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Clinical Investigations

Recombinant Human Soluble Thrombomodulin Treatment for Acute Exacerbation of Idiopathic Pulmonary Fibrosis: A Retrospective Study

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ABSTRACT

***Background*:** Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) can be fatal, and abnormalities in the coagulation system of patients with AE-IPF have been reported. Recombinant human soluble thrombomodulin (rhTM) forms a complex with thrombin to inactivate coagulation. It also inhibits high-mobility group box protein 1 (HMGB-1), which results in suppression of inflammation.

***Objectives*:** To evaluate the effectiveness of rhTM for treatment of AE-IPF.

***Methods*:** We retrospectively reviewed the medical records of 41 patients with AE-IPF who were admitted to our institution during the period from 2006 through 2013. The clinical features and outcomes of 16 patients treated with rhTM (rhTM group) were compared with those of 25 patients treated with conventional therapy (control group). Patients were treated with corticosteroid (CS) pulse therapy for 3 days, followed by maintenance treatment with a tapered dose of CS. Patients in the rhTM group also received rhTM (0.06 mg/kg/day) for 6 days as initial treatment, in combination with CS.

***Results*:** Except for d-dimer level, there were no significant differences in the baseline characteristics of the patient groups. As compared with the control group, the rhTM group had a significantly higher survival rate at 3-month (40% vs 69%, $p = 0.048$). A univariate Cox proportional hazards regression model showed that the predictive factors for survival were LDH level and rhTM treatment. Regarding adverse events, 1 patient in the rhTM

group developed mild bleeding events.

***Conclusion*:** rhTM as add-on to conventional treatment may improve survival in patients with AE-IPF.

Introduction

Idiopathic pulmonary fibrosis (IPF) is an ultimately fatal fibrotic lung disease without identifiable etiology characterized by a histologic pattern of usual interstitial pneumonia (UIP). Although the clinical course is usually chronic and slowly progressive, some patients experience rapid deterioration during the course of their illness; it is defined as acute exacerbation of IPF (AE-IPF) [1]. AE-IPF was first described by Kondoh et al [2] and is now well recognized by physicians as a clinical event with high morbidity. Because of the paucity of studies, there are no definitive treatment guidelines for AE-IPF; however, pulse corticosteroid (CS) therapy and broad-spectrum antibiotics are commonly used [3]. Although some studies indicated that cyclosporine A [4-6], polymyxin B-immobilized fiber column hemoperfusion [7, 8], and anticoagulant agents [9] might be beneficial for treating AE-IPF, mortality from AE-IPF remains high. Therefore, a new therapy that improves the prognosis for AE-IPF is urgently needed.

Thrombomodulin is a thrombin receptor on the endothelial cell surface and has an important role in regulating intravascular coagulation [10]. Recombinant human soluble thrombomodulin (rhTM) is composed of the active extracellular domain of thrombomodulin. rhTM forms a reversible complex with thrombin to convert plasma protein C into activated protein C, which inactivates coagulant factors and the proinflammatory effects of thrombin. Moreover, rhTM directly binds and sequesters high-mobility group box 1 (HMGB-1), leading to suppression of inflammation [11]. Previous studies reported coagulation abnormalities in IPF [12, 13] and elevated HMGB-1 levels in bronchoalveolar lavage fluid from AE-IPF patients [14]; thus, control of the coagulation system and suppression of inflammation by inhibiting HMGB-1 might improve outcomes of patients with AE-IPF. We examined the clinical effectiveness of rhTM and evaluated whether it had a beneficial effect on the survival

of patients with AE-IPF.

Patients and Methods

Patients

We retrospectively reviewed the medical records of 402 consecutive IPF patients who were admitted to Toho University Omori Medical Center during the period from April 2006 through March 2013. A total of 41 patients who had received a first clinical diagnosis of AE-IPF were included in this study; 16 were treated with rhTM (rhTM group), and 25 were treated without rhTM (control group).

