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Early View

Original article

Treatment with antifibrotic agents in idiopathic pleuroparenchymal fibroelastosis with usual interstitial pneumonia

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Title Page

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Treatment with antifibrotic agents in idiopathic pleuroparenchymal fibroelastosis with usual interstitial pneumonia

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Running head:

Treatment with antifibrotic agents in PPFE with UIP

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Abstract

Background: There are no established therapeutic options available for idiopathic pleuroparenchymal fibroelastosis (IPPFE), apart from supportive care and lung transplantation. Furthermore, it is known that IPPFE with a usual interstitial pneumonia (UIP) pattern and lower lobe predominance is a disease entity distinct from idiopathic pulmonary fibrosis (IPF). To our knowledge, few studies are available that report on the efficacy of antifibrotic agents for IPPFE with UIP.

Aim: The aim of this study was to compare the efficacy of antifibrotic agents between IPPFE with UIP and typical IPF in real-world clinical practice.

Patients and Methods: A retrospective analysis was performed on the medical records of all patients at 2 interstitial lung disease centres. Sixty-four patients were diagnosed as having IPPFE with UIP and 195 patients were diagnosed with typical IPF. We compared the efficacy of antifibrotic agents between these 2 groups.

Results: Survival time was significantly shorter in the patients with IPPFE with UIP. Some 125 patients were administered antifibrotic agents for over 6 months (34 with IPPFE with UIP and 91 with typical IPF). Reduced forced vital capacity (FVC) 6 months after treatment with antifibrotic agents was significantly greater in the IPPFE with UIP group than in those in the typical IPF. Moreover, the change in FVC% predicted was significantly greater during the follow-up in patients with IPPFE with UIP compared with those with typical IPF.

Conclusions: The efficacy of antifibrotic agents was limited in patients with IPPFE with UIP. Thus, IPPFE with UIP remains a fatal and progressive disease.

Abbreviations List:

IPPFE: idiopathic pleuroparenchymal fibroelastosis

UIP: usual interstitial pneumonia

IPF: idiopathic pulmonary fibrosis

MST: median survival time

ILD: interstitial lung disease

PF-ILD: progressive fibrosing interstitial lung disease

HRCT: high-resolution computed tomography

AE: acute exacerbation

BMI: body mass index

mMRC: modified Medical Research Council

KL-6: Krebs vonden Lungen-6

SP-D: surfactant protein-D

GAP: gender–age–physiology

TBE: Traction bronchiectasis

FVC: forced vital capacity

%FVC: percentage predicted FVC

DLco: diffusing capacity of the lungs for carbon monoxide

FEV_1: forced expiratory volume in 1 s

TLC: total lung capacity

PFT: pulmonary function test

CPI: composite physiologic index

PaO_2: partial pressure of oxygen in arterial blood

$PaCO_2$: partial pressure of carbon dioxide in arterial blood

IPUF: idiopathic pulmonary upper-lobe fibrosis

NSIP: non-specific interstitial pneumonia

SLB: surgical lung biopsy

ANOVA: analysis of variance

LMM: linear mixed model

CI: confidence interval

SHR: subdistribution hazard ratio

SD: standard deviation

Key words: idiopathic pulmonary fibrosis, usual interstitial pneumonia, pleuroparenchymal fibroelastosis, anti-fibrotic agents, prognosis

Introduction

Idiopathic pleuroparenchymal fibroelastosis (IPPFE) is a rare condition characterised by predominantly upper lobe pleural and subjacent parenchymal fibrosis [1]. In general, there are no established therapeutic options available for IPPFE other than supportive care and lung transplantation [2].

IPPFE has been increasingly reported in association with a variety of interstitial lung diseases (ILDs) in the lower lobes, including usual interstitial pneumonia (UIP) [3, 4]. Some patients with IPPFE with UIP pattern are diagnosed as having idiopathic pulmonary fibrosis (IPF) and are treated with antifibrotic agents in real-world clinical practice. However, IPPFE with UIP could be a disease entity distinct from IPF because patients with IPPFE with UIP had poorer prognoses compared with those of patients with IPF, as reported by several researchers [5-8].

In recent years, it has been reported that progressive fibrosing ILD other than IPF (non-IPF PF-ILD) is characterised by disease progression associated with worsening of fibrosis despite appropriate treatment for individual patients with ILD [9, 10]. Given patients with non-IPF PF-ILD have shown similarities in underlying pathogenetic mechanisms and disease behaviour to those with IPF, it appeares plausible that antifibrotic treatments could be beneficial in these conditions [11, 12]. In fact, Distler, et al. [13] had reported the potential efficacy of nintedanib in patients with systemic sclerosis-associated ILD. More recently, the annual rate of decline in forced vital capacity (FVC) was significantly lower among patients with non-IPF PF-ILD who received nintedanib than among those who received placebo in the INBUILD trial [14]. However, there is no evidence for the efficacy of antifibrotic treatment, including nintedanib and pirfenidone, for IPPFE with UIP.

