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Medication persistence rates and predictive factors for discontinuation of antifibrotic agents in patients with idiopathic pulmonary fibrosis: a real-world observational study

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Abstract

Background: In patients with idiopathic pulmonary fibrosis (IPF), continuing treatment with antifibrotic agents is crucial to decrease the reduction of forced vital capacity and mortality rate. However, predictive factors for the discontinuation of antifibrotic agents are unknown. This study aims to investigate the clinical characteristics and predictive factors for the discontinuation of antifibrotic agents in patients with IPF.

Methods: This was a double-center retrospective study that enrolled patients with IPF treated with pirfenidone or nintedanib between 2009 and 2017. We compared clinical parameters between the medication-continuing group and the discontinued group. The predictive factors were determined using Cox proportional hazards analyses.

Results: A total of 66 subjects were included: 43 received pirfenidone and 23 received nintedanib. At 1 year, 23 of 66 patients had discontinued due to adverse events ($n = 12$), disease progression ($n = 9$), or death ($n = 2$). The characteristics of the discontinuation group were poor performance status (PS) and delay from diagnosis to treatment. In the receiver operating characteristic (ROC) analysis associated with the discontinuation of antifibrotic agents, PS was the highest area under the ROC curve (AUC) value (cut-off value, 2; AUC, 0.83; specificity, 63%; sensitivity, 87%). This finding was consistent even when analyzing, except for examples of death and adjusting for the type of antifibrotic agent. The treatment persistence rate by PS was PS 0–1 = 90%, PS 2 = 65%, and PS 3 = 19%. Analysis of the relationship between PS and administration period of antifibrotic agents revealed that delays from diagnosis to treatment led to worsening of dyspnea, a decline in lung function, and deterioration of PS.

Conclusions: PS may be informative for predicting discontinuation of medication. Our data reinforced the importance of early initiation of antifibrotic treatment, and we suggest PS should be used as a guide for starting antifibrotic agents in everyday practice.

The reviews of this paper are available via the supplementary material section.

Keywords: antifibrotic agents, drug discontinuation, early treatment, IPF, performance status

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Introduction

Idiopathic pulmonary fibrosis (IPF) is characterized by chronic, progressive, fibrosing interstitial pneumonia of unknown cause, ultimately leading to respiratory failure and death within 2–5 years of diagnosis.[1] Until recently, there had been no pharmaceutical therapy for IPF. Now, two antifibrotic agents, pirfenidone and nintedanib, are recommended in international treatment guidelines.[2] Randomized clinical trials for pirfenidone and

nintedanib both showed a reduction in the annual rate of decline of lung function, with acceptable adverse events and drug tolerability.[3–5] Moreover, continuing treatment with pirfenidone is crucial to decrease the reduction of forced vital capacity (FVC) and mortality rate, even in patients with progressive IPF despite treatment with pirfenidone.[6] Patients receiving antifibrotic agents had better survival than those not on antifibrotic agents, independent of underlying disease severity.[7] The effect of pirfenidone on survival was remarkable if one takes into account that patients with comorbidities and severe disease were included in the cohort.[8]

Discontinuation rates of antifibrotic agents were reasonably low in the randomized controlled trials (RCTs): 14.4% in the pirfenidone treatment arm of ASCEND,[3] and 24.5% in the nintedanib treatment arm of INPULSIS).[5] However, a well-known problem in real-world clinical practice is the gap between RCT data and the individual patient features representing the real world of medicine. In practice, many subjects with IPF have problems such as comorbidities or baseline characteristics that exclude them from RCTs. For example, patients with severely impaired pulmonary function, such as FVC predicted to be less than 50% and diffusing capacity of the lung for carbon monoxide (DLco) predicted to be less than 30%, were excluded from the ASCEND and INPULSIS. Several investigators have reported the tolerability of antifibrotic agents in real-world clinical practice.[9–15] The discontinuation rate of antifibrotic agents in real-world data were similar to, or somewhat higher than, those in RCTs. These findings could allow physicians to prescribe antifibrotic agents for IPF patients with severely impaired pulmonary function and comorbidities.

However, in the real-world, predictive factors for the discontinuation of antifibrotic agents have not been clearly established. Herein, therefore, we investigated the clinical characteristics and predictive factors at the start of administration of antifibrotic agents for the discontinuation of antifibrotic agents in patients with IPF.

Material and methods

Study patients

A total of 68 patients with IPF who had been treated with pirfenidone or nintedanib in the Yamaguchi University Hospital and the National Hospital Organization Yamaguchi-Ube Medical Center from 2009 to 2017 were enrolled in the study. All medical records were reviewed retrospectively. As two patients were lost to follow up, 66 patients were finally evaluated. All patients met the 2011 IPF consensus criteria of the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society (JRS)/Latin American Thoracic Association.[1]

The patients were divided into two groups according to whether they had continued antifibrotic agents for 1 year: a continuation group and discontinuation group. This study was approved by the Ethics Committee of Yamaguchi University School of Medicine (approval number H29-226). Requirement for informed consent was waived by the ethics committee because no invasive procedure, intervention, or human samples were used in this retrospective study and anonymity was secured. This was compliant with the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects,[16] which do not require informed consent from patients enrolled in studies not utilizing human biological specimens. However, we provided opportunities to the subjects to opt out of the study by announcing the study information on the bulletin boards in the hospital and the hospital website.

Study assessments

Medical records were used to collect data pertaining to baseline demographic information pulmonary function test, high-resolution computed tomography (HRCT) pattern, prescribing information, and the presence and severity of comorbidities measured with the Charlson comorbidities index.[17] We evaluated adverse events and their severity at the time of the visit. The severity of adverse events was assessed by grading according to the Common Terminology Criteria for Adverse Events (CTCAE).

