Table 2. Clinical Course of 7 LAM Cases Complicated by Renal Angiomyolipomas

Case No.	R-AML*1	Size of R-AML	Rupture of R-AMLs	Intervention	Hepatic AML
1	Bilateral	Left 3→4cm; Right 0.5cm (2 years later)	-	Left nephrectomy	-
2	Left	Left 7×4cm	-		+
3	Bilateral	Left 0.5, 1and 3cm; Right 1cm	-		+
4	Bilateral	bilateral multiple 1-3cm nodules	Right	Arterial embolization	-
5	Bilateral	Left 8cm; Right 16cm	Bilateral	Bilateral nephrectomy	-
6	Left	Left 3cm(autopsy)	Left	Left nephrectomy	+
7	Bilateral	Left 36cm; Right 22cm	Bilateral	Bilateral nephrectomy	+

*1 R-AML; renal angiomyolipoma

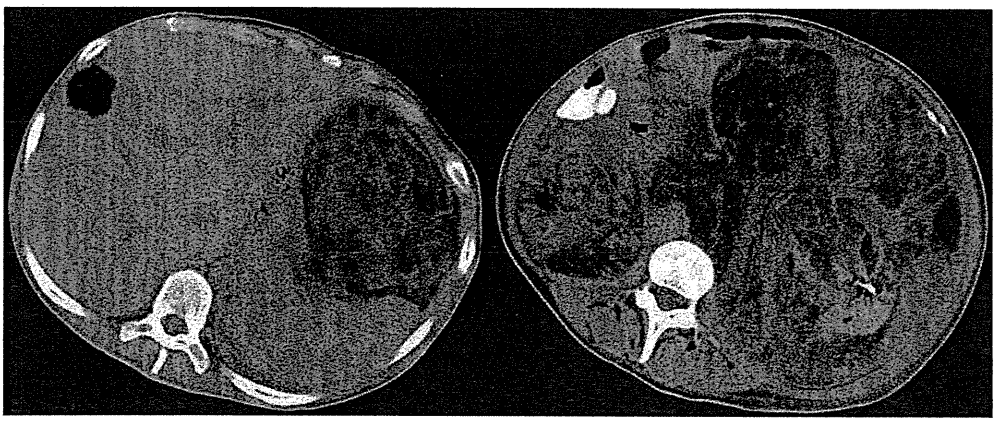

Figure 1. Giant bilateral renal angiomyolipomas in abdominal computed tomography (Case 7). Giant bilateral renal angiomyolipomas are shown in abdominal computed tomography. A hepatic angiomyolipoma is also shown. The patient experienced abdominal distention which was a symptom related to renal angiomyolipomas at the time of diagnosis.

Five patients visited our hospital due to respiratory symptoms (3 were dyspneic on exertion and 2 had symptoms related to pneumothorax) (Table 1). Although 5 patients had symptoms related to R-AMLs, only 1 patient (Case 7) experienced symptoms related to R-AMLs at the time of diagnosis (Fig. 1) (4).

We investigated the mean survival time, decline of vital capacity (VC) and decline of forced expiratory volume in 1 second ($FEV_{1.0}$). In the R-AMLs group, the mean survival time, decline of VC per year and decline of $FEV_{1.0}$ per year were 23.33±3.55 years, 36.5±67.1 mL and 40.3±43.2 mL, respectively. On the other hand, in the no R-AMLs group, the mean survival time, decline of VC per year and decline of $FEV_{1.0}$ per year were 14.20±2.50 years, 150.8±218.2 mL and 57.7±53.8 mL, respectively. There were no significant differences between the 2 groups in these 3 parameters (p=0.66, p=0.09 and p=0.65, respectively).

Discussion

In the present study, 4 patients (100%) with TSC-LAM and 3 patients (33.3%) with S-LAM had R-AMLs. These results were compatible with those in previous reports showing that patients with LAM have R-AML in approximately 93% of TSC-LAM cases and 30-50% of S-LAM cases (1). In this study, although 5 patients showed symptoms related to R-AMLs, only 1 patient experienced symptoms related to R-AMLs at the time of diagnosis (4). The symptoms were relatively atypical at the time of diagnosis and might delay diagnosis. Therefore, this case is very important if we consider the history of LAM. The Respiratory Failure Research Group of the Japanese Ministry of Health, Labour and Welfare 2003-2004 reported on the epidemiology of LAM in Japan (5). In the report, 173 patients with LAM showed common presenting features of pneumothorax (43%), dyspnea on exertion (36%), abnormal shadow on chest radiograph (11%) and other respiratory symptoms (4%) such as haemoptysis, cough and chest pain. In contrast, only 6% of patients presented with abdominal manifestations attributable to LAM or R-AMLs (5). In Japan, although 12 cases with LAM complicated by R-AMLs have been reported previously (6-9), symptoms and diagnosis related to R-AMLs preceded the other symptoms in only 2 cases. The other 10 cases showed initial symptoms related to respiration. Pa-

tients with R-AMLs rarely show symptoms and gradually present lateroabdominal pain, hydronephrosis, hematuria and renal dysfunction during follow-up.

In this study, one patient initially had R-AMLs on the left side. These R-AMLs grew and a right R-AML appeared during follow-up. The clinical course of R-AMLs varies. Rakowski et al identified R-AMLs in 10-year-old children, and reported that they grow and increase during adolescence (10). It was reported that in one case, a 3 cm R-AML which was not detected by echogram at 21 years of age appeared when the individual was 23 years old, and that in another case, multiple R-AMLs that were not detected by echogram at 18 years of age appeared at 20 years of age (10). Therefore, especially in adolescents, we should look carefully for R-AMLs if they were not detected by echogram or CT scan at the initial diagnosis. When a patient is diagnosed as TSC, we should examine for R-AMLs by echogram by 5 years of age. Rakowski et al suggested that patients should be examined by echogram at least once a year if R-AMLs are found. If no R-AMLs are found, the patient should be examined for R-AMLs by echogram at least every two or three years (10).

