treatment and the FVC at the time of nintedanib introduction (defined as ΔFVC+6M and ΔFVC+12M, respectively) multiplied by 100 and divided by the FVC at the time of nintedanib introduction, which were defined as ΔFVC+6M% and ΔFVC+12M%, respectively.

**Statistical analysis**

Data are presented as mean (standard deviation [SD]) or median (range) for continuous variables, and percentages (95% confidence interval [CI] or range) for categorical variables. Paired t-test was used to compare continuous variables; mMRC grades and CAT scores during the observation period.

**Results**

**Baseline patient characteristics**

In this study, the mean age was 74.4 years (SD: 5.6), and 4 patients (16.0%) were female and 21 (84.0%) were male. In terms of smoking status, 6 patients (24.0%) were never smokers, 14 (56.0%) were former smokers, and 5 (20.0%) were current smokers. The following results were obtained for the mMRC grade: grade 0, n = 2 (8.0%); grade 1, n = 4 (16.0%); grade 2, n = 13 (52.0%); grade 3, n = 4 (16.0%); and grade 4, n = 2 (8.0%). The mean CAT score was 13.96 (SD: 6.43). Based on chest HRCT, the presence
of honeycomb cysts was observed in 19 patients (76.0%) and emphysematous changes were observed in 13 (52.0%). One patient was previously administered pirfenidone but switched to nintedanib due to adverse events (Table 1).

Among the 25 patients, FVC data at the time of nintedanib introduction as well as 6 and 12 months after administration were obtained in 24 patients. The median FVC and %FVC at the time of nintedanib introduction in the 24 patients were 2,340 ml (range; 770 to 3,860 ml) and 80.6% (range; 27.1 to 119.0%), respectively (Table 1).

**Therapeutic Effects of Nintedanib**

Improvements in subjective symptoms (Table 2) were observed in 14 out of 25 patients (56.0%: 95% CI; 34.9 to 75.6%), and 9 patients remained stable. The subjective symptoms improved in 11 out of 19 patients with honeycomb cysts (57.9%: 95% CI; 33.5 to 79.7%) and in 3 out of 6 patients without (50.0%: 95% CI; 11.8 to 88.2%). Furthermore, the subjective symptoms improved in 8 out of 13 patients with emphysematous changes (61.5%: 95% CI; 31.6 to 86.1%) and in 6 out of 12 without (50.0%: 95% CI; 21.1 to 78.9%). Out of 24 patients with FVC data after nintedanib introduction, the full sets of FVC data including 6 months prior to nintedanib introduction were obtained from 17. The mean ΔFVC−6M (n = 17), ΔFVC+6M (n = 24), and ΔFVC+12M (n = 24) were −180.59 ml (SD; 252.08), 80.00 ml (SD; 220.39), and 87.50 ml (SD; 285.52), respectively (Fig. 1). P values between ΔFVC−6M and ΔFVC+6M, ΔFVC−6M and ΔFVC+12M, and ΔFVC+6M and ΔFVC+12M are 0.00734, 0.0223, and 0.819, respectively (Fig. 1). The mean ΔFVC+6M and ΔFVC+12M were positive, and the differences between ΔFVC−6M and ΔFVC+6M or ΔFVC+12M were statistically significant. These results suggest that nintedanib may have improved lung function during 12 months of treatment.

In 12 patients (50.0%), the FVC was improved 6 months after nintedanib introduction, and the effect was sustainable for at least 12 months (Fig. 1). Since the individual FVC change was not elucidated in INPULSIS-1 and -2 trials (Richeldi et al. 2014) and INPULSIS-ON trial (Crestani et al. 2016), this observation is unique in that a half of the patients responded to nintedanib at 6 months after treatment and that the effect was apparent during the observation period.

