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Predictive factors for the effect of pirfenidone in idiopathic pulmonary fibrosis

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Abstract. *Background:* Pirfenidone is one of the anti-fibrotic drugs used for patients with idiopathic pulmonary fibrosis. Pirfenidone exerts anti-inflammatory effects by inhibiting the influx of inflammatory cells. *Objectives:* The purpose of this study was to clarify the differences in the baseline parameters in responsive and unresponsive patients, and to assess the clinical and radiological changes after pirfenidone therapy. *Methods:* Patients with idiopathic pulmonary fibrosis who were treated with pirfenidone from April 2009 to March 2014 were retrospectively analyzed. The enrolled patients were classified into a good response group if they showed inhibition of progression, or were classified into a slowly progressive group on the basis of a decline in the vital capacity over a six-month interval after beginning treatment. The parameters of pulmonary function tests and laboratory findings were compared before and after treatment. The chest computed tomography findings were evaluated using the Sumikawa score. *Results:* Twenty patients were classified into seven good responders and eight cases with inhibition of progression. These groups had higher antinuclear antibody and autoimmune antibody values, and less ground glass attenuation at baseline. A chest computed tomography assessment at six-months after beginning pirfenidone administration showed a reduction of the ground glass attenuation findings in the good response group and an increase in airspace consolidation in the slowly progressing group compared with the baseline. *Conclusions:* Higher positive values for antinuclear antibodies and autoimmune antibodies at baseline and the location of ground glass attenuation at baseline, which indicates inflammatory lesions, may predict the efficacy of pirfenidone. *(Sarcoidosis Vasc Diffuse Lung Dis 2017; 34: 290-299)*

Key words: pirfenidone, idiopathic pulmonary fibrosis, chest computed tomography, Sumikawa score, antinuclear antibodies and autoimmune antibodies

Introduction

Idiopathic pulmonary fibrosis (IPF) is a representative interstitial pneumonia of uncertain cause, with a poor prognosis due to its being a chronic progressive lung fibrosis, and no drug therapy has been proven to be useful for improving the survival rate of patients with IPF (1).

Pirfenidone, which has anti-inflammatory and antifibrotic activity, was first approved for IPF in Japan in 2008. Several clinical trials have been reported with regard to the therapeutic effects of pirfenidone against IPF (2-6). Pirfenidone was given a "weak no" recommendation in the 2011 IPF guidelines and in 2014, the ASCEND described that pirfenidone significantly reduced the decline in the percent predicted forced vital capacity (%FVC) and improved the six-minute walk distance and progression-free

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survival (1, 7). Providing the best treatment for each case may become possible by considering the factors that can predict the therapeutic effects of pirfenidone.

Although high-resolution computed tomography (HRCT) has high specificity for diagnosing usual interstitial pneumonia (UIP) which is confirmed by histological features, the sensitivity of HRCT for UIP is relatively low, and only 60% of patients with IPF have the UIP pattern on chest HRCT (8, 9). According to a radiographic analysis during pirfenidone treatment, Iwasawa reported the utility of computed tomography (CT) for predicting the efficacy of pirfenidone (10). However, the factors predicting the efficacy of pirfenidone are still unclear, especially from the viewpoint of CT variables from a quantitative analysis. The purpose was to clarify the differences in the baseline parameters, including those of a CT analysis, in each group categorized by the response to pirfenidone, and to determine the clinical parameters and radiological changes between pre- and post- therapy.

Methods

The research protocol was approved by the human ethics committee of Chiba University Hospital, and informed consent was obtained from all patients and their family members.

Subjects

The study was conducted at a Chiba University hospital in Japan. The clinical records who were diagnosed with IPF and who showed the forced vital capacity (FVC) decline over five percent in 6months before pirfenidone administration and who started to administer pirfenidone between April 1, 2009 and March 31, 2014 were retrospectively investigated. We included the patients who met the following criteria: 1. Continuation of pirfenidone administration for at least six months, 2. Underwent examinations including CT and pulmonary function tests, who had laboratory findings available at both baseline and six months after the initiation of pirfenidone. The patients who received treatment with other antifibrotic drugs, such as N-acetylcysteine, were excluded. The patients who were diagnosed to have connective tissue disease (CTD) clinically and who received lobectomy or pneumonectomy were also excluded.