Thus, we aimed to clarify differences in the efficacy of antifibrotic agents and the prognoses between IPPFE with UIP and typical IPF.

Methods

Study population and clinical data

The study population consisted of consecutive patients at the Department of Respiratory Medicine of Tsuboi Hospital and Toho University Omori Medical Centre in Japan from April 2003 to May 2018. The diagnosis of IPPFE with UIP, which was modified from previous studies [3, 15, 16], was determined by the presence of the following features in addition to honeycombing, predominantly in the bilateral lower lobes: (i) bilateral dense subpleural consolidation in the upper lobes with traction bronchiolectasis, architectural distortion, and upper lobe volume loss; ii) exclusion of other identifiable aetiologies, such as a history of radiation therapy, active pulmonary infection, connective tissue disease and chronic hypersensitivity pneumonitis and (iii) radiologic confirmation of disease progression (defined as an increase in the upper lobe subpleural consolidation and/or a decreased in upper lobe volume on serial chest high-resolution computed tomography (HRCT). We identified IPF in accordance with the 2011 international IPF guidelines [17], and acute exacerbation of IPF was diagnosed by criteria proposed by Collard et al. [18], in which all of the following 4 conditions must be satisfied: (i) a previous or concurrent diagnosis of IPF; (i) unexplained worsening or development of dyspnea within 30 days; (ii) chest HRCT scan with new bilateral ground-glass opacities and/or consolidation superimposed on a reticular or honeycombing background pattern; (iii) no evidence of pulmonary infection by bronchoalveolar lavage, endotracheal aspiration or sputum culture, in combination with negative blood tests for other potentially infectious pathogens (e.g. Pneumocystis jirovecii,

Cytomegalovirus) and exclusion of left heart failure, pulmonary embolism and alternative causes of acute lung injury.

The diagnosis of all patients was evaluated by a multidisciplinary discussion based on patients' clinical, radiological and/or pathological findings.

The medical records were retrospectively reviewed to obtain the following clinical data: age, sex, smoking status, body mass index (BMI), modified Medical Research Council (mMRC) scale, laboratory data (Krebs von den Lungen 6 [KL-6], surfactant protein-D), pulmonary function test findings and chest HRCT findings. We examined the data on the patients' clinical course, including treatment, complications, changes in pulmonary function (every 6 months) and prognosis. The Gender–Age–Physiology (GAP) score was calculated by the data obtained at the initial evaluation [19]. To evaluate the response to treatment, we defined disease progression as a relative decline in ≥10% and stable disease as a relative decline in <10% in percent predicted FVC over a period of 6 months.

The Institutional Ethics Committee of the Toho University Omori Medical Centre approved this study (no. M1626317281) and waived the requirement for informed consent given the study was designed as a retrospective clinical review.

Visual computed tomography analysis

Helical CT scanners (Aquilion 16, Toshiba, Tokyo, Japan and Aquilion Prime, Canon, Tokyo, Japan) were applied. Thin-section CT scans were obtained at full inspiration, and the scanning protocol consisted of reconstruction of a 1- to 2-mm slice thickness with a high-spatial-frequency algorithm. Thin-section CT images of the chest were photographed at window settings appropriate for the lung parenchyma (window level from –600 to –450 Hounsfield Units [HU]; width from 1600 to 1900 HU) for all patients.

Fibrosis score (reticulation and honeycombing) was semi-quantitatively evaluated based on the extent of lung parenchymal involvement in whole lungs: 0 (absent); 1 (<25%); 2 (25% to <50%); 3 (50% to <75%) and 4 (≥75%) [15]. Traction bronchiectasis extent was also scored: 0, none; 1, 1 segment; 2, 2 segments; 3, more than 2 segments [20]. These scores were reviewed independently by 2 pulmonologists (K.S., H.O. who had 22 and 8 years' experiences in ILD practice, respectively.) and 1 radiologist (K.M. who had 20 years' experience in chest radiology.), blinded to the clinical data. The simple kappa values was 0.62 for radiological pleuroparenchymal fibroelastosis (PPFE). The weighted kappa values for fibrosis score and extent of bronchiectasis were 0.85 and 0.87, respectively.