Considering ΔFVC−6M%, ΔFVC+6M% and ΔFVC+12M% in 17 patients, the median ΔFVC−6M% was −5.6% (range; −26.7 to +11.9%), while the median ΔFVC+6M% and ΔFVC+12M% were +3.5% (range; −11.1 to +25.7%) and +2.0% (range; −9.7 to +44.7%), respectively. When disease progression was defined as “stable” for patients exhibiting a decline in FVC of less than 5% and “unstable” for patients exhibiting a decline in FVC of 5% or more, all 10 unstable patients (100%) became stable, 4 out of 7 stable patients (57.1%) remained stable and 3 patients (42.9%) became unstable after 6 months of treatment. After 12 months of treatment, 9 out of 10 unstable patients (90.0%) became stable with 1 patient (10.0%) remaining unstable, and 3 out of 7 stable patients (42.9%) remained stable and the remaining 4 patients (57.1%) became unstable.

These results suggest the efficacy of nintedanib on reducing FVC decline during a short-term period, and it

| Table 1. Baseline patient characteristics. |
|------------------------------------------|
| **Mean age (years, SD)**                 | 74.4 (5.6)  |
| **Sex (women / men; n, %)**              | 4 (16.0%) / 21 (84.0%)  |
| **Never / former / current smokers (n, %)** | 6 (24.0%) / 14 (56.0%) / 5 (20.0%)  |
| **mMRC grade 0 / 1 / 2 / 3 / 4 (n, %)**  | 2 (8%) / 4 (16%) / 13 (52%) / 4 (16%) / 2 (8%)  |
| **COPD assessment test score (mean, SD)** | 13.96 (6.43)  |
| **Median FVC (ml, range)**              | 2340 (770-3860) n = 24  |
| **Median % FVC (%, range)**             | 80.6 (27.1-119.0) n = 24  |
| **Honeycomb cysts on HRCT + / – (n, %)** | 19 (76.0%) / 6 (24.0%)  |
| **Emphysema on HRCT + / – (n, %)**      | 13 (52.0%) / 12 (48.0%)  |
| **Previous pirfenidone (n, %)**         | 1 (4.0%)  |

mMRC, modified medical research council; HRCT, high-resolution computed tomography.
Table 2. Therapeutic effects of Nintedanib.

Subjective improvement  
Overall (n, %)  
With / Without honeycomb cysts (%)  
With / Without emphysema (%)  
Objective improvement; median ΔFVC% after 6 months  
Overall (%), range  
With / Without honeycomb cysts (%), range  
With / Without emphysema (%), range  
Objective improvement; median ΔFVC% after 12 months  
Overall (%), range  
With / Without honeycomb cysts (%), range  
With / Without emphysema (%), range

HRCT, high-resolution computed tomography; FVC, forced vital capacity.

Fig. 1. Changes in the forced vital capacity during the observation period.

Changes in the forced vital capacity (FVC) from 6 months before to the baseline (ΔFVC−6M), and from the baseline to 6 (ΔFVC+6M) and 12 (ΔFVC+12M) months after nintedanib administration are shown. The error bars exhibit 2 standard deviations (SD). The mean ΔFVC−6M (n = 17), ΔFVC+6M (n = 24), and ΔFVC+12M (n = 24) were 180.59 ml (SD; 252.08), 80.00 ml (SD; 220.39), and 87.50 ml (SD; 285.52), respectively. P values between ΔFVC−6M and ΔFVC+6M, ΔFVC−6M and ΔFVC+12M, and ΔFVC+6M and ΔFVC+12M are 0.00734, 0.0223, and 0.819, respectively. These findings suggest that the decline in FVC which was observed just before nintedanib treatment turned into amelioration after 6 months of treatment. The effect of nintedanib continued during 12 months of observation period.
continued for longer periods over 12 months. These findings are in accordance with the previous INPULSIS-1 and -2 trials (Richeldi et al. 2014), and INPULSIS-ON trial (Crestani et al. 2016), which have demonstrated longer and more durable effect.