All patients presented disease progression which were illustrated by forced vital capacity (FVC) decline over five percent in 6months before pirfenidone administration (The average decline of FVC before pirfenidone was 14.2%). They were classified based on whether they had a UIP pattern or possible UIP pattern on HRCT in accordance with the 2011 IPF statement (1). The cases which had inconsistent with UIP pattern (ex. extensive ground glass abnormality and consolidation in bronchopulmonary segment/lobe) on CT findings were excluded in this study. The presence of a UIP pattern on HRCT is considered to be evidence of IPF without the need for a surgical biopsy, and the presence of a possible UIP pattern on HRCT was considered to indicate IPF, probable IPF or not IPF depending on the histological findings in the patients subjected to a surgical biopsy. The criteria for determining the UIP pattern and possible UIP pattern include the presence of traction bronchiectasis and whether it is caused by retractile fibrosis, which is one of main etiologies of IPF (11). The final diagnosis of IPF was confirmed by discussions with two radiologists after a comprehensive examination of the medical history, physical findings, laboratory findings and complications in every case.

Classification

Pulmonary function tests (PFTs) were performed by standard techniques using the CHESTAC-8900 (Chest MI Co., Tokyo, Japan) and FD-77 (Fukuda Denshi, Tokyo) at baseline and at six months after treatment initiation. The following parameters of the PFT were evaluated: FVC, %FVC, the ratio of the forced expiratory volume in the first one second to the FVC (FEV1%), the total lung capacity (TLC), diffusing capacity or transfer factor of the lung for carbon monoxide (DLco) and the ratio of the DLco to the alveolar volume (DLco/VA). The GAP (gender, age, and physiologic variables) score was also calculated (12). An efficacy evaluation was performed on the basis of the degree of FVC decline at six months after the initiation of pirfenidone therapy. Enrolled patients were classified into three groups according to the efficacy as follows: a slowly progressive group (SP), where there was a > 5% (relative) decline of the FVC; an inhibition of progression

group (IP), where there was a 0% to 5% (relative) decline of the FVC and a good response group (GR), where there was any increase of the FVC.

Laboratory findings

Laboratory evaluations were conducted at the initiation of pirfenidone treatment and six month after the start of pirfenidone administration. The parameters examined included fibrotic markers (lactate dehydrogenase (LDH), sialylated carbohydrate antigen KL-6 (KL-6), pulmonary surfactant protein-A (SP-A), pulmonary surfactant protein-D (SP-D)), inflammation markers (white blood cell count: WBC, C-reactive protein: CRP) and autoimmune markers (rheumatoid factor: RF, anti-nuclear antibodies: ANA titer and pattern, autoimmune antibody tests). The abnormal levels were defined as follows; LDH >240 IU/L, KL-6 >500 IU/mL, SP-A >50 ng/mL, SP-D >110 ng/mL, WBC >9,800/μL, CRP >0.3 mg/dL, RF >15 IU/mL, ANA titer >160 and any positive results for autoimmune antibodies.

CT images

All thin-sectional CT images at full expiration were obtained by using a 320-slice CT scanner (Aquilion One, Toshiba Medical Systems Engineering Co, Ltd) with a 0.5-mm slice thickness and a 0.35 s/rotation at 0.5-mm intervals using a standard algorithm. The window settings were appropriate for viewing the lung parenchyma (window level from -600 to -700 Hounsfield units [HU]; window width from 1,200 to 1,500 HU).

Two pulmonologists independently evaluated the CT findings based on the Sumikawa score blinded to any clinical information to detect small changes in each abnormal finding (13). The score for the extent of lung involvement (ground-glass attenuation: GGA, airspace consolidation, nodules, honeycombing, emphysema, cysts, architectural distortion, traction bronchiectasis) of each abnormal finding of the six lung zones (the level of the carina, the inferior pulmonary vein and the middle) were assessed with the pulmonologists blinded to the clinical data.

This score was based on the estimation to the nearest 5% of the lung parenchyma, and the average of the six lung zones was calculated (range, 0 to 100). Consolidation was defined as an area with a loss of volume, and was assessed to be present if the opacities obscured the underlying vessels, which is described as fibrotic consolidation (14). Traction bronchiectasis was scored from 0-3 as follows; 0, none; 1, bronchial dilatation involving the fifth generation or more distant bronchi; 2, bronchial dilatation involving fourth-generation bronchi; 3, bronchial dilatation involving third-generation or more proximal bronchi. The fibrosis score was graded from 0-4; 0: none, 1: only ground-glass opacities, 2: ground-glass opacities with reticulation, 3: reticulation with small cysts, 4: reticulation and large cysts (more than 3 mm in diameter). We reassessed the overall impressions of the findings (UIP pattern, possible UIP pattern, inconsistent with UIP pattern).

