CHEST

Recombinant Human Thrombomodulin in Acute Exacerbation of Idiopathic Pulmonary Fibrosis

Kensuke Kataoka, MD, PhD; Hiroyuki Taniguchi, MD, PhD; Yasuhiro Kondoh, MD, PhD; Osamu Nishiyama, MD, PhD; Tomoki Kimura, MD, PhD; Toshiaki Matsuda, MD; Toshiki Yokoyama, MD, PhD; Koji Sakamoto, MD, PhD; and Masahiko Ando, MD, PhD

BACKGROUND: Acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) presents as episodes of acute respiratory worsening closely associated with endothelial damage and disordered coagulopathy. Recombinant human soluble thrombomodulin (rhTM) regulates the coagulation pathway mainly by reducing thrombin-mediated clotting and enhancing protein C activation. We investigated the efficacy of rhTM for the treatment of patients with AE-IPF.

METHODS: This historical control study comprised 40 patients with AE-IPF. Twenty patients treated with rhTM (0.06 mg/kg/d) for about 6 days (rhTM group) and 20 patients treated without rhTM (control group) were evaluated. The predictors of 3-month mortality (logistic regression model) were evaluated.

RESULTS: There was no difference in baseline characteristics between the control group and the rhTM group. Three-month mortality of the rhTM group and control group was 30.0% and 65.0%, respectively. In univariate analysis, C-reactive protein and rhTM therapy were significant determinants for 3-month survival. In multivariate analysis, rhTM therapy (OR, 0.219; 95% CI, 0.049-0.978; $P = 0.047$) was an independent significant determinant for 3-month survival.

CONCLUSIONS: We found that rhTM therapy improved 3-month survival of AE-IPF. The results observed here warrant further investigation of rhTM in randomized control trials.

CHEST 2015; 148(2):436-443

Manuscript received November 4, 2014; revision accepted March 2, 2015; originally published Online First March 26, 2015.

ABBREVIATIONS: AE = acute exacerbation; APACHE = Acute Physiology and Chronic Health Evaluation; BALF = BAL fluid; CRP = C-reactive protein; IPF = idiopathic pulmonary fibrosis; KL-6 = Krebs von der Lungen-6; LDH = lactate dehydrogenase; LMWH = low-molecular-weight heparin; NIV = noninvasive ventilation; rhTM = recombinant human soluble thrombomodulin; SP-D = surfactant protein D

AFFILIATIONS: From the Department of Respiratory Medicine and Allergy (Drs Kataoka, Taniguchi, Kondoh, Kimura, Matsuda, and Yokoyama), Tosei General Hospital, Seto; Department of Respiratory Medicine and Allergology (Dr Nishiyama), Kinki University, Faculty of Medicine, Osaka; Department of Respiratory Medicine (Dr Sakamoto), Nagoya University Graduate School of Medicine, Nagoya; and Center for Advanced Medicine and Clinical Research (Dr Ando), Nagoya University Hospital, Nagoya, Japan.

FUNDING/SUPPORT: This study was partially supported by a grant to the Diffuse Lung Disease Research Group from the Ministry of Health, Labor and Welfare, Japan, and the NPO Respiratory Disease Conference.

CORRESPONDENCE TO: Hiroyuki Taniguchi, MD, PhD, Department of Respiratory Medicine and Allergy, Tosei General Hospital, 160 Nishioiwake-cho, Seto, Aichi 489-8642, Japan; e-mail: taniguchi@tosei.or.jp

DOI: 10.1378/chest.14-2746

Acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) presents as episodes of acute respiratory worsening of unknown etiology and is associated with a high rate of short-term mortality. Published clinical trials have revealed that AE is one of the leading causes of death of patients with IPF.[1] Although little is known about the pathophysiology of AE-IPF, several studies suggest that disordered coagulation and fibrinolysis play important roles in AEs.[2,3] Studies of patients with IPF have demonstrated a procoagulant and antifibrinolytic alveolar environment in AE-IPF.[4-6] A similar environment has been described in ARDS, in which pathophysiologic responses are caused by microvascular thrombosis[7,8] and endothelial injury.[9]

Treatment of AE-IPF has generally consisted of high-dose corticosteroids, although there are no data from controlled trials to prove their efficacy.[10-12] Thrombomodulin is a transmembrane glycoprotein expressed on the surface of vascular endothelial cells. Expression of thrombomodulin is tightly regulated to maintain homeostasis and to ensure a rapid and localized hemostatic and inflammatory response to injury. A novel biologic agent, recombinant human soluble thrombomodulin (rhTM), exhibits a range of physiologically important antiinflammatory, anticoagulant, and antifibrinolytic properties via complex interactions with thrombin, protein C, thrombin-activatable fibrinolysis inhibitor, complement components, the Lewis Y antigen, and the cytokine high-mobility group protein B1.[13,14] The clinical efficacy of rhTM in the treatment of intravascular coagulation was demonstrated in a randomized controlled trial,[15] and it has been approved for clinical use in Japan since 2008. Retrospective analyses reported that rhTM might improve survival rate and respiratory dysfunction in patients with severe sepsis.[16,17] Based on these findings, we hypothesized that rhTM may be effective against AE-IPF. The purpose of this pilot retrospective study was to investigate the efficacy of rhTM in the treatment of patients with AE-IPF.

