SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2019; 36 (3): 176-184 DOI; 10.36141/svdld.v36i3.7750 © Mattioli 1885

Pharmacological treatment of acute exacerbation of idiopathic pulmonary fibrosis: a retrospective study of 88 patients

Susumu Sakamoto[1], Hiroshige Shimizu[1], Takuma Isshiki[1], Atsuko Kurosaki[2], Sakae Homma[1]
[1]Division of Respiratory Medicine, Toho University Omori Medical Center; [2]Department of Diagnostic Radiology, Fukujuji Hospital

Abstract. *Background:* Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is often fatal. Although pharmacological treatments have been studied, outcomes remain poor. This study evaluated the effectiveness of pharmacological treatments for AE-IPF. *Methods:* This retrospective study comprised 88 patients who received a diagnosis of AE-IPF and were admitted to our center during the period from January 2008 through April 2017. We reviewed the clinical features, treatments, and outcomes of the 88 patients. Cox proportional hazards regression analysis was used to identify variables that were significant predictors of 3-month death. *Results:* Data from 88 AE-IPF patients (age range, 56-81 years) were analyzed. In all patients, corticosteroid (CS) pulse therapy was performed an average of 1.7 times, and the initial CS maintenance dose was 1 mg/kg for 65 patients and 0.5 mg/kg for 23 patients. The combination treatments received were sivelestat in 83 patients (94%), recombinant human thrombomodulin (rhTM) in 45 patients (51%), pirfenidone in 41 patients (47%), and cyclosporine in 71 patients (81%). Univariate analysis showed that use of rhTM, and an initial CS maintenance dose of 0.5 mg/kg were associated with better 3-month survival. In multivariate analysis, both use of rhTM and an initial CS maintenance dose of 0.5 mg/kg were associated with better 3-month survival. Other treatments, including sivelestat, cyclosporine, pirfenidone, and polymyxin B-immobilized fiber column-direct hemoperfusion, were not associated with better 3-month survival. *Conclusion:* Addition of rhTM to CS, and a low initial CS maintenance dose (0.5 mg/kg), were associated with better 3-month survival in patients with AE-IPF. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36 (3): 176-184)*

Key words: pharmacological treatment, fibrosing interstitial pneumonia, acute exacerbation, corticosteroid maintenance therapy, recombinant human thrombomodulin

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing interstitial lung disease characterized by the histological pattern of usual interstitial pneumonia (UIP). The clinical course of IFF may include periods of acute deterioration in respiratory function, which are termed acute exacerbations of IPF (AE-IPF) when a cause cannot be identified (1, 2). AE-IPF is associated with high morbidity. AE can also develop in patients with fibrotic non-specific interstitial pneumonia or interstitial pneumonia associated with collagen vascular diseases (CVD-IP). These AEs of interstitial pneumonias other than IPF can also be fatal (3).

Evidence regarding the effectiveness of pharmacological treatment for AE-IPF is limited. The international IPF guidelines include a weak rec-

Received: 11 October 2018
Accepted after revision: 6 Augusts 2018
Correspondence: Susumu Sakamoto
Division of Respiratory Medicine
Toho University Omori Medical Center
Ota-ku Omori nisi 6-11-1, Tokyo 143-8541 (Japan)
Tel. +81 3 3762 4151
Fax +81 3 3766 3551
E-mail: susumu1029@gmail.com

ommendation for corticosteroid (CS) treatment for most patients with AE-IPF (4), despite limited evidence of benefit. In clinical practice CS is given, usually in pulsed doses, to most patients who develop AE-IPF. Immunomodulators [cyclosporine (CsA), cyclophosphamide (CPA), or tacrolimus] are sometimes used in addition to CS. However, the evidence of benefit is not conclusive, as immunomodulators were found to be effective for AE-IPF in only a few small retrospective studies (5-9).

Sivelestat is a small-molecule (529 Da) neutrophil elastase inhibitor. Although a phase 3 study in Japan found that sivelestat improved investigator assessment of pulmonary function in patients with acute respiratory distress syndrome (ARDS) (10), several meta-analyses showed that the sivelestat did not improve mortality in ARDS (11). However, few studies have evaluated the effects of sivelestat for AE-IPF (12-13).

Recombinant human thrombomodulin (rhTM) is approved for treatment of disseminated vascular coagulopathy in Japan. rhTM convert plasma protein C into activated protein C, which deactivates coagulant factors and the pro-inflammatory effects of thrombin. Several small-scale studies showed that rhTM was beneficial for AE-IPF (14-16).

Pirfenidone treatment for chronic IPF slows disease progression (17). A small-scale retrospective study showed that pirfenidone was beneficial for AE-IPF (18).

Polymyxin B-immobilized fiber column-direct hemoperfusion (PMX-DHP) is a medical device that uses polystyrene fibers to immobilize polymyxin B and bind circulating endotoxins (19). Clinical reports suggest that PMX-DHP improves oxygenation in patients with ARDS, and AE-IPF (20).

We investigated the associations of various pharmacological treatments with 3-month outcome in patients with AE-IPF.