Pulmonary function testing

Spirometry and the diffusing capacity of the lung for carbon monoxide (DLco) by the single breath-holding method were measured using a pulmonary function test system (Chestac-33 and Chestac-8900, CHEST Co. Ltd., Tokyo, Japan).

Statistical analysis

Data are expressed as means with standard deviations or numbers of patients with percentages, as appropriate. The differences between 2 groups were evaluated using Pearson's chi-squared test or Fisher's exact test for categorical variables, Student's *t* test for parametric continuous variables and the Mann-Whitney U test for nonparametric variables. Mean changes in FVC values for 6 months before and after treatments with antifibrotic agents were compared between the 2 groups by a 2-way repeated measure analysis of variance with Bonferroni's multiple comparison. We compared longitudinal changes in percentage predicted FVC (%FVC) from baseline by using a linear mixed model (LMM) with random intercept and slope term (R version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria). Fine–Gray univariable and multivariable competing risks

models were used to investigate variables predictive of mortality among variables that were demonstrated to be significant in the univariate model. Variables with $P < 0.1$ were used for entry into the model. To avoid multicolinearity, only one of the highly correlated variables (correlation coefficient ≥0.7) was entered into the multivariate model (R version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria). We performed logistic regression analysis to identify predictive factors associated with efficacy of antifibrotic agents. Overall survival was defined as the time from the date of diagnosis to the date of censoring or death. Kaplan–Meier survival curves were compared using the log rank test. We considered $P < 0.05$ to represent statistical significance. We analysed the interobserver variation in various abnormalities on chest HRCT using the kappa (κ) statistic. Interobserver agreement was classified as follows: poor, κ = 0–0.20; fair, κ = 0.21–0.40; moderate, κ = 0.41–0.60; good, κ = 0.61–0.80; and excellent, κ = 0.81–1.00. All data except for LMM and Fine–Gray univariable and multivariable competing risks models were performed using JMP, version 10.0.0 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline clinical differences between patients with IPPFE with UIP and patients with typical IPF

The proportion of women, the rate of never-smokers, and the percentage of pneumothorax complications were significantly higher in patients with IPPFE with UIP than in those with typical IPF. There were no differences in the baseline disease severity (GAP staging) between both groups (stage I/II/III = 28/24/12 vs. 99/68/28, $P = 0.55$). Conversely, the percentage of primary lung cancer complications was significantly lower in patients with IPPFE with UIP than in those with typical IPF (Table 1). Baseline values of %FVC, and serum KL-6 value in patients with IPPFE with UIP were significantly lower than those in

patients with typical IPF, whereas the level of percentage predicted residual volume, and partial pressure of carbon dioxide ($PaCO_2$) were significantly higher in patients with IPPFE with UIP (Table 2).

Overall survival and prognostic significance of patients with IPPFE with UIP

The Kaplan–Meier survival curve had a significantly poorer outcome in patients with IPPFE with UIP (median survival time (MST) 34.0 months vs. 62.3 months, $P < 0.0001$) (Figure 1). Regarding prognostic factors for survival for patients with IPPFE with UIP, a univariable Fine–Gray competing risks analysis considered acute exacerbation as a competing risk showed that decreased body mass index (BMI) (subdistribution hazard ratio [SHR] 0.757; 95% confidence interval [CI] 0.632–0.907; $P = 0.003$), decreased %FVC (SHR 0.955; 95% CI 0.929–0.982; $P = 0.001$) and pneumothorax complication (SHR = 3.029; 95% CI 1.366–6.714; $P = 0.006$) were significant predictors. The multivariate Fine-Gray competing risks analysis demonstrated that the prognostic factors were decreased BMI (SHR 0.806; 95% CI 0.659–0.987; $P = 0.037$), decreased %FVC (SHR 0.952; 95% CI 0.920–0.985; $P = 0.005$) and prednisolone use (SHR 0.228; 95% CI 0.072–0.727; $P = 0.012$) (Table 3).

Causes of death

The mortality rates associated with pneumonia and chronic deterioration in IPPFE with UIP were significantly higher than those in typical IPF during follow-up (Table 4).

