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Clinical Trial Paper

Pirfenidone for acute exacerbation of idiopathic pulmonary fibrosis: A retrospective study

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ABSTRACT

Background: Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is a rapid and ultimately fatal condition, and no effective treatment has been established. Pirfenidone has antifibrotic effects in IPF; however, its efficacy for AE-IPF is unclear.
Objectives: To evaluate the efficacy of pirfenidone for AE-IPF.
Methods: We retrospectively reviewed the medical records of 135 IPF patients treated during the period from April 2008 to April 2015 and identified and extracted 47 AE-IPF patients (42 men, 5 women; mean age, 73.5 years). The clinical features and outcomes of the 20 patients treated with pirfenidone were compared with those of the 27 patients treated without pirfenidone. We then excluded the 25 patients who did not receive recombinant human soluble thrombomodulin (rhTM) and analyzed data from the remaining 22 patients (20 men, 2 women; mean age, 73.7 years). Clinical features and outcomes were compared between the 10 patients treated with pirfenidone and the 12 patients who did not receive pirfenidone.
Results: There were no significant differences between the two groups in baseline characteristics, except for pirfenidone use before onset. Three-month survival was significantly better in patients treated with pirfenidone than in the control group (55% vs 34%, $p = 0.042$). In univariate analysis, nonuse of pirfenidone was a potential risk factor for death at 3 months (hazard ratio, 6.993; $p = 0.043$) in patients treated with rhTM.
Conclusion: A regimen of pirfenidone combined with corticosteroids and rhTM may improve survival in patients with AE-IPF.

1. Introduction

Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is associated with a high mortality rate [1–4]. Although many patients with AE-IPF still receive systemic corticosteroids, no effective treatment for AE-IPF has been established [5]. Evidence from a small number of studies showed that recombinant human thrombomodulin (rhTM) was beneficial for AE-IPF [6–9]. Pirfenidone treatment slows progression of chronic IPF (as measured by changes in forced vital capacity and progression-free survival) [10], but its effects have not been demonstrated in patients with AE-IPF. The antifibrotic effect of pirfenidone is believed to be caused by suppression of inflammatory cytokines, as indicated in a mouse model of bleomycin-induced pulmonary fibrosis [11]. Pirfenidone inhibits transforming growth factor-β (TGF-β) and has antifibrotic, anti-inflammatory, and antioxidant effects [12]. Pirfenidone was recently found to be effective for a patient with AE-IPF [13], but this result requires careful evaluation. The present study investigated the efficacy of pirfenidone for AE-IPF.

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2. Material and methods

2.1. Study design

This single-center retrospective cohort study reviewed patient medical records and collected data on the clinical and laboratory characteristics of patients who received a diagnosis of AE-IPF at Toho University Omori Medical Center during the period from April 2008 to April 2015. The records investigated included case histories and computed tomography (CT) images.

2.2. IPF diagnostic criteria

The American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines [14] indicate that a diagnosis of IPF should be based on 1) exclusion of other known causes of interstitial lung disease (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity), 2) presence of a usual interstitial pneumonia (UIP) pattern on high-resolution CT (HRCT) in patients who have not undergone surgical lung biopsy, and 3) specific combinations of HRCT and surgical lung biopsy pattern in patients who have undergone surgical lung biopsy.

2.3. AE-IPF definition

In the present study, AE-IPF was defined based on the criteria proposed by The American Thoracic Society [5], as follows: 1) previous or concurrent diagnosis of IPF, 2) acute worsening or development of dyspnea typically < 1 mo duration, 3) computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern, 4) deterioration not fully explained by cardiac failure or fluid overload.