Patients and methods

Patients

This retrospective study investigated data from 253 consecutive patients with IPF admitted to Toho University Omori Medical Center during the period from January 2008 through April 2017. A total of 88 patients who had received a first clinical diagnosis of AE-IPF (65 with UIP and 23 with probable UIP, according to the 2018 international IPF guideline (21)) satisfied the inclusion criteria.

Data collection

Clinical data were collected to determine the characteristics of underlying IPF and IPF treatment before AE. We also collected data on respiratory function during the 6 months before AE. Covariates analyzed included PaO2/FiO2 ratio, white blood cell (WBC) count, and serological tests, namely, C-reactive protein (CRP), lactate dehydrogenase (LDH), Krebs von den Lungen-6 (KL-6), and surfactant protein D (SP-D), as well as D-dimer, fibrin/fibrinogen degradation products, brain natriuretic peptide (BNP), and estimated mean pulmonary artery pressure on cardiac ultrasonography, at AE onset.

Diagnosis of IPF and AE-IPF

We defined IPF as a probable UIP or definite UIP pattern on HRCT images, in accordance with the 2018 international IPF guideline. HRCT images of all the present patients were reviewed by 3 pulmonologists (H.S, T. I, S.S) and 1 chest radiologist (A. K). The Japanese Respiratory Society (JRS) classification of IPF disease severity (stage I-IV) (22) and the Gender-Age-Physiology (GAP) index (23) were used to determine IPF severity before AE.GAP index was calculated by gender, age, forced vital capacity (FVC) % predicted and diffusion capacity (DLco) % predicted and patients divided to severity of staging as stage I-III as previously described. Disease severity, pulmonary function, IPF treatment, and diagnostic findings on HRCT were assessed while IPF was chronic and stable, ie, before AE-IPF onset.

AE-IPF was defined on the basis of criteria proposed by Collard et al (1,2) and the JRS guidelines (2), with slight modifications, as follows: (1) previous or current diagnosis of IPF or probable UIP, (2) unexplained worsening or development of dyspnea typically of less than 1-month duration, (3) an HRCT scan showing new bilateral ground-glass opacities and/or consolidation superimposed on a background reticular or honeycomb pattern, (4) no evidence of pulmonary infection on bronchoalveolar lavage, endotracheal aspiration, or sputum culture and negative

results on blood tests for other potentially infectious pathogens (e.g. *Pneumocystis jiroveci*, cytomegalovirus), and (5) deterioration not fully explained by cardiac failure, fluid overload, pulmonary embolism, or other possible causes of acute lung injury. Infectious diseases were excluded by examination of several microbiological samples (e.g. cultures of sputum, blood, and urine were examined for mycobacteria, fungi, and bacteria). We also examined urinary antigens for *Streptococcus pneumonia* and *Legionella pneumophilia*, antigens for influenza A and B viruses (by using pharyngeal swabs), β-D-glucan, and serum antigen for *Aspergillus*. Left heart failure and pulmonary embolism were excluded by transthoracic echocardiography, tests of BNP and D-dimer, and contrast-enhanced CT. Using the classification of Akira et al (24), we classified the CT pattern of all patients at AE-IPF onset as diffuse, peripheral, or multifocal.

Treatment of AE-IPF

All patients were treated with high-dose CS pulse therapy (methylprednisolone 1,000 mg/day for 3 days). CS dose was tapered after pulse therapy (0.5-1.0 mg/kg/day). CsA (2.5 mg/kg/day) was combined with CS. Sivelestat was administered intravenously at a dose of 4.8 mg/kg/day for the first 14 days. rhTM was administered intravenously at a dose of 0.06 mg/kg/day for the first 6 days. Pirfenidone administration was continued in 22 patients who had received pirfenidone before AE onset. In patients who had not received pirfenidone before AE onset, pirfenidone was started at 600 mg/day within 4 days after onset in 6 patients and increased to a maintenance dose (1200-1800 mg/day).

PMX-DHP treatment administered sequentially with 2 Toraymyxin 20-R cartridge columns (Toray Industries, Tokyo, Japan) at a flow rate of 80-100 mL/min. Treatment was continued as long as possible beyond 2 hours. A double-lumen catheter was inserted into a central vein to provide blood access for direct hemoperfusion with PMX.

Endpoints

The primary endpoint was to elucidate the predictor of 3-month death after AE-IPF onset and evaluate the efficacy of pharmacological treatment. The secondary endpoint was treatment safety.

Statistical analysis

Continuous variables are expressed as median (range) unless otherwise stated and were compared using the Mann-Whitney U test. Categorical variables were compared with the χ^2 test. Survival was investigated by using the Kaplan-Meier method, and differences were assessed with the log-rank test. Cox proportional hazards regression analysis was used to identify variables that were significant predictors of death. The cut-off value was calculated by receiver-operating- characteristic curve analysis A p-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed by using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA).

Ethics

This study was approved by the Institutional Review Board of Toho University Omori Medical Center, in October 2017 (project approval number M17189).