We analyzed the differences in the clinical and radiological parameters, including the PFT, laboratory and CT findings at baseline and post-therapy in each group.

Statistical analysis

The data are presented as the means ± standard deviation (SD). A Kruskal-Wallis test or the Wilcoxon rank sum test was used to compare numerical variables among the groups. The Wilcoxon signed-rank test was used to compare changes in the CT findings between the baseline and the period six months after treatment initiation, and the data are expressed as the means ± SD. P-values <0.05 were considered to be statistically significant. The inter-observer variation of the extent of the various CT abnormalities was evaluated using Spearman's rank correlation coefficient. The inter-observer variation of the overall impression of the findings was analyzed using the k statistic. The Pearson correlation was utilized to analyze the comparison between the changes in the pulmonary function tests and CT findings at six months after beginning treatment. A statistical analysis was carried out using the JMP Statistical Software package, v. 11 (SAS Institute, Cary, NC, USA).

Results

Clinical parameters at baseline

Twenty patients with IPF treated with pirfenidone were enrolled in our study. None of the patients

were treated with corticosteroids and/or immunosuppressants during the study. Home oxygen therapy (HOT) was used in 10 enrolled patients at baseline. As shown in Table 1, the average %FVC at baseline was 61.6% and the average GAP score was 4.65; thus, most of patients were classified to have moderate to severe IPF. The mean values of the fibrotic markers were elevated as follows: KL-6, 1385 IU/mL; SP-A, 89.3 ng/mL and SP-D, 326 ng/mL. In total, eight cases (40%) had positive ANA and nine cases (45%) had positive results for any autoimmune antibodies. Four cases of GR group had positive ANA (160, 160,160, 1280), and four cases of IP group also had positive ANA (160, 320, 640, 640). Five cases of GR group had positive autoimmune antibodies (1, aldolase; 1, MMP-3; 1, ds-DNA; 2, RNP), and four cases of IP group had positive autoimmune antibodies (1, aldolase; 1 CCP; 2 SS-A).

Table 1. Clinical parameters at baseline

Characteristics	Baseline data
Total number	20
Gender (male/female)	11/9
Age (years)	68±8.2
BMI	23.4±4.2
Pulmonary function tests	
FVC (L)	1.77±0.56
%FVC (%)	59.2±16.1
FEV1% (%)	90.0±7.1
TLC (L)	3.06±0.8
DLco (ml/min/torr)	6.6±4.2
DLco/VA (ml/min/torr/L)	2.31±0.69
GAP score	4.65±1.53
Laboratory findings	
WBC (/μL)	7645±251
CRP (mg/dL)	0.7±1.5
LDH (IU/L)	260±47.6
KL-6 (IU/mL)	1385±839
SP-A (ng/mL)	89.3±27.4
SP-D (ng/mL)	326±268
RF (positive/negative number)	2/18
ANA (positive/negative number)	8/12
Autoimmune antibodies (positive/negative number)	9/11

BMI: body mass index, FVC: forced vital capacity, %FVC: percent predicted forced vital capacity, FEV1%: the ratio of the forced expiratory volume in the first one second to FVC, TLC: total lung capacity, DLco: diffusing capacity or transfer factor of the lung for carbon monoxide, %DLco: percent predicted DLco, DLco/VA: the ratio of the DLco to alveolar volume, GAP: gender, age, and physiologic variables, WBC :white blood cells count, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Sialylated carbohydrate antigen KL-6, SP-A: Surfactant protein-A, SP-D: Surfactant protein-D, RF: rhematoid factor, ANA: anti-nuclear antibody

Seven (35%) of the 20 patients were classified into the GR group (The change in FVC: 113.8±92.5mL). The IP group (-44.1±44.8mL) and SP group (-252.9±84.7mL) included eight and five patients, respectively. HOT was used for four patients (57%) in the GR group, two (25%) in the IP group and two (40%) in the SP group, and there were no significant differences among the three groups (Figure 1). As shown in Figure 1, there were significant differences in the change in FVC (GR: +113.8 mL, IP: -44.1 mL, SP: -252.9 mL; GR vs. IP: $p<0.001$, GR vs. SP: $p<0.0001$, IP vs. SP: $p=0.002$, respectively) and the change of the %FVC (GR: +4.7%, IP: -2.6%, SP: -7.9%; GR vs. IP: $p<0.0001$, GR vs. SP: $p<0.0001$, IP vs. SP: $p=0.002$, respectively).