2.4. Treatment protocol for AE-IPF

All AE-IPF patients were treated with corticosteroid (CS) pulse therapy for 3 days, followed by a maintenance dose of CS, as conventional therapy with or without pirfenidone. Pirfenidone administration was continued in patients who had received pirfenidone before AE-IPF onset. For patients who had not received pirfenidone before AE-IPF, pirfenidone was started at 600 mg/day within 4 days (median; 1, range; 1–4 day) and increased to a maintenance dose (1200–1800 mg/day) after confirming that there were no adverse events. In April 2012, pirfenidone administration was added to our institute's AE-IPF treatment protocol for patients who have not received pirfenidone before AE-IPF onset. Because several small studies showed that rhTM was beneficial for AE-IPF [6–9], rhTM use is a confounder in evaluating the efficacy of pirfenidone for AE-IPF. We therefore excluded patients treated without rhTM and performed separate analyses of patients treated with rhTM with and without pirfenidone. rhTM was administered at a dose of 0.06 mg/kg/day for 6 days from onset, after confirming the absence of hemorrhagic disease. In addition, a clinical trial of the efficacy of rhTM for AE-IPF was performed at our institute from April 2006 to March 2013 [6].

2.5. Chest CT

Chest CT was performed before (within 6 months) and after AE-IPF onset, using a SOMATOM Definition AS, Flash and Edge scanner (Siemens Co., Ltd., Munich, Germany). After AE-IPF development, the entire lung was scanned in 5.0-mm-thick sections. Additional thin-section CT scanning was performed in all patients, to obtain images of 1.0-mm thickness. Thin-section CT images were reconstructed with a fixed window setting. The CT images were then independently reviewed by one thoracic radiologist (K.M.) and two pulmonologists (K.F. and S.S.) who were blinded to the identity and clinical, physiological, and pathological characteristics of the patients.

2.6. Pulmonary function testing

Lung volumes and forced expiratory volume in 1 s (FEV 1) were measured by standard methods using a Chestac-8800 or Chestac-8900 spirometer (Chest Co., Ltd., Tokyo, Japan) and expressed as a percentage of the predicted value. These measurements were conducted before AE-IPF onset (within 6 months) but could not be repeated at or after AE-IPF because of the patients' poor general condition. Arterial blood gas analysis was conducted using an ABL510 or ABL800 FLEX analyzer (Radiometer Co., Ltd., Copenhagen, Denmark) before (within 6 months), during, and after AE-IPF onset in all patients.

2.7. Data collection

We collected data on serum values for white blood cells (WBC), C-reactive protein (CRP), lactate dehydrogenase (LDH), sialylated carbohydrate antigen Krebs von den Lungen-6 (KL-6), surfactant protein D (SP-D), and PaO2/FiO2 ratio (P/F ratio) before onset (within 6 months of onset), at onset, and at 14 days after onset. Changes in laboratory findings (Δserum value) were calculated by subtracting the value at onset from the value at 14 days after onset. We calculated presymptomatic Gender, Age, Physiology (GAP) score, Acute Physiology and Chronic Health.

Evaluation (APACHE) II score at onset, and Sequential Organ Failure Assessment (SOFA) score at onset.

2.8. Outcomes

The primary outcome was three-month survival after AE-IPF onset. Adverse events were coded according to the preferred terms in the Medical Dictionary for Regulatory Activities, version 11.0. Safety outcomes are reported as events occurring during the period from baseline to 90 days after the last dose of the study drug.

2.9. Statistical analysis

All values are expressed as the median (range), and differences between groups were analyzed using the χ^2 test and Mann-Whitney nonparametric *U* test for two independent samples. Survival was investigated using the Kaplan-Meier method, and differences were assessed by the log-rank test. Cox proportional hazards regression analysis was used to identify variables that were significant predictors of survival. All p values are two-sided and were considered to be statistically significant when less than 0.05. All statistical analyses were performed using SPSS version 11.0 (SPSS Inc, Chicago, IL, USA).

2.10. Ethical considerations

This study was conducted with the approval of the Institutional Review Board of Toho University Omori Medical Center (project approval number 27–106), which also approved the review of patient medical records.