Results

Patient characteristics

The clinical characteristics of patients before of AE onset (0-6 months) are shown in Table 1. We identified 88 consecutive patients (74 men and 14 women) who had been treated for AE-IPF. The median duration of observation from the first visit to our center was 13 months (range 1-137 months). Seventy-two patients (82%) had a smoking history. Twenty-two patients (25%) had a pathological diagnosis of UIP, as determined by analysis of a surgical lung biopsy specimen obtained 0-36 months before AE-IPF onset (n=18) or by autopsy (n=4).

Table 1 also shows the detailed clinical characteristics of patients at AE onset. WBC count, CRP, KL-6, SP-D were elevated at AE-IPF onset, and median PaO_2/FiO_2 ratio was low, at 247. HRCT imaging at AE-IPF onset showed diffuse ground-glass opacities and/or consolidation superimposed on pre-existing subpleural fibrosis. The diffuse CT pattern was the most frequent pattern at AE-IPF onset.

The detailed clinical characteristics of the patients before AE onset (0-6 months) are also shown

Table 1. Patient characteristics at AE-IPF onset and characteristics of underlying IPF before AE

Characteristic at onset of AE-IPF	(n=88)
Age, yr.	74.7 (56-89)
Male sex, no. (%)	74 (84.0)
Laboratory findings	
PaO2/FiO2 ratio	247 (45-485)
WBC count /mm3-	10650 (3300-16900)
CRP (mg/dl)	6.8 (0.2-24.3)
LDH (IU/L)	347 (193-647)
D-dimer (mg/ml)	5.1 (0.9-48.2)
FDP (μg/ml)	9.5 (2.5-107.9)
Serum makers	
KL-6 (U/ml)	1040 (366-10469)
SP-D (ng/ml)	317 (62-1070)
Estimated systolic PAP (mm Hg)	33 (10-65)
HRCT pattern of AE-IPF	
Diffuse/multifocal/peripheral, no. (%)	36 (41)/27 (31)/25 (28)
Characteristics of underlying IPF	
Smoking status (never/former/current)	
Smoking index	16/70/2
860 (0-3600)	
JRS severity stage ≥stage 3, no. (%)	48 (54.5%)
GAP stage ≥2, no. (%)	51 (58.0%)
Use of supplemental oxygen, no. (%)	40 (45.5%)
Diagnostic findings on HRCT	
Probable UIP/ definite UIP, no. (%)	23 (26.1)/65 (73.9)
Pathological UIP, no. (%)	22 (25.0)
Lung physiological features	
Forced vital capacity (L)	2.17 (1.50-3.51)
FVC, % of predicted value	73.7 (47.0- 109.1)
FEV1/FVC (%)	87.5 (67.1- 90.8)
Carbon monoxide diffusing capacity -% of predicted value	53.9 (28.8- 66.3)
IPF treatment before AE	
Pirfenidone	21/88 (24%)
N-acetylcysteine	31/88 (35%)
Corticosteroids	12/88 (14%)

IPF: fibrosing interstitial pneumonia, AE-IPF: acute exacerbation of fibrosing interstitial pneumonia, WBC: white blood cell, CRP: C-reactive protein, LDH: lactate dehydrogenase, FDP: fibrin/fibrinogen degradation products, KL-6: Krebs von der Lungen-6, SP-D: surfactant protein D, PAP: pulmonary arterial pressure, HRCT: high-resolution computed tomography, JRS: Japanese Respiratory Society, NAC: N-acetylcysteine, IS: immunosuppressant, CS: corticosteroids, UIP: usual interstitial pneumonia, rhTM: recombinant human soluble thrombomodulin

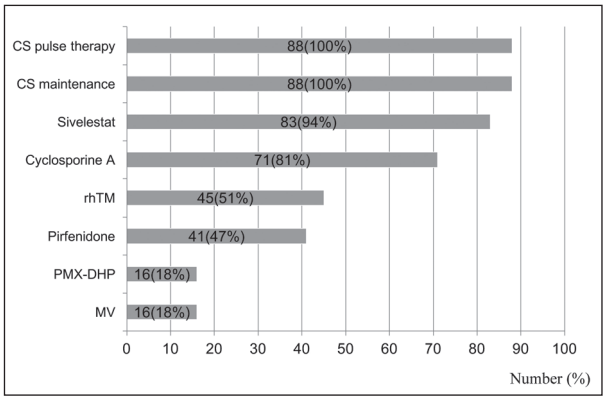
in Table 1. Over 50% of the patients had a GAP stage ≥2 and used supplemental oxygen. Median FVC and %FVC were 2.17 L and 73.7%. Twenty-one patients (24%) had received pirfenidone, 31 (35%) had received inhaled N-acetylcysteine, and 12 (14%) had received corticosteroids (CS) before AE-IPF onset.

Table 2 shows the details of pharmacological treatments for AE-IPF. CS pulse therapy was performed an average of 1.7 times, and the initial CS maintenance dose was 1 mg/kg for 65 patients and 0.5 mg/kg for 23 patients. Forty-five (51%) patients received rhTM, 41 (47%) received pirfenidone, 16 (18%) underwent PMX-DHP, 83 (94%) received sivelestat, and 71 (81%) received CsA at AE-IPF onset.