Antifibrotic treatments for patients with IPPFE with UIP

A total of 125 patients administered antifibrotic drugs for over 6 months (34 with IPPFE with UIP and 91 with typical IPF). Some 26 of 34 patients with IPPFE with UIP and 53 of 91 patients with typical IPF were treated with pirfenidone, and the remaining patients received nintedanib. In terms of baseline clinical differences between patients with IPPFE

with UIP and patients with typical IPF who were treated with antifibrotic agents, there were no differences in baseline disease severity (GAP staging) or in radiological scores between 2 groups. However, values of %FVC, serum KL-6 and BMI in patients with IPPFE with UIP were significantly lower than those in patients with typical IPF, whereas the level of $PaCO_2$ was significantly higher in patients with IPPFE with UIP. There were no differences between the groups in reduced FVC value 6 months before treatment with antifibrotic agents (IPPFE with UIP vs. typical IPF = −0.21 ± 0.16 L vs −0.20 ± 0.19 L; $P = 0.95$). However, more significantly reduced FVC values 6 months after treatment with antifibrotic agents were found in patients with IPPFE with UIP than in those with typical IPF (IPPFE with UIP vs. typical IPF = −0.15 ± 0.17 L vs −0.004 ± 0.18 L; $P = 0.0002$) (Figure 2). There was no difference in comparative efficacy between pirfenidone and nintedanib in patients with IPPFE with UIP and those with typical IPF (rate of disease progression in IPPFE with UIP: pirfenidone vs. nintedanib 35.3% vs. 2.9%, respectively; $P = 0.12$; typical IPF: pirfenidone vs. nintedanib 5.5% vs. 6.6%, respectively; $P = 0.52$). The LMM analysis showed that the decline in the slope of %FVC during follow-up was significantly different between the 2 groups ($P = 0.0003$) (Figure 3A). Moreover, patients with IPPFE with UIP during follow-up who were treated with antifibrotic agents had a significantly lower baseline %FVC and a more rapid decline in FVC compared with that in those with typical IPF treated with antifibrotic agents ($P = 0.0002$) (Figure 3B). Additionally, a predictive factor for poor response to antifibrotic agents was the presence of IPPFE with UIP in the multivariate logistic regression analysis (Table 5).

Discussion

This is the first study to compare the efficacy of antifibrotic agents such as pirfenidone and nintedanib between IPPFE with UIP and typical IPF in real-world clinical practice.

IPPFE is a rare condition characterised by predominantly upper lobe pleural and subjacent parenchymal fibrosis according to the 2013 American Thoracic Society/European Respiratory Society classification of idiopathic interstitial pneumonias [1]. These distinctive conditions had first been reported as Amitani's disease or idiopathic pulmonary upper-lobe fibrosis (IPUF) by Amitani et al. in 1992 [21], as well as initial case series in the English literature by Frankel et al., which was described as an idiopathic pleuroparenchymal fibroelastotic syndrome with unique histological findings [22]. The prognosis of IPPFE tends to be poor. Watanabe et al. [23] had reported that patients with IPUF were shown to have a histopathological tendency for a relatively rapid progression and a poor prognosis, with a survival time of 1.8 to 12.2 years after their initial visits. IPPFE has been increasingly reported in association with a variety of ILDs in the lower lobes, including UIP [3, 4]. Nakatani et al. [4] had reported 12 cases of 205 patients with ILD who were identified as having IPPFE, of who 11 had ILD in the lower lobes (definite UIP, 5; possible UIP, 4; non-specific interstitial pneumonia, 1; unclassifiable, 1).

Histopathologically, biopsied lung specimens can show mild changes in PPFE or other patterns such as UIP in patients with PPFE [1]. Raghu et al. [24] had reported that some patients with IPPFE with a UIP pattern should be regarded as having IPF after a multidisciplinary discussion based on the 2018 IPF guidelines. However, considering that the clinical characteristics, such as the proportion of women, never-smokers, lower BMI and pneumothorax complications were significantly higher in patients with IPPFE with UIP than in those with typical IPF in the present study, IPPFE with UIP may be treated as a disease entity distinct from typical IPF. As reported by several researchers, patients with IPPFE with UIP had a poor prognosis compared with those with IPF [6-8]. Recently, Oda et al. [6] had described that survival time tended to be shorter in patients with PPFE with UIP (MST 31.5 months vs. 82.1 months). More recently, Kato et al. [7] had reported that survival time for