Two radiologists with expertise in chest radiology reviewed all HRCT images to evaluate HRCT criteria for the usual interstitial pneumonia pattern. Disease severity was assessed using the gender, age and physiology (GAP) staging system and JRS severity grading,[18,19] which are based on the arterial partial pressure of oxygen at rest and minimum arterial blood hemoglobin saturation during a 6-min walk test. Eastern Cooperative

Oncology Group (ECOG) performance status (PS) and the modified Medical Research Council (mMRC) grades were assessed by the study physicians at the time of the visit. The ECOG PS is a scale used to assess how a patient's disease is progressing, and how the disease affects the daily living abilities of the patient.[20] It is comprised of five statements (0 = 'normal activity,' 1 = 'some symptoms, but no bed rest during daytime,' 2 = 'bed rest for less than 50% of daytime,' 3 = 'bed rest for more than 50% of daytime,' 4 = 'unable to get out of bed'), and poor PS was defined as ECOG PS 2 or more. The mMRC scale comprises five statements that describe the extent of respiratory disability, from no disability to almost complete incapacity.[21] We also evaluated whether the patients met the inclusion criteria of RCTs.[3,5]

Statistical analysis

Although no *a priori* sample size calculation was conducted, a convenience sample of 60 subjects was selected based on previous studies.[22,23] The characteristics of the continuation group and discontinuation group were compared using Mann–Whitney U and chi-square tests. The discontinuation rates of antifibrotic agents were calculated using the Kaplan–Meier method, and differences were compared by the log-rank test. To assess the predictive factors at the start of administration of antifibrotic agents for the discontinuation of antifibrotic agents, an univariate analysis was performed using the Cox proportional hazard model. A multivariate Cox proportional hazard analysis was not performed, because our sample size was too small to obtain statistical power by multivariate analysis. Using a receiver operating characteristic (ROC) curve, we determined the cutoff points for identifying the predictive factors for discontinuation. The accuracy of each predictive factor was assessed by the area under the ROC curve (AUC). The AUC results were considered excellent for AUC values between 0.9 and 1, good for AUC values between 0.8 and 0.9, fair for AUC values between 0.7 and 0.8, poor for AUC values between 0.6 and 0.7, and failed for AUC values between 0.5 and 0.6. The Spearman's rank-order correlation coefficient was used to determine the correlation between two variables. The decline in %FVC between groups was compared using Mann–Whitney U tests; $p < 0.05$ was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html; Kanda, 2012), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0).[24]

Results

Patient characteristics

Concerning the types of antifibrotic agents used, 43 patients received pirfenidone and 23 patients were prescribed nintedanib. At 1 year, 23 of 66 patients (35%) had discontinued their antifibrotic agents. The reasons for discontinuation were adverse events ($n = 12$), disease progression ($n = 9$), and death ($n = 2$). The characteristics of the patient comparison between the antifibrotic agents continuation and discontinuation groups are shown in Table 1. The administration period of antifibrotic agents from the IPF diagnosis was longer, and PS, mMRC scale, GAP staging system, and FVC % predicted were more severe in the discontinuation group. There were no significant differences between the two groups with regard to the age, body surface area, body mass index, JRS severity grade, kind of antifibrotic agents, comorbidities, preceding home oxygen therapy and prednisone. There were no patients undergoing pulmonary rehabilitation program.

Predictive factors of antifibrotic agents discontinuation

The results concerning the predictive factors at the start of administration of antifibrotic agents for the discontinuation of antifibrotic agent in patients with IPF by univariate analyses are shown in Table 2. A univariate analysis identified a total of five statistically significant predictors: period of administration of antifibrotic agents from IPF diagnosis, PS, mMRC scale, GAP staging system, and %FVC. Excluding death, these results were consistent with the analysis (Table 3). The accuracy of each predictive factor for detecting the discontinuation of antifibrotic agents in patients with IPF is shown in Table 4. PS had the best accuracy, and was the only factor that had a good correlation. AUC for the PS to identify the drug discontinuation was 0.83, with a cut-off of 2, and sensitivity and specificity of 87.0% and 62.8%, respectively (Figure 1). The antifibrotic agents' persistence rate by PS was PS 0–1 = 90%, PS 2 = 65%, PS 3 = 19% (Figure 2). Figure 3 shows the continuation rate and reasons for discontinuation by PS. PS was

Table 1. Patient characteristics comparison between antifibrotic agents continuation and discontinuation group.