Predictors of 3-month death

During the observation period, 75 of 88 patients (85.2%) died. All deaths during the first 3 months were from respiratory failure caused by AE-IPF. Univariate analysis showed that the factors predicting 3-month survival were a PaO2/FiO2 ratio ≥250 (the cut-off value for PaO2/FiO2 ratio was calculated by receiver- operating- characteristic curve analysis) at AE onset (hazard ratio [HR], 0.36; 95% confidence

Table 2. Proportions of patients receiving various treatments at onset of acute exacerbation of fibrosing interstitial pneumonia. mber (%)



CS: corticosteroid, rhTM: Recombinant human thrombomodulin PMX-DHP: Polymyxin B-immobilized fiber column-direct hemoperfusion, MV: mechanical ventilation

interval [CI], 0.15-0.86; p=0.02), use of rhTM (HR, 0.44; 95% CI, 0.19-0.99; p=0.04), and an initial CS maintenance dose of 0.5 mg/kg after CS pulse therapy (HR, 0.15; 95% CI, 0.04-0.49; p=0.002) (Table 3). High value of LDH (HR, 1.003; 95% CI, 0.99-1.01; p=0.01) was associated with worse outcomes, Age, sex, other serological markers (including KL-6, SP-D), and pharmacological treatments such as sivelestat, CsA, pirfenidone and PMX-DHP were not associated with 3-month outcome. Analysis of IPF characteristics before AE showed that age, smoking status, IPF severity (as determined by JRS criteria and GAP stage), HRCT pattern (probable or definite UIP), lung function, and IPF treatment before AE that included pirfenidone were not prognostic factors (Table 3). Multivariate analysis showed that 3-month survival was associated with a rhTM treatment (HR 0.32; 95% CI, 0.12-0.86; p=0.02), and an initial CS maintenance dose of 0.5 mg/kg (HR, 0.13; 95% CI, 0.04-0.46; p=0.002).

Figure 1 shows Kaplan-Meier survival curves for the rhTM-treated and non-rhTM-treated groups. Survival at 3 months was significantly better in the rhTM group than in the non-rhTM group (62.3% vs 41.9%; p=0.04).

Table 4 shows the detailed characteristics of patients at AE-IPF onset and the features of underlying IPF before AE in the rhTM and non-rhTM groups. There were no significant differences between groups.

Figure 2 shows Kaplan-Meier survival curves for initial CS maintenance doses of 1 mg/kg and 0.5 mg/kg. Survival at 3 months was significantly better in the CS 0.5 mg/kg group than in the CS 1 mg/kg group (82.6% vs 41.5%; p=0.001).

Table 5 shows patient characteristics at AE-IPF onset and the features of underlying IPF before AE in patients receiving a low CS maintenance dose (0.5 mg/kg) and a high CS maintenance dose (1 mg/kg). A diffuse CT pattern was significantly more frequent and CRP concentration was significantly higher in those receiving a high CS maintenance dose. PaO2/FiO2 ratio was significantly lower in the high CS maintenance dose group.

Table 6 shows patient characteristics at AE-IPF onset and the features of underlying IPF before AE in patients with a definite or probable UIP pattern on HRCT. The proportion of males was significantly higher among those with a UIP pattern than among those with a probable UIP pattern. The proportion of patients with more advanced disease was higher for the UIP pattern than for the probable UIP pattern. Survival at 3 months did not significantly differ between the UIP and probable UIP groups (47.8% vs 47.7%; p=0.65) (Fig. 3).

Safety

Adverse events related to CS treatment were hyperglycemia in 6 patients. There were no severe adverse events in patients treated with cyclosporine A, sivelestat, or PMX-DHP during the observation period.Mild hemoptisis and hematuria developed on the day after rhTM administration in 1 patient. These symptoms improved within a few days and did not require suspension of rhTM treatment. Severe bleeding did not develop in any patient. There were no severe adverse events during the observation period in patients treated with pirfenidone, including gastrointestinal discomfort during administration of a prokinetic agent. One patient developed pneumonia and 1 patient developed pulmonary embolism during the observation period.