patients with IPPFE with UIP was significantly shorter than that for patients without UIP (MST 12 months vs. 62 months). We have already reported that compared with patients with typical IPF, poorer survival was noted in those with atypical IPF who had imaging features on chest HRCT, such as PPFE-like lesions or multiple thick-walled large cysts, in addition to honeycombing in the bilateral lower lobe predominance [20]. Additionally, in the present study, patients with IPPFE with UIP have a poorer prognosis than those with typical IPF (MST 34.0 months vs. 62.3 months). In patients with IPPFE with UIP, decreased BMI and %FVC were associated with a significantly worse survival on both univariable and multivariable Fine-Gray competing risks analysis considered acute exacerbation as a competing risk. These results support that survival in patients with IPPFE with UIP is associated with chronic deterioration. Moreover, a significantly faster decline in FVC was observed in patients with IPPFE with UIP after antifibrotic treatments, whereas the FVC decline was suppressed in patients with typical IPF after 6 months of receiving antifibrotic agents. Notably, LMM analysis demonstrated that a decline was significantly steeper in %FVC during a follow-up in patients with IPPFE with UIP treated with antifibrotic agents compared with those with typical IPF. Although pirfenidone was described by Sato et al. as potentially effective in a case report [25], our data suggest that the efficacy of antifibrotic treatments might be limited for IPPFE with UIP. Also, we suppose that higher incidence of pneumothorax complication in IPPFE with UIP can affect a faster FVC decline in addition to be intractable to antifibrotic treatments.

Distler, et al. [13] had reported the potential efficacy of nintedanib in patients with systemic sclerosis-associated ILD. More recently, the annual rate of decline in FVC was significantly lower among patients with non-IPF PF-ILD who received nintedanib than among those who received placebo in the INBUILD trial [14]. However, there is no evidence suggesting efficacy of antifibrotic treatment, including nintedanib and pirfenidone, for

IPPFE with UIP. In our study, the multivariate logistic regression analysis showed that the presence of IPPFE with UIP was a predictive factor for poor response to antifibrotic agents.

There are some limitations in our study. First, this was a retrospective study with a relatively small sample size. Therefore, our results might not be representative of the entire IPPFE with UIP population and should be confirmed in a larger cohort. Second, most of the patients with IPPFE with UIP could not be diagnosed histologically. However, surgical lung biopsy can trigger pneumothorax [26]. Furthermore, patients with a clinical diagnosis of PPFE had similar characteristics to those of histopathologically confirmed PPFE, as described by Enomoto et al. [27]. Therefore, we diagnosed IPPFE with UIP primarily according to radiologic criteria in this study. Third, it is difficult to differentiate between PPFE lesions and apical cap on chest HRCT. However, we believe that the presence of traction bronchiectasis and volume loss in the upper lobes is useful in differentiating these conditions. Finally, this study did not investigate the comparative efficacy of nintedanib and pirfenidone. Further large-scale studies are needed to explore this issue.

In conclusion, this study demonstrated that the efficacy of antifibrotic agents was limited in patients with IPPFE with UIP. Thus, IPPFE with UIP remains a fatal and progressive disease. Future studies are required, including prospective analyses of the efficacy of antifibrotic agents for patients with IPPFE with UIP.

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Figure Legends

Figure 1: The Kaplan-Meier survival curve in patients with typical IPF (solid line) (n = 195) and IPPFE with UIP (dashed line) (n = 64). (MST 62.3 months vs. 34.0 months, $P < 0.0001$).

Figure 2: Change in FVC before and after treatments with antifibrotic agents (IPPFE with UIP/Typical IPF = 32/58 cases).

There were no differences between the groups in FVC value 6 months before treatment with antifibrotic agents (IPPFE with UIP vs. typical IPF = −0.21 ± 0.16 L vs −0.20 ± 0.19 L; $P = 0.95$). However, more significantly reduced FVC values 6 months after treatment with antifibrotic agents were found in patients with IPPFE with UIP than in those with typical IPF (IPPFE with UIP vs. typical IPF = −0.15 ± 0.17 L vs −0.004 ± 0.18 L; $P = 0.0002$) (IPPFE with UIP: before 6 months vs. at the onset of treatments vs. after 6 months = 1.96 ± 0.66 L vs. 1.75 ± 0.64 L vs. 1.61 ± 0.61 L; $P < 0.0001$, $P < 0.0001$. typical IPF: before 6 months vs. at the onset of treatments vs. after 6 months = 2.25 ± 0.61 L vs. 2.05 ± 0.62 L vs. 2.05 ± 0.64 L, $P < 0.0001$, $P = 1.00$. Two-way repeated measure ANOVA with Bonferroni's multiple comparison).

Figure 3: Change in %FVC during follow up.

A) LMM analysis showed that the decline in the slope of %FVC during follow-up was significantly different between the 2 groups ($P = 0.0003$).
   Patients with typical IPF had a significantly higher baseline %FVC than those with IPPFE with UIP (77.4±18.7% vs. 63.9±15.7%, $P < 0.0001$).
B) Patients with IPPFE with UIP during follow up who were treated with antifibrotic agents had a significantly lower baseline %FVC and a more rapid decline in FVC compared with that in those with typical IPF treated with antifibrotic agents ($P = 0.0002$). Patients with typical IPF had a significantly higher baseline %FVC than those with IPPFE with UIP

(73.8±17.8% vs. 64.6±14.9%, $P = 0.003$).