As shown in Table 2, no significant differences were observed with regard to the patient age, gender or pulmonary function, except the change in the FVC. There were no significant differences in the fibrotic markers, such as KL-6, SP-A and SP-D, among the groups. However, a higher positive value for ANA and autoimmune antibodies was seen in the GR ($P=0.005$) and IP groups ($P=0.026$) compared with the SP group.

CT assessment at baseline

The score for each abnormal CT finding and for the overall pattern at baseline are also shown in Table 3. There was good inter-observer agreement for all parameters except cysts ($\rho=0.89$ in all abnormalities and $\kappa=0.79$ in the overall pattern). Although we excluded the cases with inconsistent with UIP pattern on CT findings such as extensive GGA, the SP group had significantly more GGA ($P=0.013$) than the other two groups at baseline. There was a tendency for the GGA in the GR group to be located in the lung fields far from the fibrosis area compared to the SP group (71% vs. 20%). There was no statistically significant difference between the groups with regard to the extent of all abnormalities, reticular opacity, honeycombing, cysts, emphysema, architectural distortion and traction bronchiectasis, the fibrosis score or the HRCT patterns.

Comparison between the findings at baseline and at six months after treatment initiation

No significant difference was observed in the laboratory findings between those observed at base-

	GR	IP	SP	p-value*
Total	7	8	5	
The change in FVC (mL)	113.8 ± 92.5	-44.1 ± 44.8	-252.9 ± 84.6	0.0002
The change in %FVC	4.7 ± 2.8	-2.6 ± 1.8	-7.9 ± 2.3	0.0002

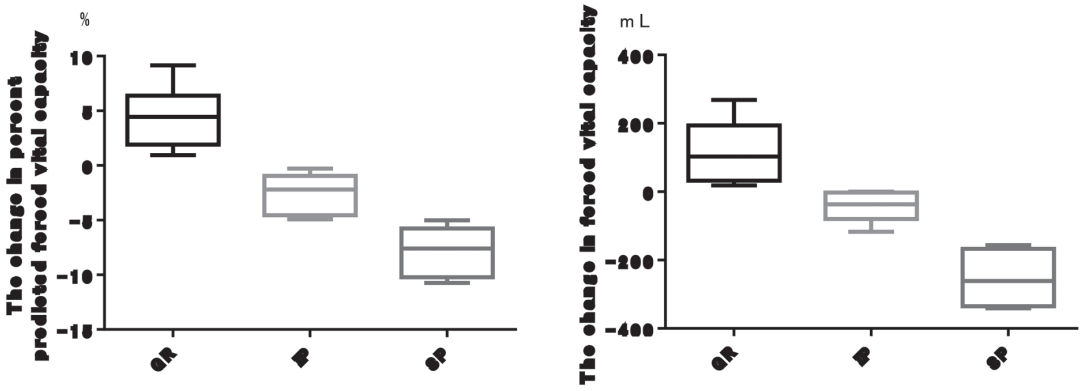

Fig. 1. The change in the percent predicted forced vital capacity (%FVC) and forced vital capacity (FVC) between baseline and the six-month interval in each group. There were significant differences in the change in FVC (GR: +113.8 mL, IP: -44.1 mL, SP: -252.9 mL; GR vs. IP: p<0.001, GR vs. SP: p<0.0001, IP vs. SP: p=0.002, respectively) and the change of the %FVC (GR: +4.7%, IP: -2.6%, SP: -7.9%; GR vs. IP: p<0.0001, GR vs. SP: p<0.0001, IP vs. SP: p=0.002, respectively). GR; good response group, IP; inhibition of progression group, SP; slowly progressive group

line and at six months after initiating pirfenidone treatment. The CT findings of both the GP and SP groups were analyzed regarding the changes in the efficacy of pirfenidone. As shown in Table 4, there was a decrease in all abnormalities (P=0.017), GGA (P=0.004) and the fibrosis score (P=0.042) in the GR group and an increase of airspace consolidation (P=0.041) in the SP group. There was a tendency for there to be increased honeycombing in the SP group after the six months of administration of pirfenidone.