**Therapeutic effects of Nintedanib on subpopulations**

For 24 patients, the median \( \Delta \text{FVC}+6\text{M\%} \) and \( \Delta \text{FVC}+12\text{M\%} \) were +4.4% (range: −11.4 to +30.3%) and +1.0% (range: −9.7 to +44.7%), respectively (Table 2), which showed favorable effects of nintedanib.

In 18 patients with honeycomb cysts observed by HRCT, the median \( \Delta \text{FVC}+6\text{M\%} \) and \( \Delta \text{FVC}+12\text{M\%} \) were +3.85% (range: −11.4 to +13.3%) and +1.0% (range: −9.7 to +15.3%), respectively, while those in 6 without honeycomb cysts were +8.4% (range: −11.1 to +30.3%) and +8.6% (range: −6.6 to +44.7%), respectively (Table 2).

In 13 patients with emphysematous changes, the median \( \Delta \text{FVC}+6\text{M\%} \) and \( \Delta \text{FVC}+12\text{M\%} \) were +6.0% (range: −11.4 to +25.7%) and +2.8% (range: −9.0 to +44.7%), respectively, while those in 11 without were 0.0% (range: −11.1 to +30.3%) and −2.5% (range: −9.7 to +31.2%), respectively (Table 2).

These data suggest that the effect of nintedanib on maintaining FVC tends to last relatively long irrespective of the presence of honeycomb cysts or emphysematous changes observed by HRCT.

**Changes in the mean mMRC grade and CAT score 6 months before, at the baseline, as well as 6 and 12 months after Nintedanib administration**

We analyzed the effects of nintedanib on PROs with mMRC grade and CAT score during the observation periods: at 6 months before treatment, baseline and 6 and 12 months after nintedanib administration.

The mean mMRC grades 6 months before, at the baseline, and 6 and 12 months after nintedanib administration were 1.88 (SD: 0.83), 2.00 (SD: 1.00), 1.84 (SD: 0.90), and 1.80 (SD: 0.91), respectively. The mean CAT score at each time point was 12.88 (SD: 6.37), 13.96 (SD: 6.43), 11.80 (SD: 6.15), and 11.72 (SD: 6.19), respectively. The plot of the mean mMRC grades and CAT scores are shown in Fig. 2. While there was significant difference in the mMRC grade between the baseline and 6 months after nintedanib introduction (\( p = 0.0429 \)), there were significant differences in the CAT scores between 6 months prior and the baseline (deterioration; \( p < 0.001 \)), the baseline and 6 months after (improvement; \( p < 0.001 \)), and the baseline and 12 months after (improvement; \( p < 0.001 \)) nintedanib introduction. The changes in the CAT scores are in accordance with the natural course of disease progression before treatment and the improvement in FVC (\( \Delta \text{FVC}+6\text{M\%} \) and \( \Delta \text{FVC}+12\text{M\%} \)) by
nintedanib treatment. In terms of subjective improvement, 14 patients were evaluated efficient 6 months after treatment. Among 14 patients, 10 patients (71.4%) were due to CAT score alone and 4 patients (28.6%) were due to improvement in both mMRC grade and CAT score. These findings suggest that the CAT score could be useful in the subjective assessment of IPF during nintedanib treatment.

**IPF-AE**

IPF-AE was observed in one patient but was resolved by pulse corticosteroid therapy. However, this case of IPF-AE occurred during a 2-week drug cessation period due to gastroenteritis. Therefore, nintedanib may have been ineffective during this time.

**Adverse events**

Adverse events included diarrhea (37.5%), nausea (28.0%), and vomiting (16.0%); however, these events were graded between 1 and 2 and were controllable. Dose reduction was performed in 11 cases (44.0%).