Discussion

Although a number of pharmacological treatments have been used for AE-IPF, the efficacy of such

Table 3. Results of univariate and multivariate Cox analysis for 3-month death

AE-IPF onset	HR	95%CI	p-value
Univariate analysis			
Age, yr.	1.01	0.95-1.08	0.18
Diffuse HRCT pattern	2.4	1.2-6.3	0.22
Laboratory findings			
PaO2/FiO2 ratio	0.99	0.986-0.998	0.02*
PaO2/FiO2 ratio ≥250	0.36	0.15-0.86	0.02*
WBC count/mm3-	1.00	1.00-1.00	0.37
CRP (mg/dl)	1.07	0.99-1.44	0.08
LDH (IU/l)	1.003	0.99-1.007	0.01*
KL-6 (U/ml)	1.00	1.00-1.00	0.57
SP-D (ng/ml)	1.001	1.00-1.00	0.18
FDP (μg/ml)	0.992	0.99-1.01	0.44
D-dimer (μg/ml)	0.979	0.94-1.02	0.36
Treatment			
CS maintenance 0.5 mg/kg	0.15	0.046-0.49	0.002*
Cyclosporine A	1.39	0.48-4.06	0.55
Sivelestat	0.34	0.06-1.84	0.46
rhTM	0.44	0.19-1.03	0.05
Pirfenidone	0.43	0.18-1.01	0.05
PMX-DHP	2.08	0.68-6.35	0.92
Mechanical ventilation	4.20	1.23-14.29	0.02*
Before AE-IPF			
Male sex	2.64	0.76-9.17	0.13
Smoking history	0.90	0.30-2.65	0.90
Advanced stage (JRS III, IV)	0.82	0.35-1.90	0.64
Advanced stage (GAP 2,3)	0.73	0.31-1.72	0.47
Definite UIP pattern on HRCT	0.99	0.38-2.58	0.99
Lung physiological features			
Forced vital capacity (L)	1.004	0.53-1.87	0.99
FVC % of predicted value	0.99	0.97-1.02	0.67
FEV1/FVC (%)	0.99	0.99-1.01	0.52
% DLco	1.01	0.98-1.04	0.55
Treatment of IPF before AE			
N-acetylcysteine	0.78	0.33-1.86	0.57
Pirfenidone	0.60	0.22-1.63	0.31
Corticosteroid	2.53	0.97-6.60	0.06
Multivariate analysis			
PaO2 / FiO2 ratio ≥250	0.42	0.12-0.85	0.08
CS maintenance 0.5 mg/kg	0.13	0.04-0.46	0.002*
rhTM	0.32	0.12-0.86	0.02*

CI: Confidence interval, HR: hazard ratio, AE-IPF: acute exacerbation of fibrosing interstitial pneumonia, HRCT: high-resolution computed tomography, WBC: white blood cell, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Krebs von der Lungen-6, SP-D: surfactant protein D, FDP: fibrin/fibrinogen degradation products, rhTM: recombinant human soluble thrombomodulin, JRS: Japanese Respiratory Society, UIP: usual interstitial pneumonia, %DLco: carbon monoxide diffusing capacity % of predicted value, PMX: polymyxin B-immobilized fiber column hemoperfusion

treatments has not been confirmed in large prospective studies. This study examined the associations of 3-month death after AE-IPF with CS maintenance dose and use of an immunomodulatory agent, sivelestat, rhTM, pirfenidone, and PMX-DHP, which are used in combination with CS in Japan.

In clinical practice, most patients who develop AE-IPF receive CS, usually in pulsed doses. However, few high-quality studies have investigated optimal CS dosing, duration of administration, and tapering. In this study, 3-month survival was better for an initial CS maintenance dose of 0.5 mg/kg than

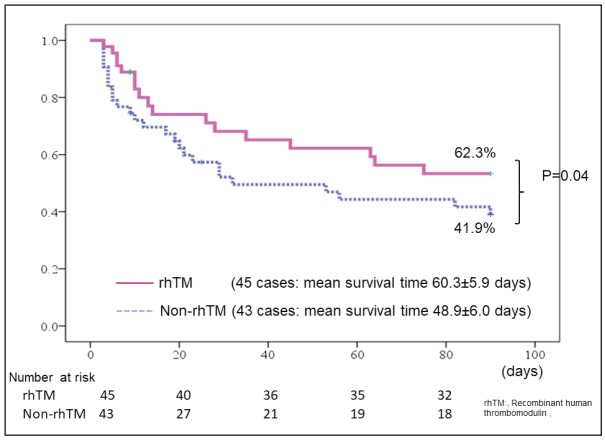


Fig. 1. Kaplan-Meier survival curves for 3-month survival after onset of acute exacerbation of idiopathic pulmonary fibrosis in patients who did and did not receive recombinant human soluble thrombomodulin (rhTM). Survival at 3 months was significantly better in the rhTM group than in the non-rhTM-treated group (62.3% vs 41.9%, p=0.04).

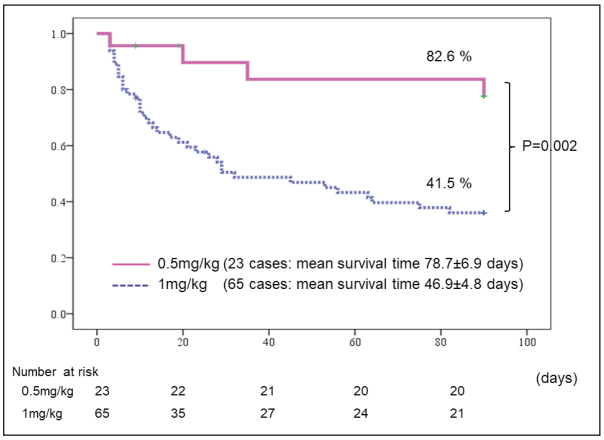


Fig. 2. Kaplan-Meier survival curves for 3-month survival after onset of acute exacerbation of idiopathic pulmonary fibrosis in patients treated with CS 0.5 mg/kg group and 1 mg/kg. Survival at 3 months was significantly better in the CS 0.5 mg/kg group than in the CS 1 mg/kg group (82.6% vs 41.5%, p=0.002).