3. Results

3.1. Patient characteristics

We extracted data from 47 AE-IPF patients (42 men; 5 women; mean age, 73.5 years) treated with CS. Median duration of follow-up was 173 days (range; 4–1137 days). Forty-three diagnoses were based on HRCT images, and four were based on histological findings from a lung biopsy. The clinical features and outcomes of the 20 patients treated with pirfenidone were compared with those of the 27 patients treated without pirfenidone (Fig. 1). There were no significant differences between the groups in baseline characteristics, laboratory data, or physiological findings, except for pirfenidone use before onset (Table 1). We excluded the 25 patients who did not receive rhTM and analyzed data from the 22 patients (20 men; 2 women; mean age, 73.7 years) treated with CS and rhTM. Nineteen diagnoses were based on HRCT images and three were based on histological findings from a lung biopsy. The clinical features and outcomes of the 10 patients treated with pirfenidone (rhTM with pirfenidone) were compared with those of the 12 patients who did not receive pirfenidone (rhTM without pirfenidone) (Fig. 1). There were no significant differences between the groups in baseline characteristics, laboratory data, or physiological findings, except for pirfenidone use before onset (Table 2). Eleven patients of all the patients, and six of the 22 patients who received rhTM, had received pirfenidone before AE-IPF onset (median duration of administration; 164 days, range; 35–1290 and 127 days, range; 35–1290, respectively); all continued pirfenidone therapy after AE-IPF onset.

3.2. Changes in laboratory findings

There were no significant differences between groups in serum WBC, CRP, LDH, KL-6, SP-D, or P/F ratio (Table 3). Among patients treated with rhTM, the mean decline in serum KL-6 from baseline to 14 days after AE-IPF onset significantly differed between the two groups (12.5 vs 505.4 U/ml in the rhTM with pirfenidone and rhTM without pirfenidone groups, respectively; $p = 0.029$). There was no significant difference between groups in serum WBC, CRP, LDH, SP-D, or P/F ratio among patients treated with rhTM (Table 4).

3.3. Survival in all the patients

During the observation period, 27 of 47 patients (57%) died: 9 (45%) had received pirfenidone and 18 (66%) had not. Twenty-four out of 27 patients died from respiratory failure caused by AE-IPF, and three died from progression of chronic IPF. The 3-month survival rate was significantly better in patients receiving pirfenidone than in patients not receiving pirfenidone (55% vs. 34%, $p = 0.042$) (Fig. 2).

There were no significant differences in 3-month survival between nine patients receiving pirfenidone at onset and 27 patients not receiving pirfenidone (44% vs. 34%, $p = 0.391$) and between nine patients receiving pirfenidone at onset and 11 patients receiving pirfenidone before onset (44% vs. 55%, $p = 0.365$). Among rhTM-treated patients, 9 of 22 (41%) died during the observation period: two (20%) had received pirfenidone and seven (58%) had not. All 9 patients died from respiratory failure caused by AE-IPF. There was no significant difference in 3-month survival rate between patients receiving rhTM with and without pirfenidone (80% vs. 42%, $p = 0.067$), however it showed a tendency (Fig. 3). One out of 4 (25%) patients died who started pirfenidone at AE-IPF onset.

3.4. Univariate cox analysis of potential risk factors for death

In univariate analysis, nonuse of rhTM was a potential risk factor for death (hazard ratio [HR], 3.717; $p = 0.035$) (Table 5). Although survivors and nonsurvivors did not significantly differ with respect to pirfenidone use (HR, 2.445; $p = 0.141$) in the analysis of all patients (Table 5), nonuse of pirfenidone was a potential risk factor for