Materials and Methods

Subjects

This was a historical control study of patients admitted for episodes of AE-IPF to Tosei General Hospital, Aichi, Japan. From August 2009 to December 2011, 22 consecutive patients with AE-IPF were treated with rhTM (rhTM group) (Fig 1). To match numbers, we used a historical control group comprising 22 consecutive patients with AE-IPF from May 2007 to July 2009 (Fig 1). AE-IPF was defined using reported criteria for AE-IPF,[10] which state that all of the following conditions must be satisfied for previous or concurrent diagnosis of IPF: unexplained worsening or development of dyspnea within 30 days; new, bilateral, ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia pattern on CT imaging; and no evidence of pulmonary infection by endotracheal aspirate or BAL. Patients with obvious causes, such as left-sided heart failure or pulmonary embolism as an identifiable cause of acute lung injury, were excluded.

Transthoracic echocardiography was performed in all patients. Cultures of sputum, blood, and urine examined for mycobacteria, fungi, and bacteria were negative in all patients. All serologic studies for respiratory viruses such as herpes simplex virus, cytomegalovirus, varicella-zoster virus, adenovirus, influenza virus, and respiratory syncytial virus, and for chlamydophila, mycoplasma, and legionella were negative. Of 40 patients who met the inclusion criteria, BAL was performed at acute exacerbation in 37. BAL could not be performed in the other three patients because of severe hypoxemic respiratory failure. Cultures of BAL fluid (BALF) for respiratory viruses were performed. In BALF samples, additional stains were used: Ziehl-Neelsen staining for mycobacteria and Grocott's methenamine silver stain for fungi and *Pneumocystis jirovecii*. In addition, polymerase chain reaction DNA test for *P jirovecii* in BALF was performed.

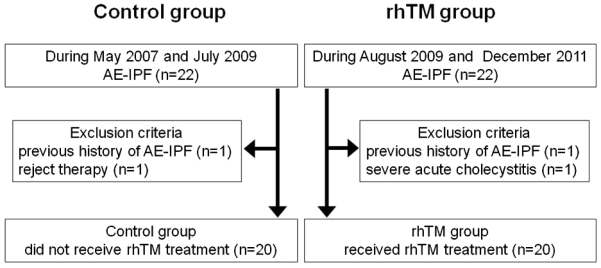

Figure 1 – *Flowchart of study design. AE-IPF = acute exacerbation of idiopathic pulmonary fibrosis; rhTM = recombinant human soluble thrombomodulin.*

The exclusion criteria in this study were as follows: more than one previous episode of AE-IPF, fatal or life-threatening bleeding (intracranial, GI, or pulmonary bleeding), history of cerebrovascular disorder (cerebral bleeding or cerebral infarction) within 1 year, age ≤ 15 years, history of hypersensitivity to protein preparations or low-molecular-weight heparin (LMWH), complication of severe disease other than AE-IPF, pregnancy or breastfeeding, and decompensated liver cirrhosis or other serious liver disorder. These data were collected retrospectively from medical records. This study was carried out in accord with the principles of the Declaration of Helsinki and approved by the institutional review board at Tosei General Hospital (IRB no. 293).

Interventions

In the rhTM group, administration of rhTM infusion (0.06 mg/kg/d) was started when patients fulfilled the criteria for AE-IPF and after they had given informed consent. RhTM therapy was continued for about 6 days, followed by continuous IV infusion of LMWH (750,000 International Units/kg/d). The control group was treated with continuous IV infusion of LMWH (750,000 International Units/kg/d) as standard anticoagulant therapy. In both groups, discontinuation of anticoagulant therapy was considered if any adverse events were present.

Data Collection

We collected information on the characteristics of the underlying IPF and treatment of IPF prior to AE. For respiratory function prior to AE, we collected respiratory data for the 6 months before AE. Patients were followed until 3 months after entry into the study. The variables at AE used to assess comparability between the two groups were age, sex, Pao_2/Fio_2, respiratory rate, APACHE (Acute Physiology and Chronic Health Evaluation) II score, WBC count, serologic tests (C-reactive