Characteristics	All *n* = 66	Continuation group *n* = 43 (65%)	Discontinuation group *n* = 23 (35%)	*p* value
Age at administration of antifibrotic agents (year)	72 (67–74)	70 (65–74)	73 (69–75)	0.093
Male	63 (95.5)	41 (95.3)	22 (95.7)	0.955
Smoking status (never/ex/current)	4/62/0	3/40/0	1/22/0	0.670
Administration period of antifibrotic agents from IPF diagnosis (year)	0.6 (0.1–2.2)	0.4 (0.1–1.4)	2.1 (0.7–4.2)	0.003
Body surface area (m^2)	1.71 (1.60–1.77)	1.71 (1.60–1.79)	1.72 (1.58–1.74)	0.497
Body mass index	23.3 (22.0–24.9)	23.5 (22.3–25.1)	22.8 (20.9–24.0)	0.160
HRCT pattern (Definite UIP/Possible UIP/Inconsistent with UIP)	57/7/2	38/4/1	19/3/1	0.591
Surgical lung biopsy	21 (31.8)	12 (27.9)	9 (39.1)	0.454
Performance status (0/1/2/3/4)	4/26/20/16/0	4/23/13/3/0	0/3/7/13/0	<0.0001
mMRC scale (0/1/2/3/4)	2/11/26/20/7	2/8/20/13/0	0/3/6/7/7	0.0048
FVC (% predicted)	64.7 (50.8–76.8)	70.1 (59.4–78.3)	52.1 (45.5–66.2)	0.0015
FEV_1/FVC (%)	88.1 (83.5–92.2)	86.9 (83.3–90.9)	91.4 (85.1–95.8)	0.052
DL_{CO} (% predicted)	44.3 (34.6–61.7)	45.8 (34.9–74.4)	38.8 (31.4–51.7)	0.083
PaO2 at rest (Torr)	75.1 (66.4–84.2)	76.0 (71.1–84.9)	75.0 (64.5–81.1)	0.443
Distance in 6MWT (m)	450 (369–501)	451 (403–512)	405 (366–468)	0.183
JRS severity grade of IP (I/II/III/IV)	19/0/30/17	13/0/21/9	6/0/9/8	0.358
GAP staging system (I/II/III)	17/31/18	15/21/7	2/10/11	0.0024
Match the inclusion criteria for RCTs	33 (50.0)	22 (51.1)	11 (47.8)	0.796
Preceding Home oxygen therapy	26 (39.4)	18 (41.9)	8 (34.8)	0.575
Preceding Prednisone	6 (9.1)	4 (9.3)	2 (9.5)	0.935
Pulmonary hypertension	21 (31.8)	11 (25.6)	10 (43.5)	0.137
COPD	9 (13.6)	5 (11.6)	4 (17.4)	0.516
Lung cancer	5 (7.6)	4 (9.3)	1 (4.3)	0.469
GERD	32 (48.5)	20 (46.5)	12 (52.2)	0.661
Chronic heart failure	3 (4.5)	2 (4.7)	1 (4.3)	0.955
Coronary artery disease	7 (10.6)	5 (11.6)	2 (8.7)	0.712
DM	22 (33.3)	13 (30.2)	9 (39.1)	0.465
Malignancy	12 (18.2)	9 (20.9)	3 (13.0)	0.429

(Continued)

Table 1. (Continued)

Characteristics	All *n* = 66	Continuation group *n* = 43 (65%)	Discontinuation group *n* = 23 (35%)	*p* value
Depression	4 (6.1)	3 (7.0)	1 (4.3)	0.670
Charlson comorbidity index	1.5 (1–3)	2 (1–3)	1 (1–2.5)	0.734
Antifibrotic agents (Pirfenidone/Nintedanib)	43/23	29/14	14/9	0.593
Antifibrotic agents dose reduction during the course of 1 year	38 (55.6)	24 (55.8)	14 (60.9)	0.692

Data are presented as *n* (%) or median (interquartile range).
6MWT, 6-min walk test; COPD, Chronic obstructive pulmonary disease; DLco, diffusing capacity of the lung for carbon monoxide; DM, diabetes mellitus; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GAP, gender, age and physiology; GERD, gastroesophageal reflux disease; HRCT, high-resolution computed tomography; IP, interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; mMRC, modified Medical Research Council; PaO2, arterial partial pressure of oxygen; RCTs, randomized controlled trials; UIP, usual interstitial pneumonia.

significantly correlated with the %FVC ($\rho = 0.65$, $p < 0.01$, Figure 4). When patients were stratified by PS; good PS group (0–1) and poor PS group (2–3), the characteristics of the patient comparison are shown in Table 5. Compared with the good PS group, the poor PS group had a longer administration period of antifibrotic agents from the IPF diagnosis, severe mMRC scale, JRS severity grade, and GAP staging, and had lower pulmonary function. The proportion of patients with preceding home oxygen therapy, and prednisone in the poor PS group was higher than in the good PS group. There was no significant difference in the age, and the prevalence of patients with comorbidities showed no significant differences between the two groups, except for pulmonary hypertension.

Relationship between PS and administration period of antifibrotic agents

PS was significantly correlated with the administration period of the antifibrotic agents ($\rho = 0.38$, $p < 0.01$, Figure 5a). Furthermore, %FVC ($\rho = -0.26$, $p < 0.05$), mMRC ($\rho = 0.35$, $p < 0.01$), and GAP staging ($\rho = 0.30$, $p < 0.05$) showed significant correlations with the administration period of the antifibrotic agents (Figure 5b–d).

Antifibrotic agent efficacy and adverse events

Antifibrotic agent efficacy was evaluated in 51 patients who underwent spirometry 52 weeks after starting antifibrotic therapy. The median time from 52 weeks was 1 day, and the range was ±28 days. Changes in %FVC from baseline through week 52 in each group are shown in Figure 6. The patients in the continuation group showed a lower decline in lung function than those in discontinuation group (–1.7% *versus* –8.8%, $p = 0.033$). Changes in %FVC were significantly lower in the good PS group than in the poor PS group (–0.5% *versus* –6.8%, $p = 0.013$). Types and proportion of adverse events are summarized in Table 6. The common adverse events were nausea (54.5%), dyspepsia (59.1%), and anorexia (59.1%). The proportion of acute exacerbations was 9.1%. Although there were no significant differences in each adverse event, including all of the severity between the continuation and discontinuation group, the prevalence of moderate to severe anorexia (CTCAE grade ⩾ II) was higher in the discontinuation group than in the continuation group ($p = 0.018$).

Discussion

We revealed two important clinical issues. PS was an accurate predictive factor for the discontinuation of antifibrotic agents in patients with IPF. A delay from diagnosis to antifibrotic treatment appeared to lead to worsening of dyspnea, decline in lung function, and deterioration in PS, which may have contributed to the discontinuation of antifibrotic agents.