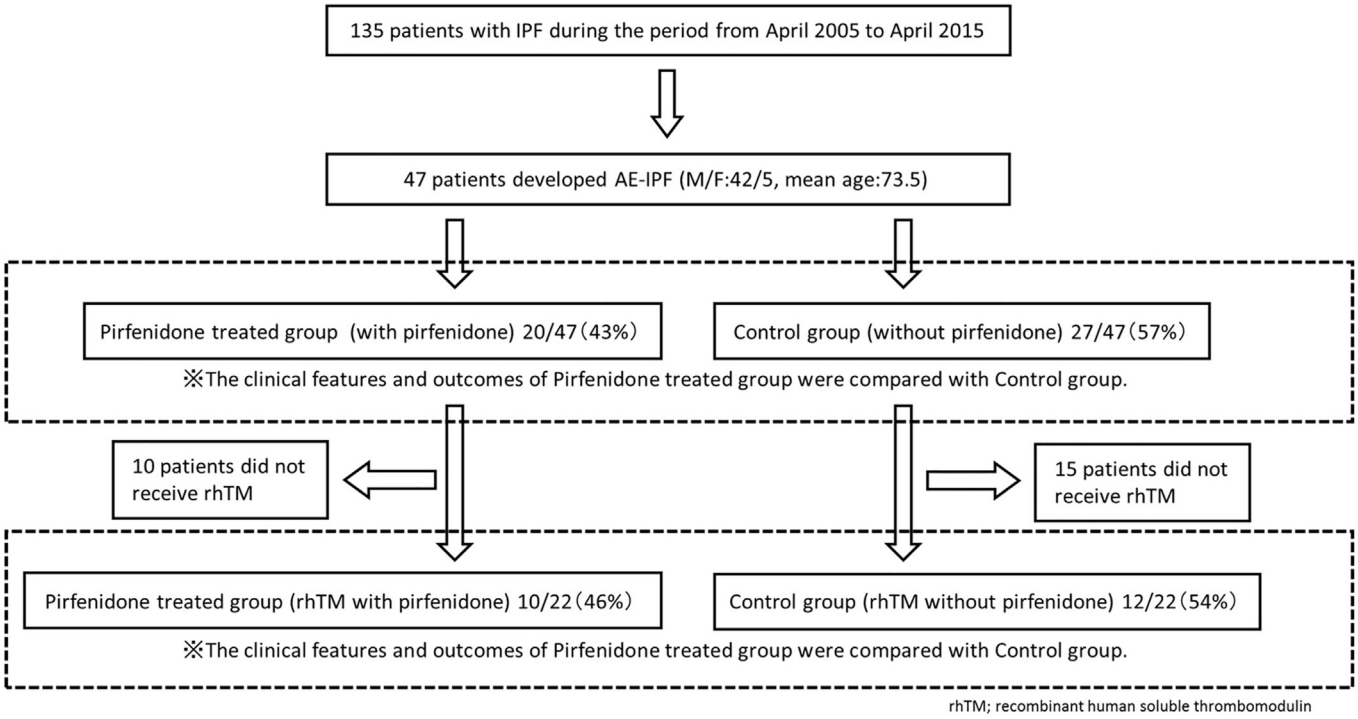

Fig. 1. Study design.

Table 1
Patient characteristics at and prior to onset of AE-IPF in all the patients.

	with pirfenidone (n = 20)	without pirfenidone (n = 27)	p value
Gender (M/F)	18/2	24/3	1.000
Age	76 (66–82)	73 (64–84)	0.511
Smoking history (packs per year)	46 (0–180)	30 (0–86)	0.418
Prednisolone use before onset [number (%)]	6 (30%)	6 (22%)	0.737
Immunosuppressant use before onset [number (%)]	4 (20%)	1 (4%)	0.148
N-acetylcysteine use before onset [number (%)]	8 (40%)	9 (33%)	0.761
Pirfenidone use before onset [number (%)]	11 (55%)	0 (0%)	0.001
Nintedanib use before onset [number (%)]	0 (0%)	0 (0%)	
Use of supplemental oxygen [number (%)]	7 (35%)	6 (22%)	0.511
GAP score (≦4) [number (%)]	14 (70%)	18 (66%)	0.748
pathological UIP [number (%)]	3 (15%)	1 (4%)	0.298
APACHE II score	10.5 (4–21)	11 (4–21)	0.761
SOFA score	2 (1–7)	2 (1–7)	0.600
WBC (mg/dl)	10000 (4900–21200)	10200 (4200–16800)	0.830
CRP (mg/dl)	5.5 (0.6–14.4)	9.2 (0.2–32.5)	0.277
LDH (U/l)	373 (194–831)	328 (193–1005)	0.914
KL-6 (U/ml)	1052 (286–4769)	996 (313–2930)	0.949
SP-D (ng/ml)	304 (85–1410)	242 (96–770)	0.245
P/F ratio	267 (46–330)	260 (60–334)	0.846
FVC (ml)	2390 (1180–3700)	2395 (1210–3300)	0.377
%FVC (%)	72.7 (39.7–100.8)	75.8 (44.5–112.8)	0.212
DLco (%)	49.2 (26.3–75.6)	55.8 (22.3–93.6)	0.525
rhTM use in AE-IPF[number (%)]	10 (50%)	12 (44%)	0.773