Table 1. Demographic and baseline patient characteristics

Variable	**IPPFE with UIP (n = 64)**	**Typical IPF (n = 195)**	***P* value**
Sex, male/female	43/21	162/33	0.012
Age (yrs)	72.7±7.1	72.7±7.1	0.972
BMI (kg/m^2)	17.6±2.9	22.7±3.5	< 0.0001
Smoking history, Current/Former/Never	6/34/24	26/136/33	0.003
mMRC score, 0/I/II/III/IV	5/25/23/6/5	22/61/60/40/12	0.248
Severity of IPF (GAP stage: I/II/III)	28/24/12	99/68/28	0.555
Primary lung cancer (%)	0 (0%)	12 (6.2%)	0.042
Pneumothorax	20 (31.3%)	3 (1.5%)	< 0.0001
Acute exacerbation	19 (29.7%)	64 (32.8%)	0.757
Nintedanib	8 (12.5%)	38 (19.4%)	0.06
Pirfenidone	26 (40.6%)	53 (27.1%)	0.06
Histological UIP diagnosis (%)	10 (15.6%)	42 (21.5%)	0.370
Histological PPFE diagnosis (%)	10 (15.6%)	0 (0%)	< 0.0001
Observation period (months)	30.7±19.7	38.9±34.2	0.07

Data are presented as mean ± SD. BMI: body mass index, mMRC: modified Medical Research Council, GAP: Gender, age, and lung physiology, IPPFE: idiopathic pleuroparenchymal fibroelastosis, UIP: usual interstitial pneumonia, IPF: idiopathic pulmonary fibrosis

Table 2. Comparison of pulmonary function tests, serum markers, and chest CT findings between patients with IPPFE with UIP and typical IPF

Variable	**IPPFE with UIP (n = 64)**	**Typical IPF (n = 195)**	***P* value**
FVC % predicted	66.7 ± 16.9	78.5 ± 18.8	0.0001
FEV_1 % predicted	86.1 ± 24.9	97.2 ± 47.3	0.073
TLC % predicted	74.4 ± 15.7	77.9 ± 16.6	0.153
RV % predicted	90.6 ± 27.3	82.9 ± 21.9	0.026
DLco % predicted	66.2 ± 25.2	60.3 ± 20.4	0.072
CPI	41.5 ± 18.2	43.0 ± 21.7	0.621
KL-6, U/ml	823 ± 485	1123 ± 743	0.003
SP-D, ng/ml	283 ± 162	293 ± 234	0.742
PaO_2, Torr	84.1 ± 13.4	80.8 ± 13.1	0.087
$PaCO_2$, Torr	43.6 ± 5.8	39.4 ± 3.9	< 0.0001
Fibrosis score	1.7 ± 0.7	1.6 ± 0.6	0.953
Extent of BE	1.8 ± 0.8	1.6 ± 0.7	0.106
CT pattern: UIP/Possible UIP/Inconsistent with UIP	—	169/22/4	—

Data are presented as mean ± SD. FVC: forced vital capacity, FEV_1: FEV1: forced expiratory volume in 1 s, TLC: total lung capacity, RV: residual volume, DLco: diffusing capacity of the lung for carbon monoxide, CPI: composite physiologic index, KL-6: Kreb von den Lungen-6, SP-D: surfactant protein D, PaO_2: partial pressure of oxygen in arterial blood, $PaCO_2$: partial

pressure of carbon dioxide in arterial blood, BE: bronchiectasis, CT: computed tomography, IPPFE: idiopathic pleuroparenchymal fibroelastosis, UIP: usual interstitial pneumonia, IPF: idiopathic pulmonary fibrosis

Table 3. Fine-Gray univariable and multivariable competing risks models demonstrating prognostic factors for survival in patients with IPPFE with UIP (n = 64)

	Univariate		Multivariate	
Variable	**SHR (95% CI)**	***P* value**	**SHR (95% CI)**	***P* value**
Age	1.000 (0.945-1.058)	0.991		
Female sex	1.659 (0.753-3.651)	0.209		
BMI	0.757 (0.632-0.907)	0.003	0.806 (0.659-0.987)	0.037
Ever-smokers	0.754 (0.350-1.625)	0.472		
mMRC score	0.996 (0.687-1.445)	0.985		
SpO_2 < 90%	1.284 (0.601-2.742)	0.518		
FVC % predicted	0.955 (0.929-0.982)	0.001	0.971 (0.946-0.995)	0.019
Prednisolne use	0.502 (0.223-1.132)	0.097	0.228 (0.072-0.727)	0.012
Pneumothorax	3.029 (1.366-6.714)	0.006		

BMI: body mass index, IPPFE: idiopathic pleuroparenchymal fibroelastosis, UIP: usual interstitial pneumonia, mMRC: modified Medical Research Council, SpO_2: peripheral capillary oxygen saturation, FVC: forced vital capacity, SHR: subdistribution hazard ratio, CI: confidence interval

Table 4. Comparison of causes of death between IPPFE with UIP and typical IPF.