**Discussion**

IPF is diagnosed by radiological and/or histopathological patterns of usual interstitial pneumonia (UIP) (Raghu et al. 2011, 2015; du Bois 2012). Considering the invasiveness of surgical lung biopsies (SLB), the diagnosis is mainly made by the presence of honeycomb cysts by HRCT (du Bois 2012). The prognosis of IPF is reported to be the same with or without SLB after adjusting sex, age, and physiology (Ley et al. 2012; Lee et al. 2016). However, the absence of honeycomb cysts does not exclude IPF since 60.8% of cases without honeycomb cysts are pathologically diagnosed as IPF (Sumikawa et al. 2014). Therefore, it is also important not to omit the possibility of IPF in cases without honeycomb cysts.

The prognostic factors during follow-up are as follows (Raghu et al. 2011): deterioration in dyspnea, deterioration in FVC of more than 10%, deterioration in DLco of more than 15% (du Bois et al. 2011b), and the progression of honeycomb cysts observed by HRCT.

In addition to the deterioration in FVC of more than 10%, the marginal decline of FVC (~5 to ~10%) over 6 months is also reported to predict poor prognosis (du Bois et al. 2011a). Therefore, patients showing marginal decline could be therapeutic targets.

In contrast to pirfenidone that required 3 phase III trials (Noble et al. 2011; King et al. 2014) to prove the efficacy of reducing the gradual decline in FVC, nintedanib succeeded in demonstrating its benefit in 2 successive independent trials (Richeldi et al. 2014). Furthermore, the INPULSIS-ON trial has shown beneficial effects of nintedanib after 52 weeks of treatment in a large population (Wuyts et al. 2016). However, its effect on FVC changes in a real-world clinical setting has not been well elucidated. In addition, its effect on PROs assessed with mMRC grade and CAT score, which are practical in the usual care setting, has never been reported.

In this study, both subjective and objective effects of nintedanib were demonstrated during 12 months of treatment, and the FVC before and after nintedanib introduction was evaluated. There were statistically significant differences between ∆FVC−6M and ∆FVC+6M or ∆FVC+12M (Fig. 1). On the other hand, while all unstable patients became stable, 57.1% and 42.9% of stable patients remained stable and became unstable, respectively, after 6 months of treatment. These trends were similarly observed after 12 months. These data suggest that nintedanib could have favorable and durable effects on slowing the decline of FVC in a real-world clinical setting that is in agreement with INPULSIS-1 and -2 trials (Richeldi et al. 2014).

Furthermore, in terms of PROs which were evaluated with mMRC grade and CAT score, these scales exhibited essentially the similar behavior during the observation periods; namely, both mMRC grade and CAT score were worsened prior to nintedanib introduction, but both improved after 6 and 12 months of nintedanib introduction (Fig. 2). However, in terms of statistical significance, there was a noticeable difference between mMRC grade and CAT score. In fact, a significant decrease (improvement) was observed in mMRC grade only between the baseline and 6 months after nintedanib treatment, whereas significant improvement was observed in CAT score between the baseline and 6 or 12 months after nintedanib treatment. Furthermore, 10 patients (71.4%) with subjective improvement are classified solely by improvement in the CAT score. There was no significant intergroup difference in the adjusted mean change in total SGRQ score from baseline to week 52 in INPULSIS-1 trial (Richeldi et al. 2014), while in INPULSIS-2 trial, a significantly smaller increase in the total SGRQ score was observed in the nintedanib group than in the placebo group (Richeldi et al. 2014). The findings in the current study are concordant with INPULSIS-2 trial. Therefore, the evaluation of subjective symptoms with mMRC grade and CAT score could be useful in the usual care settings.

In terms of PROs, three of the most relevant physical domains in IPF are considered to be dyspnea, fatigue, and cough (Swigris and Fairclough 2012). Since CAT score is consisted of 8 items including these 3 domains, CAT score could better express than mMRC the conditions of patients with IPF, and could better correlate with FVC, that was observed in the current study.