In this study, 5 patients had bilateral R-AMLs, 2 patients had unilateral R-AMLs, and 2 patients underwent bilateral nephrectomy. All 4 cases of TSC-LAM had bilateral R-AMLs, and 3 of the 4 cases showed rupture of R-AMLs. In most cases with S-LAM, R-AMLs were unilateral, small and singular. On the other hand, in TSC-LAM cases, R-AMLs, including hepatic or splenic AMLs, were bilateral, larger, and multiple, and in addition, they bled easily (1). The risk of hemorrhage from R-AMLs is greater when they are larger and more hypervascular. In this study, the mean size of R-AMLs was 17.0±12.9 cm in the ruptured group and 3.1±2.6 cm in the non-ruptured group (p=0.04). Therefore, the choice of treatment should be evaluated for R-AMLs which are larger than 4 cm by echogram or CT scan, as suggested in a previous report (1). There was no significant difference in the risk of rupture of R-AMLs between the unilateral and bilateral groups (p=0.714). However, as mentioned above, in TSC-LAM cases, R-AMLs tend to be bilateral and bleed easily. Therefore caution should be exercised regarding rupture of R-AMLs in bilateral cases. Generally, we perform renal artery embolization, enucleation, ablation and partial nephrectomy. It was reported that a patient with R-AMLs larger than 10 cm was treated by nephron-sparing nephrectomy (8, 11). But it may be necessary to perform total nephrectomy in difficult cases (1). A delay in the diagnosis of R-AMLs sometimes results in bilateral nephrectomy and hemodialysis because a greater number of patients with LAM complicated by R-AMLs have bilateral R-AMLs. Therefore, we should diagnose R-AMLs without delay and avoid total nephrectomy as long as possible (12).

In recent years, LAM and AML were included in Perivascular epithelioid cell tumors (PEComa) which Bonetti et al proposed in 1992 (13). Alterations of the TSC genes have been demonstrated in a significant number of PEComas, and they seem to have an important role in the regulation of the Rheb/mTOR (mammalian target of rapamycin)/p70S6K pathway (14, 15). As mentioned above, in this study, all 4 patients with TSC-LAM and 3 of 10 patients with S-LAM had R-AMLs. PEComas may explain why TSC-LAM is more likely to complicate R-AMLs, although we did not investigate genetic alterations. There have been several clinical trials of agents targeting the mTOR pathway. The Cincinnati Angiomyolipoma Sirolimus Trial (CAST) showed that the volume of R-AMLs decreased by almost 50% after treatment for 1 year with the mTOR inhibitor (16). In addition, the Multicenter International LAM Efficacy of Sirolimus (MILES) Trial was initiated in 2006 (1, 17). But there are limitations for patients on hemodialysis for advanced R-AMLs receiving the mTOR inhibitor. These patients also face challenges undergoing lung transplantation, especially regarding perioperative management and using postoperative immunosuppressants, and have an uncertain prognosis.

In conclusion, although only rare cases of LAM show initial symptoms related to R-AMLs, R-AMLs are a notable complication. As advanced R-AMLs rupture easily, it is important to look carefully for R-AMLs while they are smaller than 4 cm by performing periodic echograms or CT scans. The choice of treatment should be evaluated for R-AMLs which are larger than 4 cm.

The authors state that they have no Conflict of Interest (COI).

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RESPIRATORY RESEARCH

RESEARCH Open Access

The clinical significance of 5% change in vital capacity in patients with idiopathic pulmonary fibrosis: extended analysis of the pirfenidone trial

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Abstract

Background: Our phase III clinical trial of pirfenidone for patients with idiopathic pulmonary fibrosis (IPF) revealed the efficacy in reducing the decline of vital capacity (VC) and increasing the progression-free survival (PFS) time by pirfenidone. Recently, marginal decline in forced VC (FVC) has been reported to be associated with poor outcome in IPF. We sought to evaluate the efficacy of pirfenidone from the aspects of 5% change in VC.

Methods: Improvement ratings based on 5% change in absolute VC, i.e., "improved (VC ≥ 5% increase)", "stable (VC < 5% change)", and "worsened (VC ≥ 5% decrease)" at month 3, 6, 9 and 12 were compared between high-dose pirfenidone (1800 mg/day; n = 108) and placebo (n = 104) groups, and (high-dose and low-dose (1200 mg/day; n = 55)) pirfenidone (n = 163) and placebo groups. PFS times with defining the disease progression as death or a ≥ 5% decline in VC were also compared between high-dose pirfenidone and placebo groups, and low-dose pirfenidone and placebo groups. Furthermore, considering "worsened" and "non-worsened (improved and stable)" of the ratings at months 3 and 12 as "positive" and "negative", respectively, and the positive and negative predictive values of the ratings were calculated in each group.

Results: In the comparison of the improvement ratings, the statistically significant differences were clearly revealed at months 3, 6, 9, and 12 between pirfenidone and placebo groups. Risk reductions by pirfenidone to placebo were approximately 35% over the study period. In the comparison of the PFS times, statistically significant difference was also observed between pirfenidone and placebo groups. The positive/negative predictive values in placebo and pirfenidone groups were 86.1%/50.8% and 87.1%/71.7%, respectively. Further, the baseline characteristics of patients worsened at month 3 had generally severe impairment, and their clinical outcomes including mortality were also significantly worsened after 1 year.

Conclusions: The efficacy of pirfenidone in Japanese phase III trial was supported by the rating of 5% decline in VC, and the VC changes at month 3 may be used as a prognostic factor of IPF.