Table 4. Patient characteristics at AE-IPF onset and features of underlying IPF before AE in the rhTM and non-rhTM groups

	rhTM (n=45)	Non-rhTM (n=43)	P-value
Age	73.3±6.9	74.9±6.0	0.38
Male gender	39/45 (81%)	35/43 (81%)	0.57
GAP stage ≥ 2	29/45 (87%)	22/43 (51%)	0.28
Diffuse HRCT pattern	20/45 (44%)	16/43 (37%)	0.52
CRP	7.9±5.9	8.2±6.7	0.88
LDH	356.5±86.2	363.8±148.7	0.16
KL-6	1729.2±1720.7	1287.3±833.5	0.11
SP-D	387.8±271.1	372.9±315.5	0.76
PiO_2/FiO_2 ratio	237.4±96.1	246.1±96.5	0.60

rhTM: recombinant human soluble thrombomodulin, GAP: Gender-Age-Physiology, HRCT: high-resolution computed tomography, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Krebs von der Lungen-6, SP-D: surfactant protein D

Table 5. Patient characteristics at AE-IPF onset and features of underlying IPF before AE in patients receiving low-dose CS maintenance therapy (0.5 mg/kg) and high-dose CS maintenance therapy (1 mg/kg)

	CS maintenance dose 0.5 mg/kg) (n=23	CS maintenance dose 1 mg/kg (n=65)	P-value
Age	74.8±6.4	73.8±6.6	0.51
Male gender	15/23 (65%)	56/65 (86%)	0.004*
GAP stage ≥2	12/23 (52%)	39/65 (60%)	0.51
Diffuse CT pattern	5/23 (22%)	31/65 (48%)	0.03*
CRP	5.7±3.7	8.9±6.8	0.04*
LDH	352.8±81.3	362.6±131.7	0.74
KL-6	1364.5±928.3	1566.1±1500.5	0.55
SP-D	310.4±182.8	405.5±319.4	0.18
PaO2/FiO2 ratio	275.0±99.8	23.74±96.1	0.03*

CS: corticosteroid, GAP: Gender-Age-Physiology, HRCT: high-resolution computed tomography, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Krebs von der Lungen-6, SP-D: surfactant protein D

for a dose of 1 mg/kg. The initial CS dose depended on AE-IPF severity and patient comorbidities. Thus, many physicians administered a low initial CS maintenance dose (0.5 mg/kg) after a satisfactory response to CS pulse therapy. In fact, the group treated with a low initial CS maintenance dose – which was associated with a significantly higher PaO2/FiO2, lower CRP concentration, and greater likelihood of a non-diffuse CT pattern – had better outcomes. In contrast, a previous study reported that high-dose prednisolone (>0.6 mg/kg) improved AE outcomes (24). Our results indicate that some AE-IPF patients do not require high-dose CS maintenance therapy. Among such patients low-dose CS maintenance therapy might reduce long-term adverse events from steroid use. Thus, a future prospective clinical trial should investigate the optimal initial CS maintenance dose in patients with similar AE-IPF severity.

Although immunomodulators are sometimes used in combination with CS, the evidence of benefit is not conclusive (5-9). CsA primarily inhibits calcineurin which suppresses expression of interleukin (IL)-2, the most essential cytokine in T cell activa-

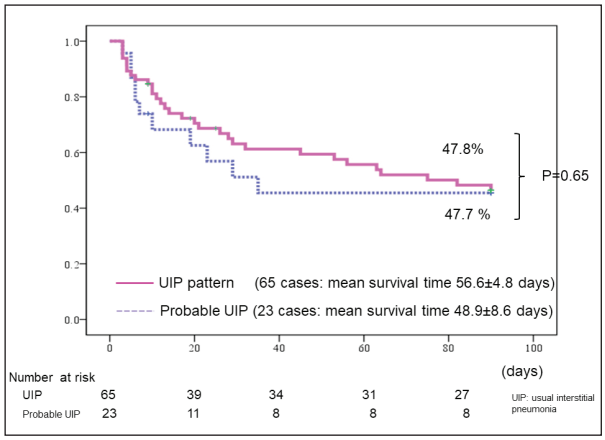


Fig. 3. Kaplan-Meier survival curves for 3-month survival after onset of acute exacerbation of idiopathic pulmonary fibrosis in patients with a definite UIP pattern and probable UIP. Survival at 3 months did not significantly differ between the groups (47.8% vs 47.7%, p=0.65)

Table 6. HRCT patterns of underlying IPF before AE, according to the international IPF guideline, 2018