The FVC improved 6 months after nintedanib introduction and the effect was sustainable for at least 12 months in 12 out of 24 patients (Fig. 1). Although the reason for the improvement in FVC remains unclear, there are a few suggestions. First, nintedanib is a multikinase inhibitor that blocks PDGFR and downstream signals, such as phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) (Bonner 2004; Wollin et al. 2015), and also inhibits FGFR and downstream signaling of PI3K, protein kinase B (Akt), and mitogen-activated protein kinase pathway, which are impor-
tant for cell growth and survival (Dey et al. 2010; Wollin et al. 2015). Since some kinases, such as PI3K and Akt, are considered to be closely associated with skeletal muscle growth (Luo et al. 2006; Glass 2010; Schiaffino and Mammucari 2011; Briata et al. 2012), the effects of nintedanib may inhibit further pulmonary fibrosis and improve muscular functions that regulate lung function that lead to the sustainable improvement in FVC.

Our findings suggested that nintedanib exhibited favorable effects from both subjective and objective evaluations, which were in accordance with INPULSIS-1 and -2 trials (Richeldi et al. 2014), and INPULSIS-ON trial (Crestani et al. 2016). On the other hand, the adverse events were similar to the previous report (Richeldi et al. 2014) and were well tolerated.

The current study has several limitations. First, since this study was retrospective observational investigation that was conducted using a small sample size, the bias observed in this study population may be different from those in larger populations. Therefore, the relationship between observed PROs and FVC in patients treated with nintedanib should be confirmed in prospective randomized trials.

In conclusion, we have shown the relationship between PROs and FVC data sets in IPF patients newly treated with nintedanib. The data indicate that nintedanib exhibits positive effects on both mMRC grade and CAT score. In particular, the CAT score is useful in the subjective assessment of IPF during nintedanib treatment. In addition, nintedanib reduced the semiannual and annual decline in FVC even in patients with a rapid decline 6 months prior to treatment. The multikinase function of nintedanib may have affected the respiratory muscle fibers.

Acknowledgments
We would like to thank Mr. Makoto Utsugi (Mirai Iryo Research Center, Tokyo) and Kentaro Motoda (Clinical Study Center, Uji-Tokushukai Medical Center) for their contributions to the statistical analysis in the current study.

Conflict of Interest
The authors declare no conflict of interest.

Author Contributions
T.T. designed and performed research and also wrote the paper, M.T. and M.S. collected data, and S.T. analyzed data.