GAP, gender, age, physiology; UIP, usual interstitial pneumonia; WBC, white blood cell; CRP, C-reactive protein; LDH, lactate dehydrogenase; KL-6, sialylated carbohydrate antigen Krebs von den Lungen-6; SP-D, surfactant protein-D; P/F, partial pressure of oxygen in arterial blood/fractional concentration of oxygen in inspired gas; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide.

Table 2
Patient characteristics at and prior to onset of AE-IPF in the patients treated with rhTM.

	rhTM with pirfenidone (n = 10)	rhTM without pirfenidone (n = 12)	p value
Gender (M/F)	9/1	11/1	0.714
Age	76 (58–80)	76 (65–86)	0.29
Smoking history (packs per year)	43 (0–100)	40 (0–88)	0.446
Prednisolone use before onset [number (%)]	3 (30%)	2 (17%)	0.468
Immunosuppressant use before onset [number (%)]	2 (20%)	0 (0%)	0.112
N-acetylcysteine use before onset [number (%)]	4 (40%)	5 (41%)	0.938
Pirfenidone use before onset [number (%)]	6 (60%)	0 (0%)	0.001
Nintedanib use before onset [number (%)]	0 (0%)	0 (0%)	
Use of supplemental oxygen [number (%)]	2 (20%)	2 (17%)	0.632
GAP score (≦4) [number (%)]	5 (50%)	8 (67%)	0.278
Pathological UIP [number (%)]	2 (20%)	1 (8%)	0.429
APACHE II score	10.5 (4–20)	11 (7–21)	0.406
SOFA score	2 (1–6)	2 (1–7)	0.412
WBC (mg/dl)	8800 (4200–15600)	8950 (6000–16800)	0.468
CRP (mg/dl)	6.5 (0.6–14.4)	5.35 (0.6–14.9)	0.792
LDH (U/l)	327 (222–433)	396 (255–620)	0.166
KL-6 (U/ml)	943 (313–1676)	1107 (286–4769)	0.429
SP-D (ng/ml)	228 (120–1050)	268 (90–1100)	0.767
P/F ratio	256 (53–334)	264 (50–309)	0.232
FVC (ml)	2665 (1500–3510)	2190 (1430–3290)	0.288
%FVC (%)	83.1 (47.0–114.3)	72.9 (44.5–85.9)	0.221
DLco (%)	48.0 (28.8–66.3)	54.7 (26.3–93.6)	0.566

Table 3
Changes in laboratory findings among the patients.

	with pirfenidone (n = 20)	without pirfenidone (n = 27)	p value
Δ WBC (mg/dl)	+550 (−6300 - +9100)	+1700 (−700 - +14900)	0.137
Δ CRP (mg/dl)	−4.7 (−8.0 - +7)	−5.6 (−20.4- +28.9)	0.934
Δ LDH (U/l)	−52 (−386 - +1255)	+63 (−313 - +505)	0.183
Δ KL-6 (U/ml)	+14 (−569 - +838)	+294 (−480 - + 1735)	0.691
Δ SP-D (ng/ml)	−26 (−557 - +103)	−37 (−451 - +844)	0.596
Δ P/F ratio	+7 (−65 - +349)	−42 (−182 - +100)	0.114

Table 4
Changes in laboratory findings among patients treated with rhTM.