First, PS was an accurate predictive factor for the discontinuation of antifibrotic agents in patients with IPF. To the best of the authors' knowledge,

Table 2. Predictive factors for the discontinuation of antifibrotic agents in patients with IPF ($n = 66$).

Variables	Per unit for hazard ratio	Hazard ratio	95% CI	*p* value
Univariate Cox analysis				
Age at administration of antifibrotic agents, year	1-year	1.06	0.99–1.13	0.061
Gender (Male/Female)	Male	1.17	0.16–8.65	0.81
Positive Smoking history	Positive	1.62	0.22–12.03	0.637
Administration period of antifibrotic agents from IPF diagnosis, year	**1-year**	**1.27**	**1.09–1.49**	**0.0026**
Body surface area	0.1 m^2	0.33	0.02–6.42	0.465
Body mass index	0.1	0.88	0.74–1.04	0.136
Performance status	**1-score**	**3.61**	**2.04–6.40**	**<0.0001**
mMRC scale	**1-grade**	**2.26**	**1.36–3.76**	**0.0017**
FVC % predicted	**1%**	**0.96**	**0.94–0.99**	**0.0021**
FEV_1/FVC	1%	0.99	0.99–1.00	0.641
DL_{CO} % predicted	1%	0.97	0.95–1.00	0.065
PaO2 at rest	1 Torr	0.99	0.96–1.02	0.496
Distance in 6MWT	10 m	0.99	0.99–1.00	0.146
JRS severity grade of IP	1-grade	1.11	0.77–1.62	0.574
GAP staging system	**1-stage**	**2.50**	**1.35–4.64**	**0.0036**
Match the inclusion criteria for RCTs	Positive	1.10	0.48–2.48	0.828
Preceding Home oxygen therapy	Positive	0.81	0.34–1.91	0.629
antifibrotic agents (Pirfenidone/Nintedanib)	Pirfenidone	0.77	0.33–1.79	0.546
Preceding Prednisone	Positive	0.93	0.22–3.98	0.923
Pulmonary hypertension	Positive	2.05	0.90–4.68	0.089
COPD	Positive	1.44	0.49–4.24	0.505
Lung cancer	Positive	0.53	0.07–3.94	0.536
GERD	Positive	1.17	0.52–2.66	0.701
Chronic heart failure	Positive	1.15	0.16–8.55	0.891
Coronary artery disease	Positive	0.89	0.21–3.81	0.878
DM	Positive	1.32	0.57–3.05	0.518
Malignancy	Positive	0.65	0.19–2.19	0.486
Depression	Positive	0.66	0.09–4.90	0.685
Charlson comorbidity index	1-point	1.05	0.87–1.26	0.597

6MWT, 6-min walk test; COPD, chronic obstructive pulmonary disease; DLco, diffusing capacity of the lung for carbon monoxide; DM, diabetes mellitus; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GAP, gender, age and physiology; GERD, gastroesophageal reflux disease; IP, interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; mMRC, modified Medical Research Council; PaO2, arterial partial pressure of oxygen; RCTs, randomized controlled trials; UIP, usual interstitial pneumonia.

Table 3. Predictive factors for the discontinuation of antifibrotic agents in patients with IPF excluding fatal cases ($n = 64$).

Variables	Per unit for hazard ratio	Hazard ratio	95% CI	*p* value
Univariate Cox analysis				
Age at administration of antifibrotic agents, year	1-year	1.06	0.99–1.13	0.106
Gender (Male/Female)	Male	1.09	0.15–8.13	0.932
Positive smoking history	Positive	1.51	0.20–11.28	0.686
Administration period of antifibrotic agents from IPF diagnosis, year	**1-year**	**1.28**	**1.09–1.50**	**0.0029**
Body surface area	0.1 m^2	0.54	0.02–12.19	0.700
Body mass index	0.1	0.91	0.76–1.08	0.282
Performance status	**1-score**	**3.48**	**1.93–6.25**	**<0.0001**
mMRC scale	**1-grade**	**2.06**	**1.23–3.45**	**0.0062**
FVC % predicted	**1%**	**0.96**	**0.94–0.99**	**0.0077**
FEV_1/FVC	1%	1.00	0.99–1.00	0.655
DL_{CO} % predicted	1%	0.98	0.95–1.01	0.152
PaO2 at rest	1 Torr	0.99	0.96–1.03	0.555
Distance in 6MWT	10 m	1.00	0.99–1.00	0.146
JRS severity grade of IP	1-grade	1.08	0.73–1.59	0.715
GAP staging system	**1-stage**	**2.31**	**1.23–4.37**	**0.0097**
Match the inclusion criteria for RCTs	Positive	0.94	0.40–2.23	0.896
Preceding Home oxygen therapy	Positive	0.64	0.25–1.64	0.348
antifibrotic agents (Pirfenidone/Nintedanib)	Pirfenidone	0.77	0.32–1.85	0.555
Preceding Prednisone	Positive	0.59	0.08–4.41	0.608
Pulmonary hypertension	Positive	1.96	0.82–4.66	0.128
COPD	Positive	1.32	0.39–4.47	0.660
Lung cancer	Positive	0.58	0.08–4.29	0.590
GERD	Positive	1.02	0.43–2.40	0.967
Chronic heart failure	Positive	0.00	0.00–Inf	0.998
Coronary artery disease	Positive	0.47	0.06–3.50	0.461
DM	Positive	1.49	0.63–3.55	0.363
Malignancy	Positive	0.71	0.21–2.40	0.579
Depression	Positive	0.71	0.10–5.31	0.740
Charlson comorbidity index	1-point	1.05	0.87–1.27	0.600

6MWT, 6-min walk test; COPD, chronic obstructive pulmonary disease; DLco, diffusing capacity of the lung for carbon monoxide; DM, diabetes mellitus; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GAP, gender, age and physiology; GERD, gastroesophageal reflux disease; IP, interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; mMRC, modified Medical Research Council; PaO2, arterial partial pressure of oxygen; RCTs, randomized controlled trials; UIP, usual interstitial pneumonia.