Diagnosis of IPF

According to the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) guideline [15], IPF is diagnosed on the basis of histologic findings from a lung biopsy, high-resolution computed tomography (HRCT) images, or both. Six patients (15%) underwent surgical lung biopsy before AE-IPF onset, and all specimens showed a UIP pattern. HRCT images of all the present patients were reviewed by 2 pulmonologists (T.I. and S.S.) and 1 chest radiologist (A.K.). In Japan, classification of IPF disease severity (stage I-IV) is used to make decisions regarding subsidization of medical care [16]. This classification scheme, which was used in the present study, was as follows: stage I (PaO_2 ≥80 Torr at rest), stage II (PaO_2 70-79 Torr at rest), stage III (PaO_2 60-69 Torr at rest), and stage IV (PaO_2 <60 Torr at rest). Patients with stage II or III disease who experience desaturation during a 6-minute walk test are classified as stage III or IV, respectively. Disease stage, pulmonary

function, and dyspnea scale were assessed while IPF was chronic and stable, before AE-IPF onset.

Definition of AE-IPF

AE-IPF was defined based on criteria proposed by Collard et al [1] and the guideline of the JRS [16], with slight modifications, as follows: (1) a previous or current diagnosis of IPF, (2) unexplained worsening or development of dyspnea in the past 30 days, (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 (eg, *Pneumocystis jiroveci*, cytomegalovirus), and (5) exclusion of left heart failure, pulmonary embolism, and other possible causes of acute lung injury. Infectious disease was excluded by examination of several microbiological samples. The results were negative for sputum culture of bacteria, urinary antigen tests for *Streptococcus pneumonia* and *Legionella pneumophila*, and serologic studies for viruses, *Chlamydia pneumonia*, and *Mycoplasma pneumonia*. Left heart failure and pulmonary embolism were excluded by echocardiography, tests of brain natriuretic peptide (BNP) and d-dimer, and, if necessary, by enhanced CT. Using the classification of CT patterns described by Akira et al [17], we classified the CT pattern of all patients at onset of AE-IPF as either diffuse, peripheral, or multifocal.

AE-IPF treatment and evaluation

AE-IPF was treated with high-dose CS pulse therapy (methylprednisolone 1,000 mg/day for 3 days) in all patients. CS dose was tapered after pulse therapy (0.5-1.0 mg/kg/day), and in almost all patients CS therapy was combined with cyclosporine A (2.5

mg/kg/day). Before November 2011 some patients in the control group received low-molecular-weight heparin (LMWH) 75 IU/kg/day for 14 days, based on the findings of a report by Kubo [9]. Since November 2011, rhTM replaced LMWH and was administered at a dose of 0.06 mg/kg/day for the first 6 days in combination with CS therapy. Outcomes after onset of the first AE-IPF episode and adverse events after the start of treatment were compared between the rhTM group and control group. We also compared outcomes between the rhTM group and patients in the control group treated with LMWH.

Statistical analysis

All clinical and laboratory data were collected from patient medical records. Continuous variables are expressed as mean ± SD unless otherwise stated and were compared using the Mann-Whitney U test. Categorical variables were compared using the χ^2 test. Survival was investigated by 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. A p value of less than 0.05 was deemed statistically significant. All statistical analyses were performed 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 (project approval number 23-168). All patients or their families provided written informed consent, and medical records were reviewed with the approval of the Institutional Review Board.

Results

Patients studied

We identified 41 patients (36 men and 5 women) who had been treated for AE-IPF. The median observation period from first consultation at our center was 12 months (range 1-143). Thirty-six patients (88%) had a smoking history. Nine patients (22%) had a pathologic diagnosis of UIP, which was revealed by analysis of a surgical lung biopsy specimen obtained 0 to 36 months before AE-IPF onset (n=6), or by autopsy (n=3). Histologic findings in all autopsy cases showed diffuse alveolar damage superimposed on the UIP pattern. Twenty-two patients (54%) received treatments such as CS or antifibrotic agents before AE-IPF onset.

Table 1 shows the clinical characteristics of the 2 patient groups. D-dimer level significantly differed between groups. There were no significant differences between groups in other baseline characteristics, including pulmonary function test results before AE-IPF onset, PaO_2/FiO_2 ratio and serological markers at AE-IPF onset. The interval from the last pulmonary function test to AE-IPF onset was short in both groups (2.3±1.7 months in the rhTM group vs 3.2±2.7 months in the control group). HRCT at AE-IPF onset showed diffuse ground-glass opacities superimposed on preexisting subpleural fibrosis. A few patients in both groups showed consolidation combined with ground-glass opacities. The diffuse CT pattern was the most frequent pattern in both groups at AE-IPF onset. There were no significant differences in the characteristics of radiologic images between groups.