Variable	**IPPFE with UIP (n = 64)**	**Typical IPF (n = 195)**	***P* value**
Lung cancer	0 (0)	6 (3.0)	0.341
Pneumonia	12 (18.7)	16 (8.2)	0.034
Acute exacerbation	9 (14.0)	32 (16.4)	0.843
Chronic deterioration	20 (31.2)	15 (7.6)	< 0.0001
Others	3 (4.6)	11 (5.6)	1.000
Unknown	4 (6.2)	2 (1.0)	0.034

IPPFE: idiopathic pleuroparenchymal fibroelastosis, UIP: usual interstitial pneumonia, IPF: idiopathic pulmonary fibrosis

Table 5. Multivariate logistic regression analysis of predictive factors for efficacy of antifibrotic agents (n = 125)

Variable	**OR**	**95% CI**	***P* value**
Age	1.013	0.948-1.086	0.699
Male sex	0.799	0.268-2.587	0.697
BMI	1.079	0.918-1.277	0.354
GAP stage	1.644	0.845-3.218	0.142
IPPFE with UIP	7.096	2.018-28.270	0.002

BMI: body mass index, GAP: Gender, age, and lung physiology, IPPFE: idiopathic pleuroparenchymal fibroelastosis, UIP: usual interstitial pneumonia, OR: odds ratio, CI: confidence interval

Figure 1

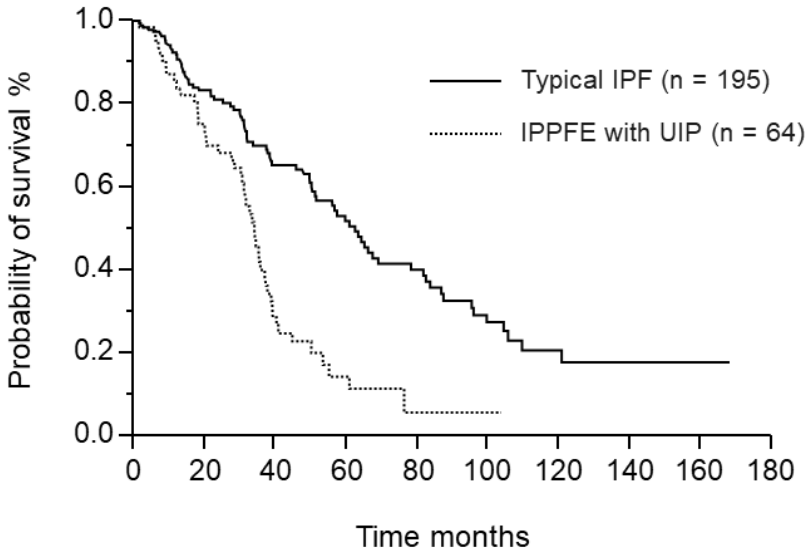

Probability of survival %
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
160
180
Time months
Typical IPF (n = 195)
IPPFE with UIP (n = 64)