Table 4. Accuracy of the predictive factors for detecting the discontinuation of antifibrotic agents in patients with IPF.

Predictive factor	AUC	95% CI	Optimal cut-off value	Sensitivity (%)	Specificity (%)
Administration period from IPF diagnosis	0.731	0.606–0.856	1 year	82.6	55.8
Performance status	0.830	0.730–0.930	2	87.0	62.8
mMRC score	0.702	0.566–0.839	3	60.9	69.8
FVC % predicted	0.739	0.616–0.862	69%	87.0	53.5
GAP staging system	0.712	0.593–0.832	3	47.8	83.7

AUC, area under the ROC curve; FVC, forced vital capacity; GAP, gender, age and physiology; IPF, idiopathic pulmonary fibrosis; mMRC, modified Medical Research Council.

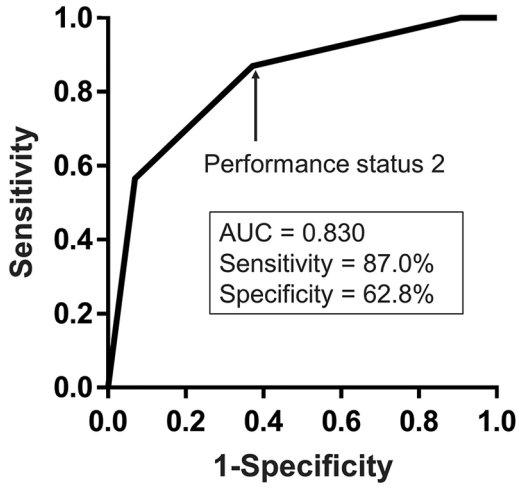

Figure 1. The area under the ROC curve for the performance status to identify the drug discontinuation.
ROC, receiver operating characteristic.

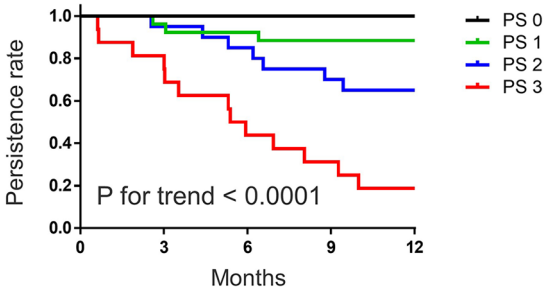

Figure 2. The persistence rate of antifibrotic agents' by the performance status.

one clinical study in patients with IPF has evaluated PS.[25] ECOG PS is a prognostic factor often used in patients with malignant tumors. It is a clinical factor frequently considered in decision-making for chemotherapy treatment in patients with cancer. Cancer patients with poor PS often have severe adverse events, and their disease progression during chemotherapy is less tolerable. Therefore, poor PS patients are subject to few clinical trials in cancer chemotherapy. Nintedanib is used as an antifibrotic agent treatment for IPF, and also as an anticancer agent for solid tumors. In a randomized phase II placebo-controlled trial of maintenance therapy using nintedanib after chemotherapy for relapsed ovarian cancer,[26] an ECOG PS of less than 2 was an inclusion criterion. Because PS and %FVC had a good correlation, PS could be used as a simple, robust surrogate marker for pulmonary function. On the other hand, according to the correlation chart, there are several cases of divergence. When PS and %FVC have deviated, it may be necessary to confirm the quality of spirometry, or search for causes such as comorbidities. Anyway, compared with spirometry, PS, which can be evaluated noninvasively and does not require any special examination, can be measured quickly and repeatedly in any medical facility. We suggest that evaluating PS could assist in the indication for antifibrotic agents in IPF patients in everyday clinical practice, and could be used as a clinical tool for prognostication.

Second, it was revealed that a delay from diagnosis to antifibrotic treatment can lead to a worsening of

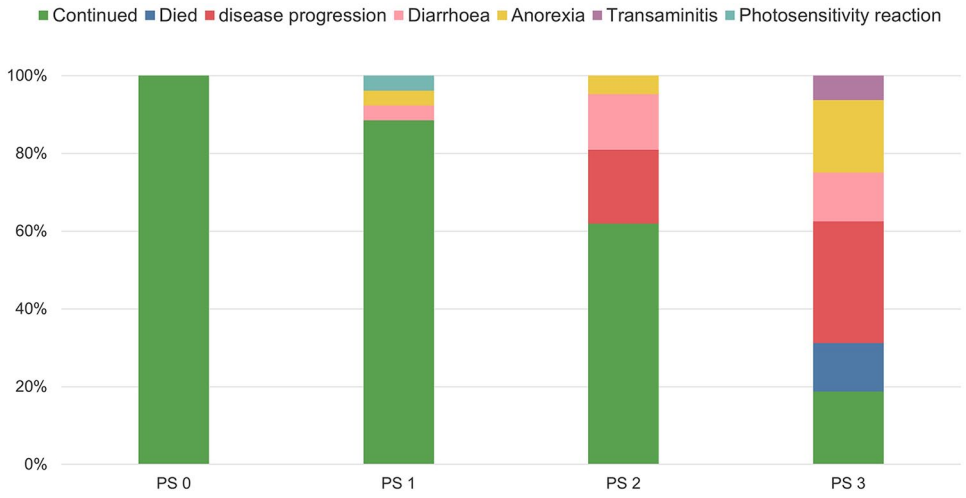

Figure 3. Continuation rate and discontinuation rate according to the reason for discontinuation by the performance status.