Treatments for AE-IPF are shown in Table 2. All patients received high-dose CS pulse therapy followed by maintenance treatment with tapered dose of CS, and most patients in both groups also received cyclosporine A. There were no significant treatment differences between groups, except for LMWH treatment: 11 of 25 (44%) patients in the control group

received LMWH at the start of treatment.

Survival

During the observation period, 29 (71%) of 41 patients died. Twenty-four (84%) patients died from respiratory failure caused by AE-IPF (n=21) or chronic disease progression of IPF (n=3). In addition, 1 (3%) died from *Pneumocystis jiroveci* pneumonia, 1 (3%) from cytomegalovirus infection, 1 (3%) from stomach cancer, and 2 (7%) from unknown causes. Fig 1 shows the survival curves for the rhTM and control groups. Survival at 3-month was significantly better in the rhTM group than in the control group (survival rate 69% vs 40%, p=0.048). Overall survival after AE-IPF onset was also significantly better in the rhTM group (median survival time: 165 vs 53 days, p=0.031; fig. 2). Fig 3 shows the survival curves at 3-month for the rhTM group and LMWH-treated patients in the control group (n=11). There was no significant difference between groups (survival rate, 69% vs 46%, respectively; p=0.17). The univariate Cox proportional hazard regression model showed that the factors predicting survival were LDH (hazard ratio [HR], 1.003; 95% confidence interval [CI], 1.000-1.006; p = 0.020) and rhTM treatment (HR, 0.446; 95% CI, 0.210-0.948; p = 0.036; Table 3). Age, gender, other serological markers (including d-dimer), CT pattern, and other treatment for AE-IPF except for rhTM were not the prognostic factors in this study.

Safety

Mild hemoptisis and hematuria developed in 1 patient in the rhTM group, on the day after rhTM administration. These symptoms improved within a few days, without stopping rhTM treatment. Severe bleeding did not develop in any patient in either group.

Discussion

This is the first retrospective study of rhTM treatment for AE-IPF. Survival at 3-month was significantly better in the rhTM group than in the control group, and rhTM treatment predicted survival in a univariate Cox proportional hazard regression model. Any severe bleeding events developed by rhTM treatment. Our findings suggest that rhTM treatment improves outcomes in AE-IPF and is safe under conditions of routine clinical monitoring.

Several studies reported an association between the presence of coagulation disorders and AE-IPF. Kotani et al found that procoagulant tissue factor levels in bronchoalveolar lavage fluid were higher in IPF patients than in normal subjects and that these levels correlated with disease activity [12]. Collard et al reported significant elevations in plasma biomarkers of endothelial cell injury and coagulation in patients with AE-IPF. In addition, serum thrombomodulin level was a significant prognostic marker [13]. HMGB-1 may be a late inflammatory mediator, and elevated HMGB-1 concentrations were observed in patients with sepsis [18] and acute lung injury [19]. Ebina et al found that [14] HMGB-1 level was elevated in bronchoalveolar lavage fluid from AE-IPF patients. rhTM directly inhibits HMGB-1, leading to an anti-inflammatory effect. It also binds thrombin and inactivates the coagulation system. Therefore, rhTM treatment is likely to have a beneficial effect in AE-IPF patients.

Previous reports showed that rhTM was effective in treating disseminated intravascular coagulation (DIC) and sepsis [20-24]. Kato et al reported that DIC score on day 7 was significantly lower in an rhTM treatment group than in a control group [21]. In addition, Saito et al noted a better rate of DIC improvement as compared with a heparin-treated group [20]. Little is known about the effectiveness of anticoagulant agents in IPF. Kubo et al reported that anticoagulant agents, including heparin and warfarin, resulted in a significant survival

benefit for IPF patients when coadministered with CS, as compared with CS alone [9]. In contrast, in the ACE-IPF trial [25], warfarin use among patients with progressive-stable IPF was associated with increased mortality as compared with placebo, which suggests that warfarin should not be used to treat chronic IPF. However, there are no data on rhTM therapy for AE-IPF.

Previous studies reported that conventional CS treatment resulted in a 3-month survival rate of 30-40% after AE-IPF onset [3, 26]. In the present study, the control group receiving conventional treatment had a similar survival rate. Survival rate was significantly better in the rhTM group than in the control group, and rhTM treatment was a significant prognostic factor for survival in univariate analysis, which suggests that rhTM treatment has a beneficial effect on survival in AE-IPF.