	UIP pattern (n=65)	Probable UIP pattern (n=23)	P-value
Age	74.5±6.1	72.7±7.4	0.25
Male gender	59/65 (91%)	15/23 (65%)	0.004*
GAP stage ≥ 2	44/65 (68%)	7/23 (30%)	0.002*
Diffuse HRCT pattern	26/65 (40%)	10/23 (43%)	0.77
CRP	7.8±5.7	8.7±7.8	0.95
LDH	361.4±129.1	356.2±92.8	0.86
KL-6	1477.4±1065.5	1614.9±2026.5	0.68
SP-D	398.7±310.0	329.4±232.2	0.33
PiO_2/FiO_2 ratio	234.5±95.0	245.6±101.0	0.63

CS: corticosteroid, GAP: Gender-Age-Physiology, HRCT: high-resolution computed tomography, CRP: C-reactive protein, LDH: lactate dehydrogenase, KL-6: Krebs von der Lungen-6, SP-D: surfactant protein D

tion. T cells and alveolar macrophages are important in AE-IPF pathogenesis; thus, CsA may modulate the clinical course of IPF. Previous studies using a regimen of high-dose corticosteroid pulses followed by cyclophosphamide in patients with AE-IPF reported 3-month mortality rates of 45% and 73% (8-9). In this study, use of an immunomodulatory agent was not associated with 3-month survival.

Sivelestat is approved for ARDS in Japan. It is widely used for treatment of AE-IPF, which has a pathophysiology similar to that of diffuse alveolar damage (DAD) (12, 13). Neutrophil elastase may contribute to worsening of DAD pathophysiology and it is therefore reasonable to use this agent for AE-IPF. No large randomized controlled trials have examined the effectiveness of such agents for AE-IPF. In this study, sivelestat was well tolerated but was not associated with 3-month survival.

Several previous studies reported disordered coagulation, fibrinolysis, and endothelial damage in AE-IPF (15, 26). Collard et al reported significant elevations in plasma biomarkers of endothelial cell injury and coagulation in AE-IPF patients. (26). rhTM activates protein C, which deactivates coagulant factors and the pro-inflammatory effects of thrombin. Moreover, the N-terminal lectin-like domain of rhTM deactivates high-mobility group box 1 (HMGB1), which has anti-inflammatory effects. Elevation of serum HMGB1 was observed in patients with acute lung injury (27). rhTM treatment is likely to benefit AE-IPF patients.

A small-scale study showed that pirfenidone was beneficial for AE-IPF (18). In the present study, use of pirfenidone was not a predictor of 3-month survival; however, pirfenidone appeared to improve outcomes of patients with AE-IPF receiving rhTM. Pirfenidone also suppresses inflammatory cytokines such as transforming growth factor (TGF)-β and basic fibroblast growth factor (b-FGF), which are related to fibrosis progression and subsequent anti-inflammatory and antifibrotic effects. These results suggest that outcomes could be improved by suppressing both acute inflammation and subsequent fibrosis.

PMX-DHP was originally developed to remove endotoxins and improve hemodynamics and PaO2/FiO2 ratio in patients with sepsis. Recent studies suggest that PMX-DHP improves outcomes for patients with AE-IPF, and most of these studies report that PMX-DHP improves PaO2/FiO2 ratio. Abe et al reported a 3-month survival rate of 34.5% after AE-IPF with PMX-DHP treatment, which was better than the rate reported in a previous study (28). The mechanism by which PMX-DHP improves pulmonary oxygenation in AE is unclear. Several studies reported that PMX-DHP reduces inflammatory mediators, platelet-derived growth factor, vascular endothelial growth factor, and TNF-α (19) However, PMX-DHP therapy was not associated with survival in the present study.

Limitations

This study has several limitations. First, because it was a retrospective single-center study, prospective studies are needed in order to confirm our results. Second, initial prednisolone dose and use of an immunomodulatory agent, sivelestat, and PMX-DHP depended on AE-IPF severity and patient comorbidities; thus, patients with more severe disease received more-intensive treatment. This may explain why patients receiving these treatments had worse outcomes.

Conclusion

Addition of rhTM to CS, and a low initial CS maintenance dose (0.5 mg/kg), were associated with better 3-month survival among patients with AE-IPF. Decisions regarding whether to use high-dose CS, sivelestat, antifibrotic agents, rhTM, or PMX-DHP may depend on stratification of AE-IPF severity. Large, placebo-controlled, randomized trials will be necessary in order to confirm our results.