	rhTM with pirfenidone (n = 10)	rhTM without pirfenidone (n = 12)	p value
Δ WBC (mg/dl)	+1250 (−4300 - +9100)	+2700 (−2700 - +14900)	0.346
Δ CRP (mg/dl)	−4.4 (−10.0 - +7)	−2.9 (−10.4 - +28.9)	0.910
Δ LDH (U/l)	−22 (−159 - +1255)	−30 (−376 - +505)	0.923
Δ KL-6 (U/ml)	+24.5 (−569 - +838)	+206 (−17 − +1735)	0.029
Δ SP-D (ng/ml)	−55 (−148 - +126)	+22 (−128 - +844)	0.063
Δ P/F ratio	+25 (−86 - +349)	+5 (−151 - +161)	0.936

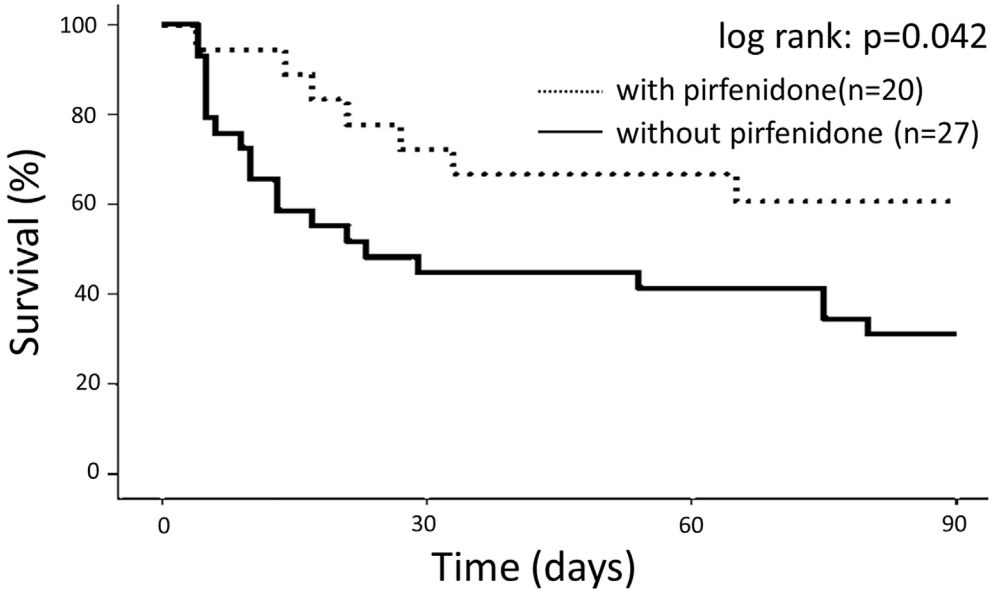

Fig. 2. The 3-month survival rate was significantly better for patients receiving pirfenidone than for patients not receiving pirfenidone (55% vs 34%, p = 0.042) in an analysis of all patients.