D-dimer is a final product of cross-linked fibrin degradation and is released into circulation during endogenous fibrinolysis. It is believed to be a useful marker of abnormal coagulation balance [27] and may be influenced by increased intra-alveolar fibrin deposition [9]. In the present study, plasma d-dimer level was higher in the control group at AE-IPF onset. Although it is possible that coagulation imbalance was worse among patients in the control group, d-dimer level was not a prognostic factor in univariate analysis. Previous reports found that prognostic factors for AE-IPF were a diffuse distribution on HRCT images, LDH level, CRP level after AE-IPF onset, greater impairment of pulmonary function, and longer duration between admission and start of AE-IPF treatment [17, 25, 28]. However, to our knowledge no previous study reported that d-dimer level was a predictive factor for prognosis or severity in patients with AE-IPF. The prognostic importance of d-dimer level in AE-IPF requires future study.

Increased risk of bleeding is the greatest concern with rhTM administration. At clinical blood concentrations, the mechanism of action for rhTM is such that thrombin generation is

suppressed via activated protein C, without direct inhibition of thrombin activity. rhTM has a greater safety margin than other anticoagulant agents such as heparin [29], and rhTM dosage can be set so as to provide potent anticoagulant activity while minimizing bleeding, thus allowing for stable outcomes. In the present study, we found that the incidence of bleeding complications was not increased by rhTM administration, which suggests that rhTM therapy can be safely used during routine clinical monitoring.

This study has several limitations. First, this was a retrospective study at a single center and we were unable to conduct multivariate analysis because of the relatively small sample size. Therefore, larger-scale prospective studies are needed in order to confirm our results. Second, some of the patients in the control group were treated with LMWH, as recommended by Kubo [9]. There was no significant difference in survival between the rhTM group and LMWH-treated patients. Future studies should compare the effectiveness of rhTM and LMWH for treating AE-IPF in large sample size. Third, d-dimer level significantly differed between groups. It is possible that coagulation imbalance was worse among patients in the control group; however; to our knowledge no study reported that d-dimer level was a predictive factor for prognosis or severity in patients with AE-IPF. Fourth, not all patients in our series underwent bronchoalveolar lavage and enhanced CT to rule out the possibility that respiratory failure was caused by infection or pulmonary embolism. In all non-bronchoscopy cases, because of severe respiratory failure, infection was ruled out by using less invasive procedures such as sputum and/or blood culture, urinary antigen tests, and serologic analysis. In patients who did not undergo enhanced CT, because of renal dysfunction or allergy to contrast medium, pulmonary embolism was excluded by echocardiography, serum BNP level, and d-dimer level. Fifth, PaO_2 in ambient air was not examined in some patients in both groups because of the severe respiratory failure. Therefore, PaO_2/FiO_2 ratio at the onset of AE-IPF was compared and did not differ between groups. Finally, AE-IPF can be fatal and

required various supportive cares. Since the quality of general supportive care might improve the outcome, similarity in baseline features between groups does not guarantee that the outcome would be the same if the therapy were really ineffective.

In conclusion, rhTM can be used safely and may have a significant beneficial effect on mortality in patients with AE-IPF. AE-IPF is a fatal condition and therapeutic guidelines have not been established. rhTM therapy in combination with conventional treatment appears to be a promising treatment for improving the poor prognosis of AE-IPF. However, this study provides only preliminary data with several limitations and the effectiveness of rhTM on AE-IPF couldn't be established. Therefore, large placebo-controlled randomized trials are required in order to confirm our findings.

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Table 1. Comparison of clinical characteristics between groups.

	rhTM (n=16)	Control (n=25)	P value
Baseline characteristics			
Sex, Male (n)	16 (100%)	20 (80%)	0.06
Age (yrs)	72 ± 7	73 ± 6	0.63
Smoking history, yes (n)	15 (94%)	21 (84%)	0.55
Severity of IPF (Stage I/II/III/IV)	(7/0/3/4) (n = 14)	(11/4/4/5) (n = 24)	0.44
mMRC score (0/I/II/III/IV)	0/6/4/4/0 (n=14)	0/8/11/5/0 (n=24)	0.95
Duration (days)	8 ± 9	6 ± 5	0.80
Treatment before AE-IPF			
Corticosteroids	1 (6%)	6 (23%)	0.14
Cyclosporine A	0 (%)	3 (12%)	0.15
Pirfenidone	2 (13%)	5 (20%)	0.53
N-acetylcysteine	4 (25%)	12 (48%)	0.14
Last pulmonary function test results before AE-IPF			
%FVC (%)	82 ± 18 (n = 13)	77 ± 18 (n = 22)	0.43
$FEV_{1.0}$% (%)	82 ± 9 (n = 13)	87 ± 8 (n = 22)	0.07