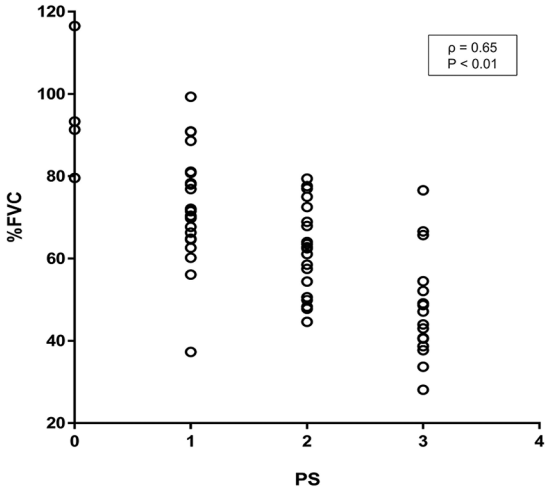

Figure 4. The correlation chart between PS and %FVC.
%FVC, Forced vital capacity; PS, performance status.

dyspnea, decline in lung function, and, therefore, deterioration of PS, which may contribute to the discontinuation of antifibrotic agents. This suggestion is supported by the correlation among the univariate statistically significant factors of antifibrotic agents. Our finding was compatible with previous studies showing that, in the clinical course of IPF, as time proceeds, dyspnea worsens, while lung function will decline.[27,28] On the other hand, PS might vary among individuals and be associated with multiple factors, such as comorbidities other than respiratory disease. Although we evaluated the influence of comorbidities, there were no significant differences between the good PS and poor PS groups. Moreover, comorbidities other than respiratory disease were not related to treatment discontinuation. Consequently, we speculated that delays from diagnosis to antifibrotic treatment could lead to disease progression accompanied by a worsened PS. In our study, patients with a poor PS were in more advanced stages of IPF.

It is interesting to note that, although there were no significant differences in each adverse event, including all of the severity between the continuation and discontinuation group, the prevalence of moderate-to-severe anorexia was higher in the discontinuation group. From the details of reasons given for discontinuation by the PS, discontinuation caused by disease progression increased with PS severity. In the postmarketing surveillance of pirfenidone, Ogura and colleagues showed that the discontinuation rates due to adverse events were comparable independently of disease severity, while the discontinuation rate due to disease progression increased with disease severity.[9] It may be reasonable that more patients with severe PS would discontinue treatment due to the combination of disease progression and the cumulative experience of adverse events related to antifibrotic agents.

In the present study, we demonstrated that the rate of discontinuing antifibrotic agents for at least 1 year was higher than that in RCTs. The rate of discontinuation for nintedanib in the

Table 5. Patient characteristics comparison between good performance status (0–1) group and poor performance status (2–3) group.

Characteristics	Good performance status group *n* = 30 (45%)	Poor performance status group *n* = 36 (55%)	*p* value
Age at administration of antifibrotic agents (year)	72 (66–74)	72 (68–74)	0.498
Male	29 (96.7)	34 (94.4)	0.666
Smoking status (never/ex/current)	1/29/0	3/33/0	0.397
Administration period of antifibrotic agents from IPF diagnosis (year)	0.2 (0.0–1.0)	1.1 (0.4–3.1)	0.004
Body surface area (m^2)	1.72 (1.63–1.79)	1.67 (1.58–1.76)	0.142
Body mass index	23.6 (22.4–25.1)	22.9 (20.6–24.7)	0.168
HRCT pattern (Definite UIP/Possible UIP/ Inconsistent with UIP)	26/3/1	31/4/1	0.982
Surgical lung biopsy	9 (30.0)	12 (33.3)	0.772
mMRC scale (0/1/2/3/4)	2/10/17/1/0	0/1/9/19/7	<0.0001
FVC (% predicted)	72.0 (65.2–81.0)	54.5 (46.5–65.9)	<0.0001
FEV_1/FVC (%)	85.2 (80.6–88.2)	91.5 (85.6–94.8)	0.0001
DL_{CO} (% predicted)	57.5 (44.3–75.1)	36.0 (29.6–48.0)	0.0007
PaO2 at rest (Torr)	79.5 (75.4–85.9)	72.0 (63.8–76.0)	0.0002
Distance in 6MWT (m)	467 (415–516)	380 (363–462)	0.017
JRS severity grade of IP (I/II/III/IV)	14/0/15/1	5/0/15/16	<0.0001
GAP staging system (I/II/II)	14/15/1	3/16/17	<0.0001
Match the inclusion criteria for RCTs	20 (66.7)	13 (36.1)	0.013
Preceding Home oxygen therapy	6 (20.0)	20 (55.6)	0.0032
Preceding Prednisone	0 (0.0)	6 (16.7)	0.019
Pulmonary hypertension	3 (10.0)	18 (50.0)	0.005
COPD	3 (10.0)	6 (16.7)	0.432
Lung cancer	1 (3.3)	4 (11.1)	0.234
GERD	14 (46.7)	18 (50.0)	0.787
Chronic heart failure	0 (0.0)	3 (8.3)	0.106
Coronary artery disease	3 (10.0)	4 (11.1)	0.884
DM	10 (33.3)	12 (33.3)	1.000
Malignancy	7 (23.3)	5 (13.9)	0.322
Depression	2 (6.7)	2 (5.6)	0.851