References
Azuma, A. (2010) Pirfenidone: antifibrotic agent for idiopathic pulmonary fibrosis. Expert Rev. Respir. Med., 4, 301-310.
Bonner, J.C. (2004) Regulation of PDGF and its receptors in fibrotic diseases. Cytokine Growth Factor Rev., 15, 255-273.
Briata, P., Lin, W.J., Giovarelli, M., Passero, M., Chou, C.F., Trabucchi, M., Rosenfeld, M.G., Chen, C.Y. & Gherzi, R. (2012) PI3K/AKT signaling determines a dynamic switch between distinct KSRP functions favoring skeletal myogenesis. Cell Death Differ., 19, 478-487.
Collard, H.R., Moore, B.B., Flaherty, K.R., Brown, K.K., Kaner, R.J., King, T.E. Jr., Lasky, J.A., Loyd, J.E., Noth, I., Olman, M.A., Raghu, G., Roman, J., Ryu, J.H., Zisman, D.A., Hunninghake, G.W., et al. (2007) Acute exacerbations of idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med., 176, 636-643.
Collard, H.R., Yow, E., Richeldi, L., Anstrom, K.J. & Glazer, C.; IPFnet investigators (2013) Suspected acute exacerbation of idiopathic pulmonary fibrosis as an outcome measure in clinical trials. Respir. Res., 14, 73.
Cottin, V. (2015) Nintedanib: a new treatment for idiopathic pulmonary fibrosis. Clin. Invest., 5, 621-632.
Crestani, B., Quaresma, M., Kaye, M., Stansen, W., Stowasser, S. & Kreuter, M. (2016) Long-term treatment with nintedanib in patients with IPF: an update from INPULSIS®-ON. Eur. Respir. J., 48, OA4960.
Dey, J.H., Bianchi, F., Voshol, J., Bonenfant, D., Oakeley, E.J. & Hynes, N.E. (2010) Targeting fibroblast growth factor receptors blocks PI3K/AKT signaling, induces apoptosis, and impairs mammary tumor outgrowth and metastasis. Cancer Res., 70, 4151-4162.
du Bois, R.M. (2012) An earlier and more confident diagnosis of idiopathic pulmonary fibrosis. Eur. Respir. Rev., 21, 141-146.
du Bois, R.M., Weycker, D., Albera, C., Bradford, W.Z., Costabel, U., Kartashov, A., King, T.E. Jr., Lancaster, L., Noble, P.W., Sahn, S.A., Thomeer, M., Valeyre, D. & Wells, A.U. (2011a) Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am. J. Respir. Crit. Care Med., 184, 1382-1389.
du Bois, R.M., Weycker, D., Albera, C., Bradford, W.Z., Costabel, U., Kartashov, A., Lancaster, L., Noble, P.W., Raghu, G., Sahn, S.A., Szwarzberg, J., Thomeer, M., Valeyre, D. & King, T.E. Jr. (2011b) Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med., 184, 459-466.
Glass, D.J. (2010) PI3 kinase regulation of skeletal muscle hypertrophy and atrophy. Curr. Top. Microbiol. Immunol., 346, 267-278.
Gruden, J.F., Panse, P.M., Leslie, K.O., Tazelaar, H.D. & Colby, T.V. (2013) UIP diagnosed at surgical lung biopsy, 2000-2009: HRCT patterns and proposed classification system. Am. J. Roenigenol., 200, W458-467.
Jones, P.W., Harding, G., Berry, P., Wiklund, I., Chen, W.H. & Kline Leidy, N. (2009) Development and first validation of the COPD Assessment Test. Eur. Respir. J., 34, 648-654.
Katoh, T., Ohishi, T., Ikuta, N., Kawabata, Y., Takagi, K. & Hayakawa, T. (1995) A rapidly progressive case of interstitial pneumonia. Intern. Med., 34, 388-392.
Kim, D.S., Collard, H.R. & King, T.E. Jr. (2006) Classification and natural history of the idiopathic interstitial pneumonias. Proc. Am. Thorac. Soc., 3, 285-292.
King, T.E. Jr., Bradford, W.Z., Castro-Bernardini, S., Fagan, E.A., Glaspole, I., Glassberg, M.K., Gorina, E., Hopkins, P.M., Kardatzke, D., Lancaster, L., Lederer, D.J., Nathan, S.D., Pereira, C.A., Sahn, S.A., Sussman, R., et al. (2014) A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N. Engl. J. Med., 370, 2083-2092.
Lee, S.H., Kim, S.Y., Kim, D.S., Kim, Y.W., Chung, M.P., Uh, S.T., Park, C.S., Jeong, S.H., Park, Y.B., Lee, H.L., Shin, J.W., Lee, E.J., Lee, J.H., Jegal, Y., Lee, H.K., et al. (2016) Predicting survival of patients with idiopathic pulmonary fibrosis using GAP score: a nationwide cohort study. Respir. Res., 17, 131.
Ley, B., Ryerson, C.J., Vittinghoff, E., Ryu, J.H., Tomassetti, S., Lee, J.S., Poletti, V., Buccioli, M., Elicker, B.M., Jones, K.D., King, T.E. Jr. & Collard, H.R. (2012) A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann. Intern. Med., 156, 684-691.
Luo, J., Sobkow, C.L., Hirshman, M.F., Logsdon, M.N., Li, T.Q., Goodyear, L.J. & Cantley, L.C. (2006) Loss of class I PI3K signaling in muscle leads to impaired muscle growth, insulin response, and hyperlipidemia. Cell Metab., 3, 355-366.
Matsuda, T., Taniguchi, H., Ando, M., Kondoh, Y., Kimura, T., Kataoka, K., Sakamoto, K., Suzuki, A., Furukawa, T. & Hasegawa, Y. (2017) COPD Assessment Test for measurement of health status in patients with idiopathic pulmonary fibrosis: a cross-sectional study. Respirology, 22, 721-727.