Figure 2

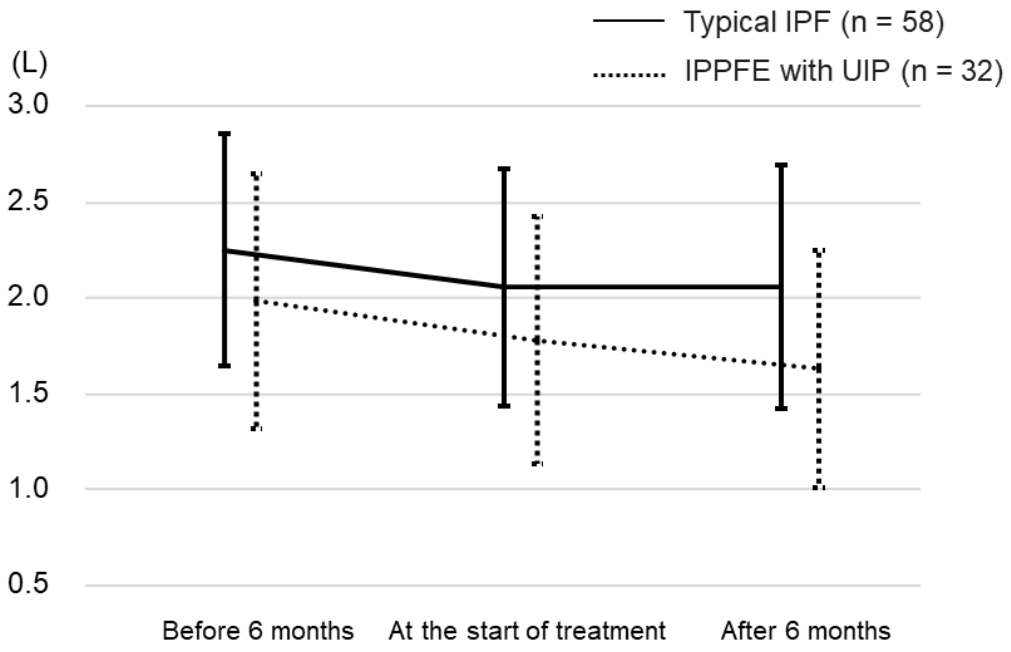
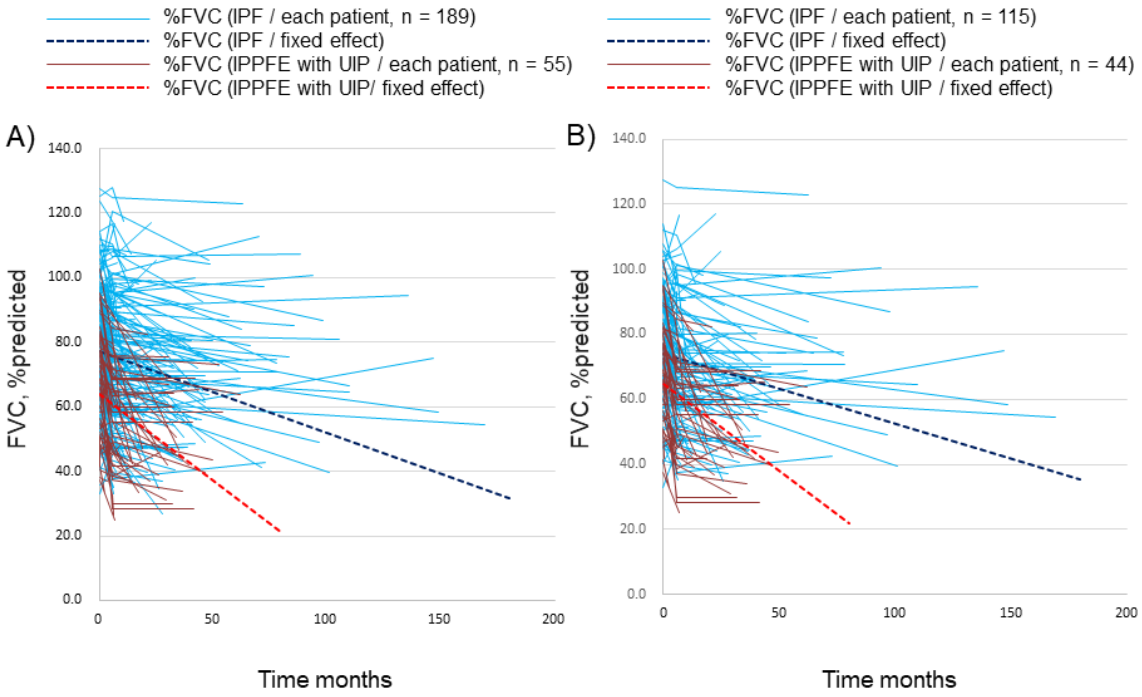

Typical IPF (n = 58)
IPPFE with UIP (n = 32)
(L)
3.0
2.5
2.0
1.5
1.0
0.5
Before 6 months
At the start of treatment
After 6 months

Figure 3


%FVC (IPF / each patient, n = 189)
%FVC (IPF / fixed effect)
%FVC (IPPFE with UIP / each patient, n = 55)
%FVC (IPPFE with UIP/ fixed effect)
A)
FVC, %predicted
Time months
%FVC (IPF / each patient, n = 115)
%FVC (IPF / fixed effect)
%FVC (IPPFE with UIP / each patient, n = 44)
%FVC (IPPFE with UIP / fixed effect)
B)
FVC, %predicted
Time months