(Continued)

Table 5. (Continued)

Characteristics	Good performance status group *n* = 30 (45%)	Poor performance status group *n* = 36 (55%)	*p* value
Charlson comorbidity index	2 (1–3)	1 (1–3)	0.633
Antifibrotic agents (Pirfenidone/Nintedanib)	21/9	22/14	0.450
Antifibrotic agents dose reduction during the course of 1 year	15 (50.0)	23 (63.9)	0.256

Data are presented as *n* (%) or median (interquartile range).
6MWT, 6-min walk test; DLco, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GAP, gender, age and physiology; HRCT, high-resolution computed tomography; IP, interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; mMRC, modified Medical Research Council; PaO2, arterial partial pressure of oxygen; RCTs, randomized controlled trials; UIP, usual interstitial pneumonia.

Japanese subgroup analyses of INPULSIS was slightly greater than in the overall population (28.9% *versus* 24.5%).[29] Moreover, in the Japanese postmarketing surveillance of pirfenidone, at 1 year, 51% of the study population had discontinued pirfenidone.[9] We consider that our discontinuation rate did not greatly differ from those of previous reports.

In our study, patients with a good PS comprised about one-half of all patients with IPF. Many pulmonologists make their decision about antifibrotic agent interventions while evaluating the disease behavior of IPF, and a 'watch and wait' approach may be made if the disease behavior is stable. However, the disease behaviors of IPF are diverse and difficult to predict.[30] There are cases in which intervention with antifibrotic agents is not possible due to disease progression prior to therapeutic intervention, or because treatment is discontinued after the intervention. Patients with IPF and preserved lung volume have the same rate of FVC decline and receive the same benefit from antifibrotic agents as patients with more impaired lung volume.[31,32] On the other hand, in Italian real-world studies, pirfenidone provided significant treatment benefit for patients with moderate–severe disease or rapidly progressive disease.[33,34] In addition, the discontinuation rate in the latter studies was very low or not evaluated. Perhaps if patients with progressive disease can continue antifibrotic agents, they could benefit. Considering the value of antifibrotic agent persistence rate by PS; although it is strongly suggested that a patient with good PS can continue antifibrotic agents, it is not always suggested that a patient with poor PS cannot continue. In our study, patients in the good PS group showed a high continuation rate and a lower annual decline in %FVC than those in the poor PS group. Our data support the importance of early antifibrotic treatment intervention in patients with IPF.[35] Importantly, the finding of a –6.8% decline in FVC at 12 months in the poor PS group is also satisfactory efficacy. For this reason, it is important not to give up antifibrotic treatment intervention even if in patients with poor PS. Patients with poor PS require various plans and considerations not to discontinue. With regard to dose of antifibrotic agents, the annual rate of decline in FVC in patients with a low dose antifibrotic agents was similar to that of patients with high dose antifibrotic agents.[36,37] Thus, starting with a low dose of antifibrotic agents may be considered, or it may be necessary to be more careful with countermeasures for adverse events.

The current study has some limitations. First, it was a retrospective study with a small number of patients. Because multivariate analysis could not be performed due to sample size, we could not exclude the possibility that confounding factors affected the result. Moreover, the possibility of unintentional selection bias in the selection of patients could not be completely excluded. Regarding selection bias, our study has included fatal cases in the discontinued group. Although there may be an opinion that this group of patients may have influenced the results of our study, we judged that excluding fatal cases would be a greater selection bias. Even when excluding fatal cases, univariate analysis revealed that PS was associated with the