Natsuizaka, M., Chiba, H., Kuronuma, K., Otsuka, M., Kudo, K., Morii, M., Bando, M., Sugiyama, Y. & Takahashi, H. (2014) Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am. J. Respir. Crit. Care Med., 190, 773-779.

Noble, P.W., Albera, C., Bradford, W.Z., Costabel, U., Glassberg, M.K., Kardatzke, D., King, T.E. Jr., Lancaster, L., Sahn, S.A., Szwarcberg, J., Valeyre, D. & du Bois, R.M.; CAPACITY Study Group (2011) Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet, 377, 1760-1769.

Raghu, G., Collard, H.R., Egan, J.J., Martinez, F.J., Behr, J., Brown, K.K., Colby, T.V., Cordier, J.F., Flaherty, K.R., Lasky, J.A., Lynch, D.A., Ryu, J.H., Swigris, J.J., Wells, A.U., Ancochea, J., et al. (2011) An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am. J. Respir. Crit. Care Med., 183, 788-824.

Raghu, G., Rochwerger, B., Zhang, Y., Garcia, C.A., Azuma, A., Behr, J., Brozek, J.L., Collard, H.R., Cunningham, W., Homma, S., Johkoh, T., Martinez, F.J., Myers, J., Protzko, S.L., Richeldi, L., et al. (2015) An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am. J. Respir. Crit. Care Med., 192, e3-19.

Richeldi, L., du Bois, R.M., Raghu, G., Azuma, A., Brown, K.K., Costabel, U., Cottin, V., Flaherty, K.R., Hansell, D.M., Inoue, Y., Kim, D.S., Kolb, M., Nicholson, A.G., Noble, P.W., Selman, M., et al. (2014) Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N. Engl. J. Med., 370, 2071-2082.

Schiaffino, S. & Mammucari, C. (2011) Regulation of skeletal muscle growth by the IGF1-Akt/PKB pathway: insights from genetic models. Skelet. Muscle, 1, 4.

Song, J.W., Hong, S.B., Lim, C.M., Koh, Y. & Kim, D.S. (2011) Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur. Respir. J., 37, 356-363.

Sumikawa, H., Johkoh, T., Fujimoto, K., Arakawa, H., Colby, T.V., Fukuoka, J., Taniguchi, H., Kondoh, Y., Kataoka, K., Ogura, T., Baba, T., Ichikado, K., Gyobu, T., Yanagawa, M., Honda, O., et al. (2014) Pathologically proved nonspecific interstitial pneumonia: CT pattern analysis as compared with usual interstitial pneumonia CT pattern. Radiology, 272, 549-556.

Swigris, J.J. & Fairclough, D. (2012) Patient-reported outcomes in idiopathic pulmonary fibrosis research. Chest, 142, 291-297.

Wollin, L., Wex, E., Pautsch, A., Schnapp, G., Hostettler, K.E., Stowasser, S. & Kolb, M. (2015) Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur. Respir. J., 45, 1434-1445.

Wuyts, W.A., Kolb, M., Stowasser, S., Stansen, W., Huggins, J.T. & Raghu, G. (2016) First data on efficacy and safety of Nintedanib in patients with idiopathic pulmonary fibrosis and forced vital capacity of ≤ 50% of predicted value. Lung, 194, 739-743.