Table 5 shows the results of a comparison between the changes in the pulmonary function tests (percent of baseline) and CT findings (percent of baseline) at six months after starting treatment. The change in the %FVC had negative correlations with the change in all abnormalities (r=-0.533, P=0.023), airspace consolidation (r=-0.637, P=0.005) and reticular shadows (r=-0.543, P=0.020).

Discussion

Taniguchi demonstrated the relationship between the short-term effects and the long-term effects in the continuation of pirfenidone (15). They mentioned that a 5% change of the VC had a higher sensitivity than a 10% change to evaluate the efficacy of pirfenidone. A decline in the FVC of ≥5% in a six-month period was previously reported to be associated with an increase in the risk of mortality (14, 15). Therefore, we classified the subjects into three groups by referring to these findings, and analyzed the clinical parameters, including the CT findings. With regard to the baseline CT findings, the SP group had more GGA and consolidation than the other two groups. The CT assessment at six months after starting pirfenidone treatment showed a decrease in all abnormalities and in the GGA in the GR group, and an increase in the airspace consolidation in the SP group compared with the baseline.

Some factors predicting the efficacy of pirfenidone have been reported previously (18-20). Azuma mentioned that a better response to pirfenidone was observed in patients with a baseline %VC ≥70% and a lowest oxygen saturation (SpO_2) <90% during the six-minute steady-state exercise test (18). Arai described that the factors predicting the effects of treatment were the IPF severity grade (I/II), as defined

Table 2. Clinical parameters of each group at baseline

	GR	IP	SP	p-value*
Total number	7	8	5	
Gender (male/female)	5/2	3/5	3/2	0.067
Age (years)	68.7±6.7	70.1±7.5	65.4±11.8	0.780
BMI	25.8±4.6	22.1±3.1	21.7±2.5	0.196
Pulmonary function tests				
FVC (L)	1.97±0.65	1.59±0.43	1.76±0.63	0.444
%FVC (%)	62.2±15.7	56.4±18.5	59.6±15.3	0.840
FEV1% (%)	92.8±6.2	86.7±8.1	91.3±5.4	0.296
TLC (L)	3.35±0.9	2.85±0.76	2.99±0.94	0.543
DLco (ml/min/torr)	5.79±3.8	7.71±5.19	5.94±3.52	0.780
DLco/VA (ml/min/torr/L)	2.18±1.38	3.31±1.77	2.66±1.12	0.410
GAP score	4.86±1.07	4.38±1.92	4.80±1.64	0.922
Laboratory findings				
WBC (/μL)	7871±3172	6887±2034	8540±2315	0.736
CRP (mg/dL)	1.24±2.41	0.15±0.09	0.82±1.13	0.898
LDH (IU/L)	274.1±54.4	258.1±44.4	243.0±46.4	0.462
KL-6 (IU/mL)	1678±1214	1204±619	1264±477	0.686
SP-A (ng/mL)	79.0±8.0	84.9±29.5	87.2±34.5	0.084
SP-D (ng/mL)	345.5±407.6	306.1±79.2	325.6±253.2	0.183
RF (positive/negative number)	0/7	1/7	1/4	0.060
ANA (positive**/negative number)	4/3	4/4	0/5	0.049
Autoimmune antibodies (positive***/negative number)	5/2	4/4	0/5	0.046

GR: good response group, IP: inhibition of progression group, SP: slowly progression group, BMI: body mass index, FVC: forced vital capacity, %FVC: percent predicted forced vital capacity, FEV1%: the ratio of the forced expiratory volume in the first one second to FVC, TLC: total lung capacity, DLco: diffusing capacity or transfer factor of the lung for carbon monoxide, %DLco: percent predicted DLco, DLco/VA: the ratio of the DLco to alveolar volume, GAP: gender, age, and physiologic variables, WBC: white blood cells count, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Sialylated carbohydrate antigen KL-6, SP-A: Surfactant protein-A, SP-D: Surfactant protein-D, RF: rhematoid factor, ANA: anti-nuclear antibody.

* p value with Kruskal-Wallis test

** The positive ANA was defined as ANA titer >160. Four cases of GR group had positive ANA (160, 160,160, 1280) and four cases of IP group also had positive ANA (160, 320, 640, 640).