%DLco (%)	53 ± 22 (n = 11)	56 ± 12 (n = 20)	0.58
Clinical parameters at AE-IPF onset			
PaO_2/FiO_2 ratio	258 ± 96	246 ± 99	0.20
PaO2 in ambient air (mm Hg)	64 ± 6 (n = 11)	62 ± 19 (n = 12)	0.21
APACHE II score	12.3 ± 3.4	13.3 ± 2.9	0.30
WBC (/μl)	9100 ± 2429	11008 ± 3527	0.07
CRP (mg/dl)	6.3 ± 5.8	9.2 ± 7.6	0.18
LDH (IU/l)	321 ± 75	390 ± 185	0.24
KL-6 (U/ml)	1417 ± 1113	1436 ± 939	0.76
D-dimer (μg/ml)	3.9 ± 3.5	10.1 ± 11.4	0.02
esPAP (mm Hg)	37 ± 13 (n = 14)	33 ± 12 (n = 22)	0.31
Mechanical ventilation or NPPV (n)	3 (19%)	5 (20%)	0.92
Radiologic findings at AE-IPF onset			
Ground-glass opacity	16 (100%)	25 (100%)	>0.99
Consolidation	2 (13%)	6 (24%)	0.96
CT pattern (D/P/M)	8/1/7	20/0/5	0.09

rhTM; recombinant human soluble thrombomodulin, IPF: idiopathic pulmonary fibrosis,

mMRC score: modified medical research council dyspnea score, AE-IPF: acute exacerbation of idiopathic pulmonary fibrosis, Duration: duration between symptom onset and initiation of treatment, esPAP: estimated systolic pulmonary arterial pressure, NPPV: noninvasive positive pressure ventilation, CT pattern, D: diffuse, P: peripheral, M: multifocal.

Table 2. Treatments for acute exacerbation of idiopathic pulmonary fibrosis in the two groups.

	rhTM (n=16)	**Control (n=25)**	**P value**
Corticosteroid pulse (n)	16 (100%)	25 (100%)	>0.99
Corticosteroid maintenance therapy (n)	16 (100%)	25 (100%)	>0.99
CsA (n)	15 (94%)	23 (92%)	0.83
Antibiotics (n)	12 (75%)	22 (88%)	0.28
LMWH (n)	0 (0%)	11 (44%)	0.002

rhTM; recombinant human soluble thrombomodulin, CsA: cyclosporine A, LMWH: low-molecular-weight heparin.

Table 3. Results of univariate Cox analysis.

	HR	95%CI	P value
Age	0.982	0.932-1.034	0.483
Smoking	0.496	0.118-2.088	0.339
Duration	0.969	0.914-1.026	0.281
LDH	1.003	1.000-1.006	0.020
D-dimer	0.987	0.950-1.025	0.485
PaO_2/FiO_2 ratio	0.998	0.994-1.002	0.300
%FVC	0.991	0.972-1.011	0.391
%DLco	1.008	0.985-1.031	0.499
LMWH	0.839	0.385-1.825	0.658
rhTM	0.446	0.210-0.948	0.036

Duration: duration between symptom onset and start of treatment, CsA: cyclosporine A,

LMWH: low-molecular-weight heparin, rhTM; recombinant human soluble thrombomodulin.

FIGURE LEGENDS

Fig. 1. Kaplan-Meier survival curves for patients treated with recombinant human soluble thrombomodulin (rhTM) and the control group. The rhTM group had significantly better survival at 3-month, as compared with the control group (69% vs 40%, p=0.048).

Fig. 2. Kaplan-Meier survival curves for patients treated with recombinant human soluble thrombomodulin (rhTM) and the control group, after onset of acute exacerbation of idiopathic pulmonary fibrosis. The rhTM group had better overall survival, as compared with the control group (median survival time: 165 vs 53 days, p=0.031).

Fig. 3. Kaplan-Meier survival curves for patients treated with recombinant human soluble thrombomodulin (rhTM) and those in the control group treated with low-molecular-weight heparin (LMWH). There was no significant difference between groups (69% vs 46%, p=0.17).