Trial Registration: This clinical trial was registered with the Japan Pharmaceutical Information Center (JAPIC) on September 13th, 2005 (Registration Number: JAPICCTI-050121).

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Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal lung disease for which there is no known cause or proven effective therapy [1,2]. Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone; Shionogi & Co., Ltd., Osaka, Japan; MARNAC Inc., Dallas, TX, USA) [3-6] is a pyridone compound with therapeutic potential for IPF that has been shown in animal models to have wide-ranging effects including antifibrotic, anti-inflammatory and antioxidant activity, although its precise mode of action is unknown [2,7-11]. A multi-centere, double-blind, placebo-controlled, randomized phase III clinical trial was conducted in Japanese patients with IPF to determine the efficacy and safety of pirfenidone over 52 weeks [12]. Significant differences were observed in the decline of vital capacity (VC; primary endpoint) between placebo group and high-dose (1800 mg/day) group; and in the secondary end point, the progression free survival (PFS) time, between the two groups. Treatment with pirfenidone was associated with a decreased rate of decline in VC and increased the PFS time over 52 weeks.

A 10% change in forced VC (FVC) have been reported to be a promising prognostic indicator, because patients with ≥ 10% decline in FVC within 6 or 12 months have a poor prognosis [13-15]. In the treatment guidelines published by the American Thoracic Society (ATS)/European Respiratory Society (ERS) as well, a ≥ 10% change in FVC and ≥ 15% change in diffusing capacity of the lung for carbon monoxide (DLCO) are described as indices of improvement or worsening of disease [16]. To evaluate changes over a period from 6 months to 1 year, however, the method using a 10% change in FVC as an index is not sensitive enough and may not be suitable for actual clinical setting. Recently, Zappala *et al.* have reported that marginal decline in FVC is associated with a poor outcome in IPF [17]. In this report, the authors demonstrated that IPF patients had a significantly poor prognosis when the decline in FVC after 6 months was either 5% to 10% or ≥ 10%. This information is considered useful for selecting patients with progressive disease and evaluating therapeutic effects in clinical studies.

Based on this report, we reviewed the efficacy of pirfenidone in the phase III trial in an exploratory manner using a 5% change in VC as indices, evaluated the coincidence of the ratings based on 5% change in VC between months 3 and 12, and examined the usefulness and significance of the 5% change.

Methods

Overall Study Design

This study was a multicentre, double-blind, randomized, placebo-controlled trial. The diagnosis of IPF was in accordance with the ATS/ERS Consensus statement [16] and 4th version of the guideline of clinical diagnostic criteria for idiopathic interstitial pneumonia in Japan [18]. Eligible patients were adults (20 to 75 years old) with IPF diagnosis based on above criteria and meeting the following SpO_2 criteria: 1) demonstrate oxygen desaturation of > 5% difference between resting SpO_2 and the lowest SpO_2 during a 6-minute steady-state exercise test (6MET), and 2) the lowest SpO_2 during the 6MET > 85% while breathing air. Using the data in our pirfenidone phase III trial [12], we performed a series of exploratory analyses of physiologic variables and characteristics in patients receiving high-dose pirfenidone [1800 mg/day], low-dose pirfenidone [1200 mg/day] or placebo.

Setting, Participants, and Randomization

In this phase III study, 325 patients were screened at 73 centers in Japan, and 275 patients were randomized to one of the three groups: the high-dose, low-dose and placebo groups. Of the 275 patients, 267 (108, 55 and 104 patients in the high-dose, low-dose and placebo groups, respectively) were deemed eligible for the full analysis set (FAS). Eight patients were excluded due to having no post-baseline data.

Measurements

The primary endpoint was the change in VC from baseline to Week 52. Secondary endpoints were PFS time and the change in the lowest SpO_2 during 6MET. VC was measured every 4 weeks, while the lowest SpO_2 during the 6MET and other PFTs were determined every 12 weeks.

Statistical Analysis

In order to examine the characteristics of the improvement ratings and PFS based on 5% change in VC in the comparison of efficacy among treatment groups, and the clinical significance of the 5% decline in VC at month 3, we performed following analyses. Significance level of tests was set at 0.1 (two-sided) according to the phase III study [12].

• ***Categorical analysis based on 5% change in VC***

Improvement ratings were defined based on 5% relative changes in absolute VC from baseline as "improved (≥ 5% increase)", "stable (< 5% change)", and "worsened (VC ≥ 5% decrease)", using VC values measured at 12, 28, 40, and 52 weeks after the start of treatment, and these ratings were used as those at months 3, 6, 9, and 12, respectively. Then, the distributions of the improvement ratings were compared between, high-dose pirfenidone (n = 108) and placebo (n = 104) groups, and (high- and low-dose) pirfenidone (n = 163) and placebo (n = 104) groups, with Wilcoxon rank sum test. The risk ratio was also calculated as the ratio of proportion of "worsened" in pirfenidone group to the proportion in placebo group at each time

point. The principle of the last observation carried forward (LOCF) was adopted to impute missing values if patient data were available for ≥ 4 weeks after the baseline. The number of patients prematurely dropped and for whom missing observations were imputed was shown in online supplemental materials of the preceding reports in details [12,19].

• Comparison of PFS times based on 5% decline in VC or death

PFS times by definition of disease progression as death or ≥ 5% relative decline in absolute VC were obtained. (In our previous paper, we used ≥ 10% instead of ≥ 5% decline in VC to define PFS times [12].) Then, the cumulative PFS rates were estimated with Kaplan-Meier (K-M) method and the distributions of PFS times were compared with log-rank test between high-dose pirfenidone and placebo groups, and low-dose pirfenidone and placebo groups. In addition, the disease progression was defined also by ≥ 5% decline in VC on two consecutive data points or death and similar analyses of PFS times thus defined were performed.