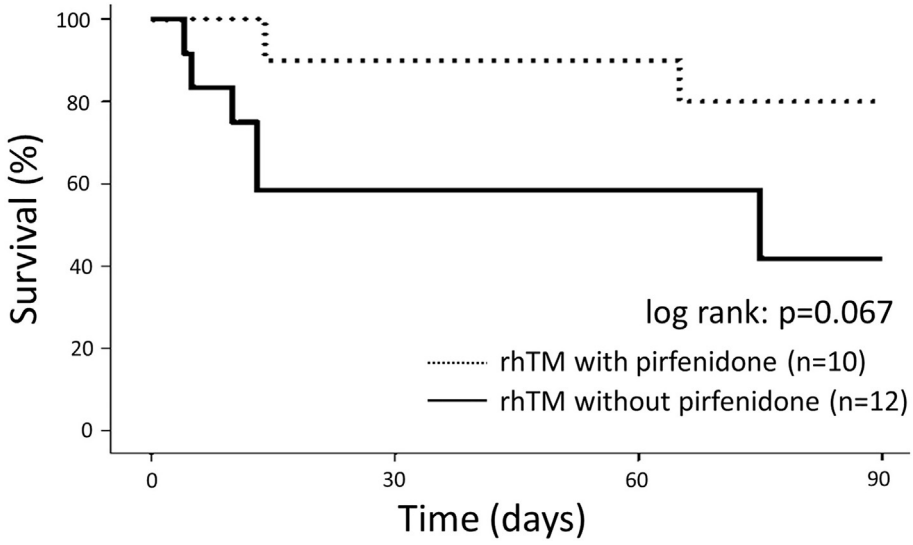

Fig. 3. Among patients treated with rhTM, there was no significant difference in 3-month survival rate between rhTM treatment with and without pirfenidone (80% vs 42%, p = 0.067).

death (HR, 6.993; p = 0.043) among patients treated with rhTM (Table 6). Survivors and nonsurvivors did not significantly differ with respect to prior treatment of pirfenidone among all patients (HR, 2.404; p = 0.244) and in patients receiving pirfenidone (HR, 0.457; p = 0.394).

3.5. Adverse events

There were no severe adverse events, including gastrointestinal discomfort during administration of a prokinetic agent, in patients treated with pirfenidone during the observation period.

Table 5
Univariate Cox analysis of potential risk factors for death: all patients.

	HR	95% CI	p value
Male	2.206	0.332–14.635	0.413
Age	0.998	0.912–1.093	0.971
Smoking history (packs per year)	1.001	1.000–1.002	0.045
GAP score (≦4)	2.864	0.809–10.142	0.103
Use of supplemental oxygen	1.263	0.342–4.665	0.762
APACHE II score	1.125	0.969–1.305	0.121
SOFA score	1.313	0.874–1.973	0.189
CRP (mg/dl)	1.139	1.003–1.294	0.045
LDH (U/l)	1.004	0.999–1.009	0.141
KL-6 (U/ml)	1.000	0.999–1.001	0.847
SP-D (ng/ml)	1.002	1.000–1.005	0.069
P/F ratio	0.995	0.989–1.002	0.140
FVC (ml)	1.104	0.596–2.045	0.753
%FVC (%)	1.004	0.984–1.024	0.724
DLco (%)	1.005	0.981–1.029	0.711
Nonuse of pirfenidone in AE-IPF	2.445	0.124–1.345	0.141
Nonuse of rhTM in AE-IPF	3.717	0.080–0.910	0.035

Table 6
Univariate Cox analysis of potential risk factors for death in patients treated with rhTM.

	HR	95% CI	p value
Male	1.222	0.067–22.401	0.892
Age	1.027	0.913–1.155	0.658
Smoking history (packs per year)	1.000	0.999–1.002	0.766
GAP score (≦4)	1.463	0.829–2.582	0.189
Use of supplemental oxygen	0.800	0.091–7.002	0.840
APACHE II score	1.111	0.897–1.376	0.335
SOFA score	1.074	0.634–1.817	0.792
CRP (mg/dl)	1.199	0.957–1.503	0.114
LDH (U/l)	1.007	0.997–1.016	0.169
KL-6 (U/ml)	1.001	1.000–1.002	0.304
SP-D (ng/ml)	1.004	0.999–1.010	0.111
P/F ratio	0.993	0.940–1.003	0.182
FVC (ml)	0.643	0.171–2.420	0.514
%FVC (%)	0.984	0.941–1.029	0.470
DLco (%)	1.015	0.963–1.069	0.580
Nonuse of pirfenidone in AE-IPF	6.993	0.022–0.937	0.043