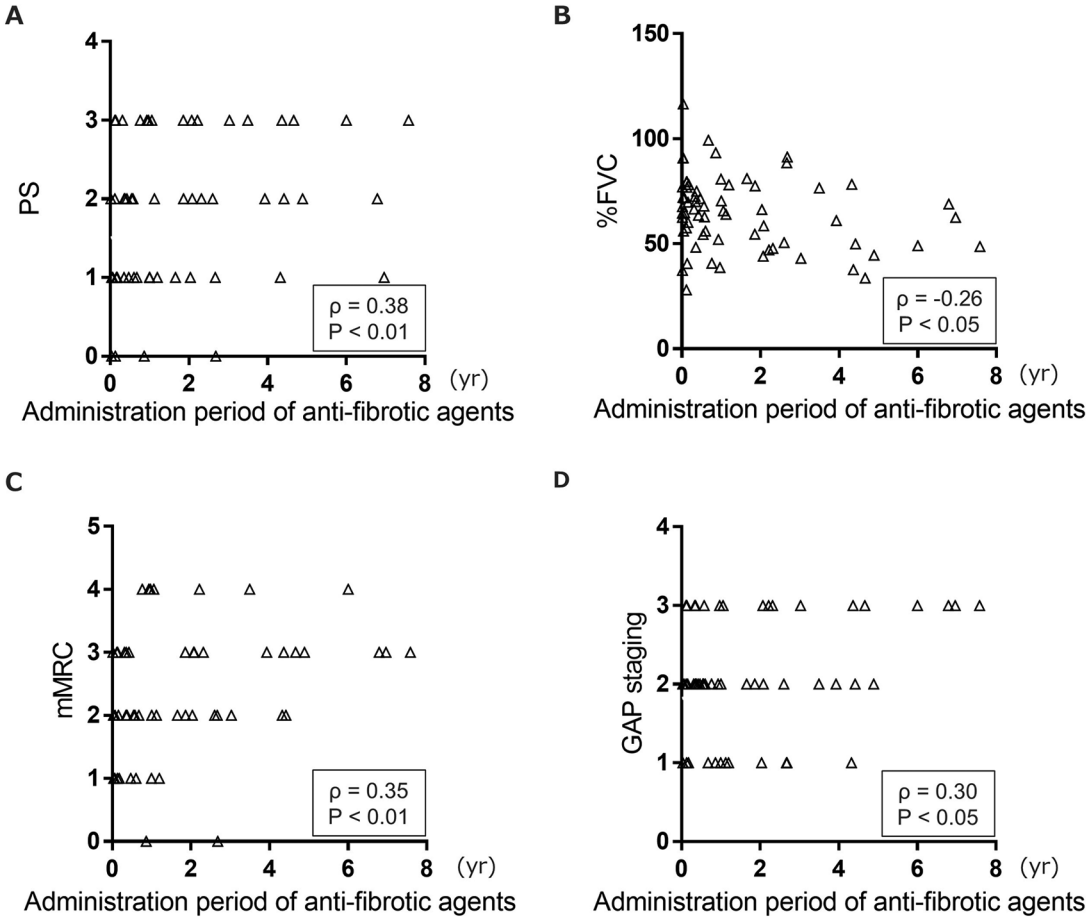

Figure 5. Delays from diagnosis to antifibrotic treatment lead to worsening of dyspnea, decline in lung function and deterioration of PS.
PS, Performance status.

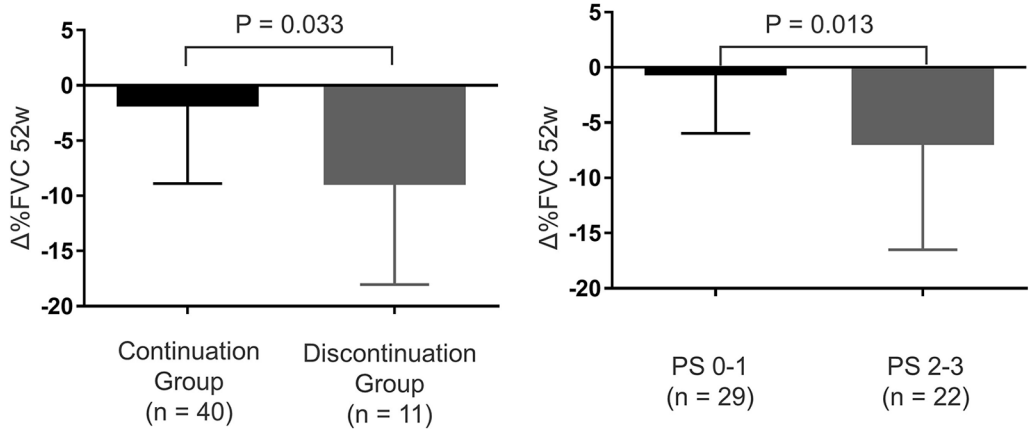

Figure 6. Changes in %FVC (Δ%FVC) from baseline through week 52 in each group.
%FVC, Forced vital capacity.

Table 6. Types and proportion of adverse events of antifibrotic agents.

Adverse events	CTCAE all grade / CTCAE grade ⩾ II	All *n* = 66	Continuation group *n* = 43 (65%)	Discontinuation group *n* = 23 (35%)	*p* value
Nausea		36 (54.5) 6 (9.1)	22 (51.1) 2 (4.7)	14 (60.9) 4 (17.4)	0.450 0.086
Vomiting		7 (10.6) 1 (1.5)	4 (9.3) 1 (2.3)	3 (13.0) 0 (0.0)	0.638 0.461
Diarrhea		20 (30.3) 11 (16.6)	13 (30.2) 5 (11.6)	7 (30.4) 6 (26.1)	0.986 0.133
Elevated transaminases		22 (33.3) 5 (7.6)	16 (37.2) 3 (7.0)	6 (26.1) 2 (8.7)	0.361 0.801
Dyspepsia		39 (59.1) 8 (12.1)	24 (55.8) 5 (11.6)	15 (65.2) 3 (13.0)	0.459 0.867
Anorexia		39 (59.1) 22 (33.3)	23 (53.5) 10 (23.3)	16 (69.6) 12 (52.2)	0.206 0.018
Rash/photosensitivity		6 (9.1) 5 (7.6)	3 (7.0) 2 (4.7)	3 (13.0) 3 (13.0)	0.414 0.220
Acute Exacerbation		6 (9.1) 6 (9.1)	4 (9.3) 4 (9.3)	2 (8.7) 2 (8.7)	0.935 0.935

Data are presented as *n* (%). CTCAE, Common Terminology Criteria for Adverse Events.

discontinuation of antifibrotic agents. Second, because of the low prevalence of comorbidities compared with other respiratory diseases, it was not suitable as a group to consider the influence of comorbidities other than respiratory disease. The reason for this was that many patients were collected from specialized pulmonary hospitals. Further study is required to assess the long-term clinical outcomes and the effects of various comorbidities. Despite these limitations, our data may provide a basis for future, prospective clinical trials on antifibrotic treatments for IPF patients stratified by PS.

Conclusion

Our findings underscore the fact that PS is an accurate predictive factor for the discontinuation of antifibrotic agents in patients with IPF. Additionally, a delay from diagnosis to antifibrotic treatment can lead to worsening of dyspnea, a decline in lung function, and deterioration of PS, which may contribute to the discontinuation of antifibrotic agents. Our data reinforce the importance of early initiation of antifibrotic treatment in IPF. In conclusion, we suggest that PS should be used as a guide for starting antifibrotic agents of IPF patients in everyday practice and that, in the case of patients with poor PS, various plans and considerations not to discontinue are required.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

The reviews of this paper are available via the supplementary material section.

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