• Coincidence of the improvement ratings based on 5% change in VC at months 3 and 12, in terms of positive and negative predictive values

In order to examine the coincidence of the improvement ratings at month 3 and 12, that were derived as shown in the subsection "Categorical analysis based on 5% change in VC", we calculated positive and negative predictive values in high- and low-dose pirfenidone and placebo groups, and compared the positive and negative predictive values between the 2 (or pirfenidone and placebo) groups. Then, "worsened" and "non-worsened (stable or improved)" were considered "positive" and "negative", respectively.

• Comparison of the baseline characteristics between 'worsened' and 'non-worsened' patients at month 3

To examine the profiles of patients with ≥ 5% and < 5% decline in VC ("worsened" and "non-worsened" patients) at month 3, the baseline characteristics (i.e. age, body mass index (BMI), alveolar-arterial oxygen tension (PaO_2), SpO_2, VC, %VC, total lung capacity (TLC), %TLC, DLCO, %DLCO, KL-6, surfactant protein (SP)-A, SP-D, and dyspnea in daily living assessed with Hugh-Jones (H-J) classification [20]) between "worsened" and "non-worsened" patients at month 3 were compared with Welch's t-test.

• Comparison of the clinical outcome after 1 year between 'worsened' and 'non-worsened' patients at month 3

The clinical outcome (i.e. H-J classification, death, and acute exacerbation) after 1 year were compared between "worsened" and "non-worsened" patients at month 3. Analysis of the H-J classification was performed with Welch's T-test. Analyses of the mortality ratio and incidence of acute exacerbation were with Fisher's exact test.

• Comparison of PFS times with origin at month 3 between 'worsened' and 'non-worsened' patients at month 3

PFS times with origin at month 3 were obtained in a similar manner as described above. Then, the cumulative PFS rates were estimated with K-M method and the distributions of PFS times were compared with log-rank test between "worsened" and "non-worsened" patients at month 3.

Results

Categorical analysis based on 5% change in VC

Improvement ratings (improved, stable, worsened) based on 5% relative change in absolute VC at months 3, 6, 9 and 12 are shown in Figures 1-a (for high-dose pirfenidone and placebo groups) and 1-b (for high- and low-dose pirfenidone and placebo groups). Significant differences in the distributions of the ratings were consistently observed between high-dose pirfenidone and placebo groups (p = 0.0136, 0.0447, 0.0166, and 0.0053, Risk ratio; 0.578, 0.640, 0.671, and 0.665 at months 3, 6, 9, and 12, respectively) (Figure 1-a). Significant differences were also seen between high- and low- dose pirfenidone and placebo groups (p = 0.0064, 0.0381, 0.0091, and 0.0010, Risk ratio; 0.561, 0.652, 0.674, and 0.642 at months 3, 6, 9, and 12, respectively) (Figure 1-b), and between low-dose pirfenidone and placebo groups (**data not shown**). At months 6, 9, and 12, the risk ratios in (high- and low-dose) pirfenidone group to those in placebo group were approximately 65%., and the risks to be judged 'worsened' were consistently lower in pirfenidone group by approximately 35%.

Evaluation using modified progression-free survival based on 5% decline in VC or death

The modified progression of disease was defined by a ≥ 5% decline in absolute VC from baseline or death. K-M plots of PFS times based on the definition and the results of comparison of the distributions of PFS times among the groups with log-rank test are shown in Figure 2-a. Significant differences were shown in the distributions of PFS times between high-dose and placebo groups (p = 0.0149), and between low-dose and placebo groups (p = 0.0034) (Figure 2-a), and between (high-dose and low-dose) pirfenidone and placebo groups (p = 0.0015) (**data not shown**).

The progression of disease was also defined by ≥ 5% decline in VC on two consecutive data points or death, and K-M plots of the PFS times thus defined and the results of comparison with log-rank test are shown in Figure 2-b. Significant differences in the PFS times were seen between high-dose and placebo groups (p = 0.0011), between low-dose and placebo groups (p = 0.0349) (Figure 2-b), and between (high- and low-dose) pirfenidone and placebo groups (p = 0.0006) (**data not shown**).