*** The positive autoimmune antibodies was defined as any positive results for autoimmune antibodies. Five cases of GR group had positive autoimmune antibodies (1, aldolase; 1, MMP-3; 1, ds-DNA; 2, RNP) and four cases of IP group had positive autoimmune antibodies (1, aldolase; 1 CCP; 2 SS-A)

Table 3. CT findings at baseline

CT findings	CT score				Inter-observer agreement	
	GR	IP	SP	p-value*	ρ or k value	p-value
All abnormalities	28.3±14.4	25.6±14.8	37.2±13.2	0.379	0.89**	<0.0001
Ground-glass attenuation	8.9±5.0	5.8±2.1	14.0±4.0	0.013	0.47**	<0.0348
Airspace consolidation	1.8±2.1	3.8±3.7	5.8±6.4	0.169	0.88**	<.0001
Reticular opacity	7.6±4.1	7.5±2.6	9.7±3.6	0.473	0.45**	<0.04
Honeycombing	11.6±9.1	12.5±16.3	10.8±14.8	0.826	0.82**	<0.0001
Cysts	1.3±1.2	1.2±1.0	2.1±1.6	0.616	0.37**	0.178
Emphysema	0.6±1.0	0.0 0 0.0	1.0±2.2	0.161	0.89**	<0.0001
Architectural distortion	1.0±0.0	1.0±0.0	1	0.488		
Traction bronchiectasis	1.7±0.6	1.5±0.6	1.8±0.3	0.432	0.69**	0.001
Fibrosis score	3.3±0.5	2.6±0.8	2.8±0.7	0.131	0.74**	0.0002
Patterns UIP/probable UIP / Inconsistent with UIP	3/4/0	5/3/0	3/2/0	0.978	0.79***	<.0001**

GR: good response group, IP: inhibition of progression group, SP: slowly progression group, CT: computed tomography, UIP: usual interstitial pneumonia

* p value with Kruskal-Wallis test

** ρ value with Spearman's rank correlation coefficient

*** statistic Kappa with 95% confidence interval

Table 4. The clinical parameters at the six-month interval after treatment

	GR: post	% of baseline	p value*	IP: post	% of baseline	p value*	SP: post	% of baseline	p value*
Pulmonary function tests									
FVC (mL)	1867±504	107.7	0.017	1429±557	93.8	0.012	1947±398	88.6	0.003
%FVC	66.8±17.1	107.5	0.004	53.8±19.6	94.3	0.004	51.8±14.0	86.7	0.002
FEV1%	92.8±5.7	99.2	0.365	92.6±11.7	104.9	0.122	102.7±8.3	104.4	0.301
TLC (L)	3.10±0.35	101.9	0.778	2.32±0.87	89.0	0.116	3.67±0.83	100.6	0.965
DLco (ml/min/torr)	5.13±8.45	94.8	0.631	5.73±4.32	92.1	0.047	7.72±1.07	87.5	0.171
DLco/VA (ml/min/torr/L)	2.24±0.42	101.9	0.856	1.81±0.82	89.0	0.225	2.23±1.07	79.8	0.142
Laboratory findings									
LDH (IU/L)	1476±890	106.0	0.205	837±678	116.1	0.013	1233±755	100.3	0.925
KL-6 (IU/mL)	85.9±24.3	85.2	0.907	279.3±143.1	67.3	0.483	279.5±154.7	107.4	0.984
SP-D (ng/mL)	256.5±51.7	117.8	0.412	215.5±25.7	87.2	0.101	253±66.1	63.8	0.790
CT findings									
All abnormalities	21.7±8.5	90.6	0.017	2.64±0.82	101.4	0.397	36.9±13.2	100.2	0.621
Ground-glass attenuation	5.8±2.9	80.9	0.033	6.25±2.67	106.5	0.198	12.6±5.4	94.4	0.603
Airspace consolidation	1.8±2.5	67.2	0.203	3.92±4.10	104.3	0.456	4.8±2.2	171.5	0.042
Reticular opacity	6.6±3.4	98.1	0.419	12.2±14.5	102.9	0.689	5.2±2.3	141.8	0.200
Honeycombing	9.1±7.3	98.4	0.235	8.7±3.9	115.7	0.111	14.3±6.4	98.1	0.866
Cysts	1.1±1.2	103.3	0.363	1.25±1.04	102.1	0.351	1.3±0.6	119.4	0.704
Emphysema	0.4±0.6	72.2	0.259	0			0.9±2.1	97.9	0.374
Architectural distortion	1	101.5	0.363	0.98±0.04	100		1	100	
Traction bronchiectasis	1.6±0.6	100.5	0.611	1.57±0.59	106.4	0.179	1.6±0.5	82.1	0.080
Fibrosis score	3.1±0.6	98.0	0.042	2.64±0.82	101.4	0.171	2.6±0.7	88.4	0.061