4. Discussion

AE-IPF is defined as acute, idiopathic, clinically significant deterioration in a patient with underlying IPF. The prognosis is poor, and no effective treatment has been established. In the absence of better therapeutic options, high-dose corticosteroid therapy is administered to patients with AE-IPF [5]. Evidence from a small number of studies indicates that recombinant human thrombomodulin (rhTM) is beneficial for AE-IPF [6–9], as it appears to suppress inflammation by inhibiting high mobility group box protein. In our analysis of all patients with AE-IPF, rhTM improved survival; thus, rhTM use might be a confounder in an analysis of the efficacy of pirfenidone for AE-IPF. However, pirfenidone appeared to improve the outcomes of patients with AE-IPF receiving rhTM in this study. Pirfenidone also suppresses inflammatory cytokines such as TGF-β and basic fibroblast growth factor (b-FGF), which are related to fibrosis progression and subsequent anti-inflammatory and antifibrotic effects [15–17]. In a mouse model of bleomycin-induced lung fibrosis, pirfenidone suppressed TGF-β and b-FGF [11]. Although corticosteroids have anti-inflammatory activity, they do not act on TGF-β or b-FGF, which are related to the fibrotic process. Increased serum TGF-β activity promotes diffuse alveolar damage (DAD) by reducing.

alveolar fluid clearance, and involvement of TGF-β in the development of AE-IPF has.

been suggested [18]. AE-IPF usually manifests histopathologically as DAD, and TGF-β elevation was reported during AE-IPF onset [19]. Past findings suggest that administration of pirfenidone in combination with corticosteroids is a reasonable treatment option for patients with AE-IPF, as it inhibits DAD. KL-6 originates from type 2 pneumocytes and reflects tissue damage in peripheral lung tissue. It was reported to be a useful indicator of disease activity in patients with interstitial lung disease [20]. KL-6 is also elevated in AE-IPF, as it reflects lung injury, and decreases in parallel with the course of improvement [21,22]. In the present study, the mean decline in serum KL-6 was significantly greater in patients treated with rhTM and pirfenidone than in those treated with rhTM without pirfenidone; the results for SP-D were similar. These results may reflect the therapeutic effects of conventional therapy with pirfenidone. Several previous studies reported that some patients developed adverse events such as decreased appetite and photosensitivity reaction during pirfenidone treatment [10,23,24]. In the present study, no patients developed adverse events, including gastrointestinal discomfort during administration of a prokinetic agent, during the observation period. Our results suggest that pirfenidone is efficacious and well tolerated. The efficacy of pirfenidone for chronic IPF has already been shown and it is possible that prior treatment of pirfenidone affects the response in the acute phase of AE-IPF because TGF-β has been shown to be involved in the progression of chronic IPF [25,26], similar to AE-IPF [19]. However, pirfenidone has not been suggested to reduce risk and to improve survival of AE-IPF in large studies [10,24]. Because the present study is a small study, it is difficult to compare the efficacy between the groups administered pirfenidone before onset and at onset. Therefore, it is difficult to clarify whether pirfenidone is acting to prevent worsening or to actually treat AE-IPF because only minority of patients were taking pirfenidone at onset. However, it is thought that pirfenidone exerts a therapeutic effect via suppressing inflammation in the acute phase and inhibiting of progression of fibrosis after acute phase. Our results indicate that pirfenidone is safe and improves survival in patients with AE-IPF. Although AE-IPF is a fatal condition with no effective treatment, our findings may help improve the poor prognosis for this patient subgroup. Of course, it is possible that other drugs, such as CS and rhTM, or synergistic effects with other treatments were responsible for the present results. This study may add to the current knowledge of how to manage AE-IPF. Additional data are needed to fully understand the impact of therapies on the outcome of AE-IPF. Large, randomized, placebo-controlled trials of pirfenidone are thus warranted in order to resolve this uncertainty.

5. Limitations

The present study was a single-center retrospective study with a small sample size. It remains to be determined if pirfenidone treatment for patients with AE-IPF improves survival or quality of life. Another limitation is that, because of the large number of early deaths, we lack data on laboratory findings. Thus, future longitudinal studies are warranted.

6. Conclusions

A regimen of pirfenidone combined with CS and rhTM was well tolerated and may improve survival in patients with AE-IPF. Large, placebo-controlled, randomized trials are required in order to confirm the effectiveness of pirfenidone in patients with AE-IPF.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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