References

1. Collard HR, Ryerson CJ, Corte TJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis: An International Working Group Report. Am J Respir Crit Care Med 194: 265-75, 2016.
2. Collard HR, Ryerson CJ, Corte TJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis: An International Working Group Report. Am J Respir Crit Care Med. 194: 265-75, 2016.
3. Tachikawa R, Tomii K, Ueda H, et al. Clinical features and outcome of acute exacerbation of interstitial pneumonia: collagen vascular diseases-related versus idiopathic. Respiration. 83: 20-27, 2012.
4. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Am J Respir Crit Care Med 183:788-824, 2011.
5. Inase N, Sawada M, Ohtani Y, et al. Cyclosporin A followed by the treatment of acute exacerbation of idiopathic pulmonary fibrosis with corticosteroid. Intern Med 42: 565-70, 2003.
6. Sakamoto S, Homma S, Miyamoto A, et al.: Cyclosporin A in the treatment of acute exacerbation of idiopathic pulmonary fibrosis. Intern Med 49: 109-15, 2010.
7. Horita N, Akahane M, Okada Y, et al. Tacrolimus and steroid treatment for acute exacerbation of idiopathic pulmonary fibrosis. Intern Med 50; 189-95 2011.
8. Morawiec E, Tillie-Leblond I, Pansini V, et al. Exacerbations of idiopathic pulmonary fibrosis treated with corticosteroids and cyclophosphamide pulses. Eur Respir J 38; 1487-9, 2011.
9. Novelli L, Ruggiero R, De Giacomi F et al. Corticosteroid and cyclophosphamide in acute exacerbation of idiopathic pulmonary fibrosis: a single center experience and literature review. Sarcoidosis Vasc Diffuse Lung Dis. 33: 385-391, 2016.
10. Tamakuma S, Ogawa M, Aikawa N, Kubota T et al. Relationship between neutrophil elastase and acute lung injury in humans, Pulm. Pharmacol Ther 17 271-279, 2004.
11. Iwata K, Doi A, Ohji G, et al. Effect of neutrophil elastase inhibitor (sivelestat sodium) in the treatment of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS): a systematic review and meta-analysis. Intern Med 49: 2423-32, 2010.
12. Nakamura M, Ogura T, Miyazawa N et al. The outcome of patients with acute exacerbation of idiopathic interstitial fibrosis (IPF) treated with sivelestat and the prognostic value of serum KL-6 and surfactant protein D. Nihon Kokyuki Gakkai Zasshi 45: 455-459, 2007 (abstract in English).
13. Sato N, Sutani A, Oya H et al. Prognostic significance of neutrophil elastase inhibitor in patients with acute lung injury and interstitial pneumonia. Nihon Kokyuki Gakkai Zasshi 45: 237-242, 2007 (abstract in English).
14. Isshiki T, Sakamoto S, Kinoshita A, et al. Recombinant human soluble thrombomodulin treatment for acute exacerbation of idiopathic pulmonary fibrosis: a retrospective study. Respiration 89: 201-7, 2015.
15. Kataoka K, Taniguchi H, Kondoh Y, et al. Recombinant human thrombomodulin in acute exacerbation of idiopathic pulmonary fibrosis. Chest 148: 436-43, 2015.
16. Tsushima K, Yamaguchi K, Kono Y, et al. Thrombomodulin for acute exacerbations of idiopathic pulmonary fibrosis: a proof of concept study. Pulm Pharmacol Ther 29: 233-40, 2014.
17. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 29; 370: 2083-92, 2014.
18. Furuya K, Sakamoto S, Shimizu H, et al. Pirfenidone for acute exacerbation of idiopathic pulmonary fibrosis: A retrospective study. Respir Med 126: 93-99, 2017.
19. Oishi K, Mimura-Kimura Y, Miyasho T, et al. Association between cytokine removal by polymyxin B hemoperfusion and improved pulmonary oxygenation in patients with acute exacerbation of idiopathic pulmonary fibrosis. Cytokine 61: 84-9, 2013
20. Enomoto N, Mikamo M, Oyama Y, et al. Treatment of acute exacerbation of idiopathic pulmonary fibrosis with direct hemoperfusion using a polymyxin B-immobilized fiber column improves survival. BMC Pulm. Med 15: 15, 2015.
21. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 198: e44-e68, 2018.
22. Homma S, Sugino K, Sakamoto S. The usefulness of a disease severity staging classification system for IPF in Japan: 20 years of experience from empirical evidence to randomized control trial enrollment. Respir Investig. 2015; 53: 7-12.
23. Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med. 2012; 156: 684-91.
24. Akira M, Kozuka T, Yamamoto S, et al. Computed tomography findings of acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 178: 372-78 2008.
25. Arai T, Tachibana K, Sugimoto C, et al. High-dose prednisolone after intravenous methylprednisolone improves prognosis of acute exacerbation in idiopathic interstitial pneumonias. Respirology 22: 1363-70, 2017
26. Collard HR, Calfee CS, Wolters PJ, et al. Plasma biomarker profiles in acute exacerbation of idiopathic pulmonary fibrosis. Am J Physiol Lung Cell Mol Physiol 299: L3-L7, 2010.
27. Ueno H, Matsuda T, Hashimoto S, et al. Contributions of high mobility group box protein in experimental and clinical acute lung injury. Am J Respir Crit Care Med 170: 1310-16, 2004.
28. Abe S, Azuma A, Mukae H et al. Polymyxin B-immobilized fiber column (PMX) treatment for idiopathic pulmonary fibrosis with acute exacerbation: a multicenter retrospective analysis. Intern. Med 51: 1487-91 2012.