CT: computed tomography, GR: good response group, IP: inhibition of progression group, SP: slowly progression group, FVC: forced vital capacity, %FVC: percent predicted forced vital capacity, FEV1%: the ratio of the forced expiratory volume in the first one second to FVC, TLC: total lung capacity, DLco: diffusing capacity or transfer factor of the lung for carbon monoxide, %DLco: percent predicted DLco, DLco/VA: the ratio of the DLco to alveolar volume, LDH: lactate dehydrogenase, KL-6: Sialylated carbohydrate antigen KL-6, SP-D: Surfactant protein-D.
* p value with Wilcoxon signed-rank test in comparison with value of baseline

Table 5. The comparison between the changes of pulmonary function tests and CT findings at the six-month interval after treatment

Pulmonary function tests	%FVC		FEV1%		DLco	
CT findings	r value	p value	r value	p value	r value	p value
All abnormalities	-0.533	0.023	0.682	0.015	0.031	0.933
Ground-glass attenuation	-0.145	0.567	0.291	0.358	0.622	0.055
Airspace consolidation	-0.637	0.005	-0.088	0.785	-0.343	0.332
Reticular opacity	-0.543	0.020	0.384	0.218	-0.972	<0.0001
Honeycombing	-0.062	0.806	0.298	0.347	0.402	0.249
Cysts	-0.184	0.464	0.000	1.000	0.721	0.019
Emphysema	-0.414	0.088	0.136	0.673	-0.153	0.673
Architectural distortion	0.105	0.680	-0.214	0.505	0.104	0.775
Traction bronchiectasis	0.327	0.186	-0.077	0.813	0.479	0.161
Fibrosis score	0.304	0.221	0.221	0.491	0.401	0.251

%FVC: percent predicted forced vital capacity, FEV1%: the ratio of the forced expiratory volume in the first one second to forced volume capacity, DLco: diffusing capacity or transfer factor of the lung for carbon monoxide
* r value with Pearson correlation

by the Japan Respiratory Society, a diagnosis by surgical lung biopsy, or both (20). The information about the factors associated with the CT evaluation, such as quantitative or qualitative data, are still limited, despite the importance of the CT features for evaluating patients with IPF (1, 16). Our study showed a significant difference in the CT findings at baseline and at six months after starting pirfenidone administration. GGA was commonly seen on the HRCT of the patients with IPF, but it is usually less extensive than the reticulation (1). GGA indicates the presence of fibrosis, active inflamma-

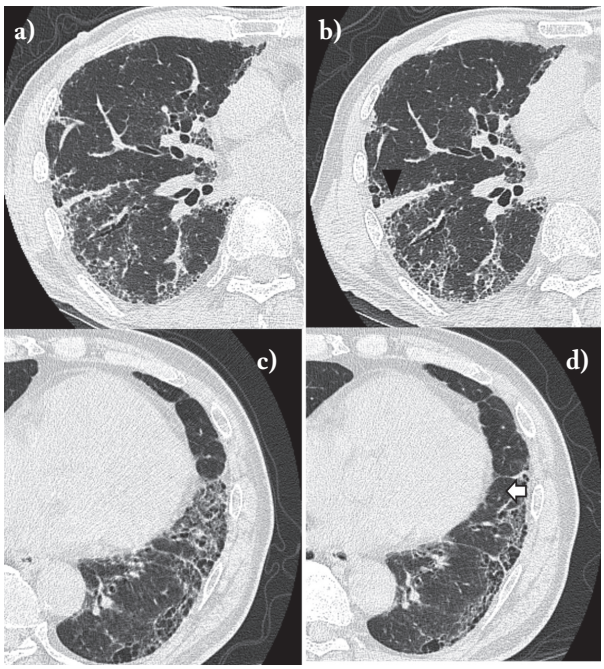

Fig. 2. The change in CT findings between baseline and the six-month interval in a slowly progressive group and good response group. A: at baseline in a slowly progressive group, B: at the six-month after pirfenidone initiation in a slowly progressive group, C: at baseline in a good response group, D: at the six-month after pirfenidone initiation in a good response group
The increase of pleural thickness with fibrosis was seen in a slowly progressive group (black triangle). On the other hand, the reduction of ground glass attenuation was observed in a good response group (arrow)