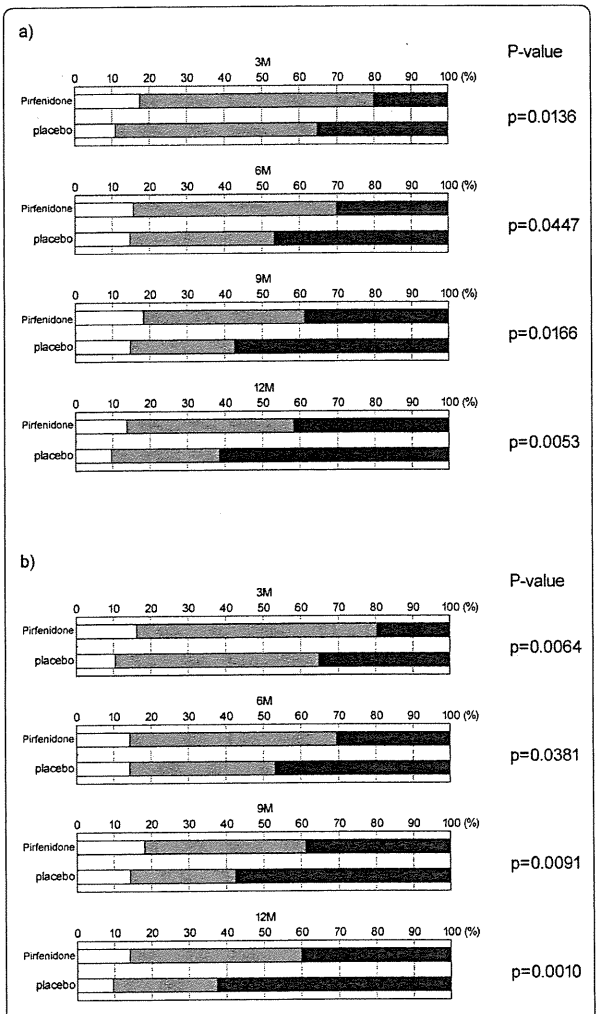

Figure 1 Categorical analysis based on 5% changes in VC at months 3, 6, 9, and 12. Improvement ratings based on 5% changes in VC were defined as "improved (VC 5% increase)", "stable (VC < 5% change)", and "worsened (VC 5% decrease)", using VC values measured at months 3, 6, 9, and 12. a) high-dose vs. placebo groups, b) pirfenidone-treated (high + low-dose) vs. placebo groups. The results are shown by the frequencies of improved (white areas), stable (gray areas), and deteriorated (black areas). P-values by Wilcoxon's test are indicated at the right.

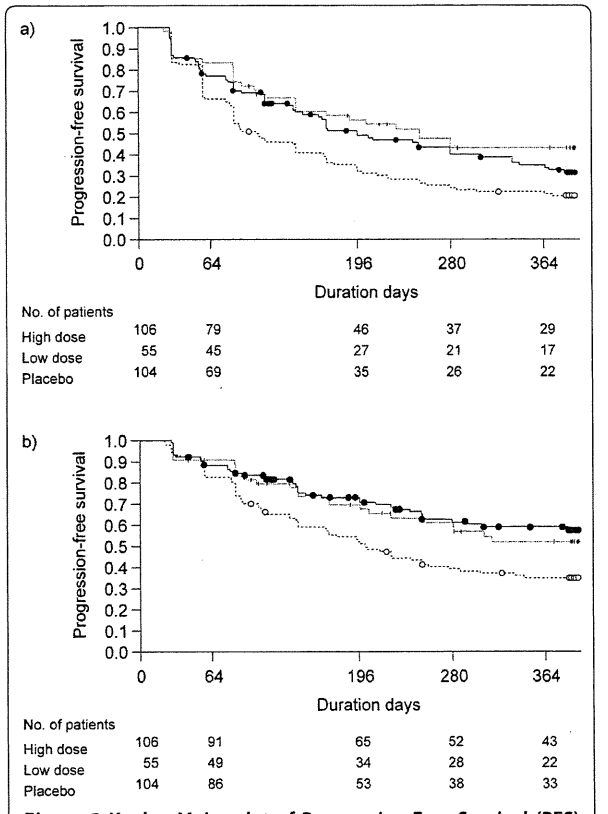

Figure 2 Kaplan-Meier plot of Progression-Free Survival (PFS) times in groups of IPF patients. a) The disease progression was defined by a ≥ 5% decline in VC from baseline or death. b) The disease progression was defined by a ≥ 5% decline in VC from baseline on two consecutive occasions or death. Solid line: high-dose; broken line: low-dose; bold broken line: placebo. The distribution of PFS times were compared with log-rank test.

Positive predictive value, negative predictive value with the ratings at month 3

Positive and negative predictive values with the ratings at month 3 in the prediction of those at month 12 in placebo and pirfendone (high- + low-dose) groups are shown in Table 1. In the placebo group, a ≥ 5% decline in VC at month 3 was still present at month 12 at highly rate (positive predictive value; 86.1% (31/36)) and no decline at month 3 was stable at month 12 at a rate of about 50% (negative predictive value; 50.8% (34/67)). On the other hand, in the treated (high- and low-dose

Table 1 Positive and negative predictive values of the ratings at month 3 in the prediction of the ratings at month 12

Placebo group(n = 103)

		12M worsened/non-worsened		
		Worsened	**Non-worsened**	
3M worsened/ non-worsened	Worsened	31 (86.1%)	5 (13.9%)	36
	Non-worsened	33 (49.2%)	34 (50.8%)	67
		64	39	103

Pirfenidone(high + low-dose) group (n = 158)

		12M worsened/non-worsened		
		Worsened	**Non-worsened**	
3M worsened/ non-worsened	Worsened	27 (87.1%)	4 (12.9%)	31
	Non-worsened	36 (28.4%)	91 (71.7%)	127
		63	95	158

pirfenidone) groups, decline at month 3 was still highly present (positive predictive value; 87.1% (27/31), nearly equal to one in the placebo group), and no decline at month 3 was also still stable at month 12 in relatively highly rate (negative predictive value; 71.7% (91/127) (Table 1). To put it briefly, the positive predictive values for pirfenidone and placebo groups were 87.1% and 86.1% respectively, and the difference was not significant. On the other hand, the negative predictive values for pirfenidone and placebo groups were 71.7% and 50.8%, respectively, and significant difference was seen ($p = 0.0046$).

Comparison of the baseline characteristics between 'worsened' and 'non-worsened' patients at month 3

The baseline characteristics between 'worsened' and 'non-worsened' patients at month 3 were compared. Patients with VC declined by 5% at month 3 generally had lower means of BMI, PaO_2, VC, %VC, TLC, %TLC, and DLCO at baseline ($p = 0.0011$, 0.0047, 0.0036, 0.0127, 0.0219, 0.0722, 0.0639, respectively), and had higher means of SP-A, SP-D and H-J classification score at baseline ($p = 0.0281$, 0.0344, 0.0765, respectively) (Table 2).

Comparison of the clinical outcome after 1 year between 'worsened' and 'non-worsened' patients at month 3

We compared the change in H-J classification score from baseline to month 12 with t-test between 2 classes of patients, i.e., those with "worsened (VC ≥ 5% decrease)" and others with "non-worsened (VC < 5% decrease)" at month 3. As a result, significant difference was seen for H-J classification score ($p = 0.0002$) (Table 3). Additionally, mortality rates for the patients with "non-worsened" and those with "worsened" at month 3 were 2.0% (4/194) and 9.0% (6/67), respectively, and significant difference was recognized ($p = 0.0203$). Marginal trend was also seen in the prevalence of acute exacerbation between the 2 classes of patients ($p = 0.1031$) (Table 4).

Comparison of PFS times with origin at month 3 between 'worsened' and 'non-worsened' patients at month 3

K-M plot of the PFS times with origin at month 3 for patients with and without 5% decline of VC at month 3, added the result of log-rank test, is shown in Figure 3. There was no significant difference in the distributions of PFS times between the 2 classes of patients ($p = 0.8835$).

Discussion

We report that the efficacy of pirfenidone in Japanese phase III trial was supported by the evaluation using the improvement ratings, PFS times and positive/negative predictive values based on 5% decline in VC. Further, the baseline characteristics of patients with ≥ 5% decline at month 3 were generally severe, and the clinical outcomes of those patients including mortality were also significantly worsened after 1 year.

According to a preceding report [12], comparison of the distributions of the improvement ratings (improved, stable, or worsened) based on 10% change in VC did not show significant differences between pirfenidone and placebo groups. The comparison of the ratings using 5% change in VC, however, revealed significant differences between pirfenidone and placebo groups at months 3, 6, 9 and 12 (Figure 1), and approximately 35% reduction in risk in this malignant disease would support the use of pirfenidone in clinical practice. Thus, when the 5% change in VC was used as an index, efficacy of the drug was evaluated with higher sensitivity than when the 10% change in VC was used. The 5% change in VC may seem only a slight change, but the annual decline in VC in the placebo group is said to be approximately 150 to 200 mL in many recent clinical trials [12,21-25]. In the phase III trial of pirfenidone, the annual decline in VC in the placebo group was 160 mL on average [12], and the mean baseline VC in the placebo group was 2472.3 mL, from which the annual rate of decline is calculated to be approximately 6.5%. That is, if a ≥ 10% change in VC is used as an index for evaluation over a period of a year, it may not be sensitive enough to detect efficacy of the drug, especially for changes within a shorter period of time such as 3 months and 6 months. Results of this sub analysis revealed that using a 5% change as an index improved the chances of detecting efficacy of the drug. Our results are considerably similar to those of extended analysis of the IFIGENIA study investigating the effect of N-acetylcysteine (NAC) in IPF, which also showed significance of a 5% threshold [26]. However, it should be noted that use of a smaller change as an index may require more accurate VC measurements.

According to the preceding report, the progression of disease was defined by the ≥ 10% decline in VC or death for evaluation of progression-free survival [12]. Results showed that the p-value of the difference between groups high-dose and placebo was 0.0280 and between groups low-dose and placebo was 0.0655. In this paper, the progression of disease was defined by the ≥ 5% decline in VC from baseline or death, and K-M plots were generated using thus defined PFS time. As a result, there were significant difference between groups high-dose and placebo and between groups low-dose and placebo ($p = 0.0149$ and $p = 0.0034$, respectively), (Figure 2-a) which seems to be more evident than those in the previous analysis by 10% decline [12]. When the progression of disease was defined by a ≥ 5% decline in VC from baseline on two successive occasions or death, the highly significant differences were also observed (Figure 2-b), which supported the result of Figure 2-a.

Table 2 Summary statistics of baseline characteristics for patients with ≥ 5% and < 5% decline in VC at month 3

Characteristics		5% decline in VC at Month 3			
		No	Yes	Total*	P-value
Age	Subjects	194	67	261	0.3623
	Mean ± S.D.	65.1 ± 6.5	64.1 ± 7.9	64.9 ± 6.9	
BMI	Subjects	194	67	261	0.0011
	Mean ± S.D.	24.7 ± 2.9	23.3 ± 2.9	24.3 ± 3.0	
PaO_2	Subjects	192	67	259	0.0047
	Mean ± S.D.	81.5 ± 9.6	78.1 ± 7.9	80.6 ± 9.3	
SpO_2	Subjects	193	67	260	0.1114
	Mean ± S.D.	89.1 ± 2.2	88.6 ± 2.2	89.0 ± 2.2	
VC	Subjects	194	67	261	0.0036
	Mean ± S.D.	2.51 ± 0.67	2.24 ± 0.63	2.44 ± 0.67	
%VC	Subjects	194	67	261	0.0127
	Mean ± S.D.	79.4 ± 17.2	73.3 ± 17.1	77.8 ± 17.3	
TLC	Subjects	193	67	260	0.0219
	Mean ± S.D.	3.76 ± 0.92	3.43 ± 1.01	3.68 ± 0.95	
%TLC	Subjects	193	67	260	0.0722
	Mean ± S.D.	75.0 ± 15.1	70.6 ± 17.8	73.9 ± 15.9	
DLCO	Subject	193	67	260	0.0639
	Mean ± S.D.	9.82 ± 3.23	9.00 ± 3.07	9.61 ± 3.20	
%DLCO	Subjects	193	67	260	0.1768
	Mean ± S.D.	54.4 ± 17.8	51.0 ± 18.0	53.6 ± 17.9	
KL-6	Subjects	194	67	261	0.4436
	Mean ± S.D.	1308.2 ± 771.0	1401.9 ± 889.2	1332.2 ± 802.3	
SP-A	Subjects	194	67	261	0.0281
	Mean ± S.D.	88.0 ± 43.0	108.3 ± 69.7	93.2 ± 51.8	
SP-D	Subjects	194	67	261	0.0344
	Mean ± S.D.	223.1 ± 130.5	282.1 ± 210.9	238.2 ± 156.8	
H-J classification	Subjects	194	67	261	0.0765
	Mean ± S.D.	2.0 ± 0.7	2.2 ± 0.7	2.1 ± 0.7	

* Patients for whom the changes in VC at month 3 couldn't be calculated were deleted from the analysis. The differences in the number of subjects among the variables at column 'Total' were due to missing values at baseline.