tion and secretions in the area of honeycombing (17-19). Our results showed that there was less GGA at baseline in the GR group compared with that of the SP group, and a reduction of GGA was seen after six months of treatment with pirfenidone in the GR group, while no improvements of the reticular shadows and honeycombing were seen. Although no difference in the extent of honeycombing was seen six months after the start of treatment, a reduction of GGA and reticular opacities was reported in 15% of the pirfenidone group compared with 7% of the placebo group in that study (5). With regard to GGA, Remy-Jardin reported that GGA should be considered to represent inflammation in cases of pulmonary fibrosis (20). Furthermore, the GGA findings were located in lung fields distant from areas of fibrosis in approximately 25% of cases (18). Similar to these findings, there was a tendency for the GGA findings in the GR group to be located central and distant from the fibrosis in the present study. In contrast, the GGA findings in the SP group were located close to and around the fibrotic area. Pirfenidone exerts anti-inflammatory effects by inhibiting the influx of inflammatory cells, such as neutrophils, macrophages and lymphocytes, in addition to causing antifibrotic reactions (3, 21, 22). Therefore, pirfenidone may have effects on the area of reversible GGA distant from the fibrotic areas.

Our study demonstrated an increase of consolidation in the SP group after six months of administration of pirfenidone. Our definition of consolidation was based on fibrotic consolidation, as described previously, and which was reported to be seen in 59% of patients with IPF (14). Significant matrix deposition occurs due to the progression of fibrosis in IPF, resulting in parenchymal consolidation seen in the radiological and pathological findings of IPF (23-25). In this study, the change in the %FVC had negative correlations with the changes in airspace consolidation and reticular shadows, as shown in Table 5. Therefore, consolidation findings on chest CT could be considered a consequence of the presence of and chronic progression of fibrosis, and pirfenidone might have an insufficient effect on the consolidation area of completely fibrotic components shown as reticular shadows and honeycombing.

Fifteen (75%) out of 20 patients with a less than 5% decrease in the FVC at six months after starting treatment were considered to have a stable disease, and to have responded to pirfenidone. A half of enrolled patients had a severe decline in the %FVC (<60%) and eight patients (40%) had moderate progression of IPF (40% <%FVC <60%), furthermore, the average GAP score was 4.65 and there was no significant difference among the groups. Therefore, the results showed a more favorable effect of pirfenidone compared to the previous clinical trials (5, 7, 26). This was assumed to be the high value of ANA and autoantibodies at baseline in the GR and IP groups, although the cases with obvious development of CTD at presentation were excluded from this study. There is a type of interstitial lung disease which has features of autoimmune disease, which Kinder et al. reported as a distinct clinical entity of undifferentiated connective tissue disease (UCTD) (27). In this report, 11% of the UCTD cases had honeycombing and 64% had traction bronchiectasis, such as a UIP pattern on chest HRCT. Some

studies have indicated that these are associated with a good prognosis for the patients with a high value of autoantibodies. Kono reported that the patients with occult CTD had a better prognosis than patients with IPF and more germinal centers in the pathological features (28). Germinal centers are assumed to reflect lymphatic inflammation; therefore, IPF patients with positive autoimmunity would be supposed to have more inflammation with lymphocytes and plasma cell infiltration in the lung lesions (28). Therefore, there is a possibility that pirfenidone may also have effects in patients positive for autoimmune activity.

There are several potential limitations associated with our research. First, our study was conducted retrospectively. As it was stated previously, the findings showed that there were differences in the clinical background, including autoimmunity, in the three pirfenidone response groups. Second, there is also a limitation in the number of cases since the study was performed at a single institution. Third, the diagnosis of IPF was entirely carried out in a clinical manner; thus, no pathological diagnosis was included. Therefore, we will investigate larger numbers of patients in a prospective study of pirfenidone treatment for patients with IPF.

Conclusion

Higher positive values of ANA and autoimmune antibodies at baseline and the location of GGA findings on chest CT at baseline predict the efficacy of pirfenidone for patients with IPF.

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