TLC, total lung capacity; PaO_2, arterial oxygen tension; SpO_2, oxygen saturation by pulse oximetry; DLCO, diffusing capacity for carbon monoxide; SP-A (or D), Surfactant protein-A (or D); BMI, Body Mass Index.

Early identification of the response to therapeutic medication provides a clue in clinical decision making on treatment policy. We analyzed the positive/negative predictive values using the improvement ratings of months 3 and 12 based on 5% decline in VC. From the results of the differences of negative predictive values between placebo (50.8%) and pirfenidone (71.7%) groups, the efficacy of pirfenidone was also demonstrated (p = 0.0046). Thus, about 70% of patients assessed as non-progression at month 3 in pirfenidone group might remain in the state at 1 year. However, the

Table 3 Outcome of patients; Change from baseline to month 12 in H-J classification for patients with ≥ 5% and < 5% decline in VC

	5% decline in VC at month 3			
	No	Yes	Total*	P-value
Subjects	194	67	261	
Mean ± S.D.	0.1 ± 0.7	0.6 ± 0.9	0.2 ± 0.8	0.0002

Table 4 Outcome after month 12; Mortality ratio and incidence of acute exacerbation in patients with ≥ 5% and < 5% decline in VC

	5% decline in VC at Month 3			
	No	Yes	Total*	P-value
Subjects	194	67	261*	
Mortality (%)	4 (2.04)	6 (8.96)	10	0.0203
Acute exacerbation (%)	7 (3.61)	6 (8.96)	13	0.1031

* Patients for whom the changes in VC at month 3 couldn't be calculated were deleted from the analysis.

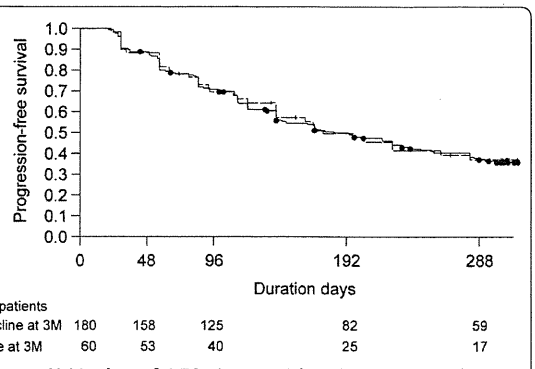

Figure 3 K-M plot of PFS times with origin at month 3 in groups of patients with and without 5% decline in VC at month 3. Solid line with closed circle: No decline in VC at month 3; broken line with plus: a ≥ decline in VC at month 3. P-value was 0.8835 with log-rank test.

results of the positive predictive values of placebo and pirfenidone groups showed that both values were very high, i.e., 86.1% and 87.1%, respectively. These results showed that the progression detected at month 3 remained (not reversed) at month 12 in most cases. These analyses suggested the possibility of identifying whether patients respond to pirfenidone or not at early phase after intervention, and of motivating patients to continue medication.

On the other hand, it will be a crucial question whether treatment should be withdrawn in patients who decline by ≥ 5% in VC at month 3. Patients with VC declined by 5% at month 3 generally had lower means of PaO2, VC, %VC, TLC, %TLC, and DLCO at baseline, and had higher means of SP-A, SP-D and dyspnea in daily living assessed with H-J classification score at baseline (Table 2). It was suggested that those patients with impairment of these baseline characteristics may lead to be corresponded to relatively "rapid progressors" in IPF, and treatment of any additional therapy would be recommended as soon as allowed. The effect of additional therapy strategies, such as combination with NAC [22] or BIBF-1120 [27], should be addressed in further clinical trials.

In order to translate the 5% decline in VC into a clinical relevant outcome, we compared the clinical outcomes (dyspnea in daily living assessed with H-J classification, mortality rate, and incidence of acute exacerbation) between 2 classes of patients, i.e., those with "worsened (VC ≥ 5% decrease)" and others with "non-worsened (VC < 5% decrease)" at month 3 (Table 3, 4). In short, dyspnea in daily living and mortality rate of patients with worsened at month 3 were significantly worsened after 1 year. Similar trend was also seen in the prevalence of acute exacerbation between the 2 classes of patients, which marginally supported the significance of the 5% change in VC. We speculated that the patients with 5% decline in VC at month 3 have further progression more easily; however, PFS times with origin at month 3 were not different between patients with or without 5% decline in VC at month 3 (Figure 3). Namely, it is noted that declines in VC at month 3 do not mean the possibility of further progression in next 9 months, i.e., month 3 to 12. In summary, except for the results of PFS times, it was suggested that a 5% decline in VC at month 3 is a clinically meaningful indicator in IPF and may be a useful prognostic factor. As the potential limitation, it should be addressed that these analytical results were obtained by the small number of subjects with death or prevalence of acute exacerbation within a one year study period.

Conclusion

Results shown in this paper suggested that when 5% change in VC was used as an index instead of the 10% change, the efficacy of pirfenidone could be evaluated with higher sensitivity and robustness over the 12 month study. It was also shown by the results that the 5% change in VC at month 3 is suggested to be a clinically useful and significant promising prognostic factor of IPF.

Abbreviations used in this paper

IPF: idiopathic pulmonary fibrosis; VC: vital capacity; FVC: forced vital capacity; TLC: total lung capacity; PaO_2: alveolar-arterial oxygen tension; PFS: progression-free survival; SpO_2: oxygen saturation by pulse oximetry; DLCO: diffusing capacity for carbon monoxide; FAS: full analysis set; PFT: pulmonary function test; 6MET: 6-minute steady-state exercise test; SP-A (or D): Surfactant protein-A (or D); K-M: Kaplan-Meier; BMI: Body Mass Index; H-J: Hugh-Jones; ATS: American Thoracic Society; ERS: European Respiratory Society.

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Authors' contributions

HT and YK contributed equally to this extended analysis and should be considered co-first authors. All authors listed made significant conceptual and intellectual contributions to the design and conception of this phase III trial, substantially contributed to the article, and have provided final approval of the version submitted.

Competing interests

HT, ME, AA, YT, MS, HT, KN, AS, SK, and TN have received consultancy fees for advisary board, and HT, YK, ME, TO, AA, YS, and TN have received fees for speaking from Shionogi & Co., Ltd.

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An epidemiological study of the effects of statin use on airflow limitation in patients with chronic obstructive pulmonary disease

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1 SUMMARY AT A GLANCE

Statins have a variety of effects in patients with COPD. The prevalence of airflow limitation was approximately five times lower among patients using statins than among those not using statins. This is the first study from Japan demonstrating that statin use has a potential impact on airflow limitation.

2

ABSTRACT

Background and objective: COPD is considered to be a systemic inflammatory disease, and systemic inflammation has been noted as a factor contributing to cardiovascular disease, which is one of the comorbidities associated with COPD. On the other hand, pleiotropic effects, such as the anti-inflammatory effects of statins, have attracted attention in recent years, and there have been a variety of reports regarding the usefulness of statins for patients with COPD.

Methods: We investigated whether the use or non-use of statins influenced the prevalence of airflow limitation. All outpatients who were over the age of 40 years and who regularly visited a primary health care facility were invited to participate. Each participant underwent spirometry and completed a questionnaire regarding their clinical status, which was used to screen for COPD. A variety of factors that are potentially related to airflow limitation were assessed.

Results: Of the 853 patients included in the study, 81 (9.5%) had airflow limitation. The prevalence of airflow limitation was 2.3% among the 89 patients with a history of statin use, which was five times lower than the prevalence of airflow limitation among patients who had not used statins (10.5%). Among the 347 patients with a history of past or current smoking, airflow limitation was not observed in the 30 patients who had

used statins. However, by multivariate analysis, statin use was not significantly associated with a lower prevalence of airflow limitation.

Conclusions: This is the first cross-sectional study from Japan that has demonstrated that statin use has a potential impact on airflow limitation in patients with COPD.

INTRODUCTION

COPD is characterized by chronic airflow limitation and a range of pathological changes in the lungs, as well as significant extra-pulmonary effects and important comorbidities that may contribute to the severity of the disease.[1] The levels of inflammatory markers, such as serum CRP, TNF-α, IL-6 and IL-8, have been reported to be elevated in COPD patients,[2-5] and Young *et al.*[6] demonstrated the role of IL-6 in the pulmonary inflammation and matrix remodelling that underlies COPD. Recently, it has been suggested that COPD should be considered as a chronic systemic inflammatory disease.[7] In addition, it has been suggested that systemic inflammation in COPD may be strongly associated with cardiovascular disease, osteoporosis, weight loss, and skeletal muscle atrophy.[1,6,8] With regard to the pathogenesis of COPD, the potential systemic spread of localized pulmonary inflammation is associated with smoking and other factors, and it is possible that pulmonary and systemic inflammation are induced by common risk factors such as current smoking; however, at present, the mechanisms associated with the pathogenesis of systemic inflammation in patients with COPD remain unknown.[9]

Statins play an important role in the prevention and treatment of hyperlipidaemia and atherosclerotic disease, and recently have been reported to have pleiotropic effects,

including anti-inflammatory, anti-fibrotic and immunomodulatory effects.[10-12] Statins have also been reported to have a variety of effects in patients with COPD,[13-17] and it has been noted that they may represent a new treatment strategy for COPD.[6,18] Young *et al.*[6, 19] suggested that through their anti-inflammatory effects, statins may confer a mortality benefit in patients with COPD and associated comorbidities, specifically coronary artery disease, chest infections, and lung cancer. Although randomized controlled trials are needed to confirm and quantify these pulmonary effects, there is no doubt that statins reduce systemic inflammation and mortality, and are potentially useful in the management of COPD.[20]

In this study, we investigated whether the use or non-use of statins influenced the prevalence of airflow limitation. Each participant underwent spirometry and completed a questionnaire regarding their clinical status. A variety of factors that are potentially related to airflow limitation were assessed. Clinical parameters, including smoking status, current respiratory symptoms (cough, sputum, dyspnoea, wheeze) and use of statins for hyperlipidaemia and anti-hypertensive drugs for high blood pressure, were analyzed.

METHODS

Subjects

This cross-sectional epidemiological study was conducted during the one-year period from November 2007 to October 2008. All outpatients over the age of 40 years, who regularly visited one of 16 primary health care facilities affiliated with Jichi Medical University, were invited to participate in the study. Participants were recruited using poster advertisements or were orally invited to participate. Each participant underwent spirometry and completed a questionnaire regarding their clinical status, which was used to screen for COPD. A variety of factors that are potentially related to airflow limitation were analyzed. The questionnaire was used to obtain information regarding the reason for the visit (treated disease), any respiratory disease that was previously diagnosed or treated, history of smoking, occupational history, other past medical history, the presence or absence of current respiratory symptoms (cough, sputum, dyspnoea, wheeze), and current use of medications [statins, angiotensin receptor blockers (ARB) and angiotensin converting enzyme inhibitors (ACEI)], and this information was subsequently confirmed by the primary physicians.

Spirometry was performed for those patients whose disease was stable, excluding those who had a previous history or treatment for COPD and asthma, which may cause