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Original article

Efficacy of recombinant human soluble thrombomodulin in preventing walled-off necrosis in severe acute pancreatitis patients

Takaaki Eguchi [a], Yoshihisa Tsuji [b], Hiroshi Yamashita [a], Takumi Fukuchi [a], Atsushi Kanamori [a], Kei Matsumoto [a], Takashi Hasegawa [a], Akio Koizumi [a], Ryuki Kitada [a], Masahiro Tsujimae [a], Taro Iwatsubo [a], Shintaro Koyama [a], Satoshi Ubukata [a], Mikio Fujita [a], Akihiko Okada [a, *]

[a] Department of Gastroenterology and Hepatology, Osaka Saiseikai Nakatsu Hospital, 2-10-39 Shibata Kitaku, Osaka 530-0012, Japan
[b] Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kawaramachi 54, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

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ABSTRACT

Objective: To investigate the efficacy of recombinant human soluble thrombomodulin (rTM) in preventing the development of walled-off necrosis (WON) in severe acute pancreatitis (SAP) patients.
Methods: We retrospectively analyzed 54 SAP patients divided into two groups: SAP patients treated by rTM (rTM group, 24 patients) and not treated by rTM (control group, 30 patients). rTM was administered to patients with disseminated intravascular coagulation (DIC). Initially, on the admission day, we recorded patient severity and pancreatic necrosis/ischemia positive or negative. Then we investigated development of WON using 4 weeks later CT/MRI. Finally we compared the proportions of patients developing WON in the rTM group and the control group.
Results: On the admission day, the condition of patients treated by rTM was significantly worse than patients in the control group; rTM group vs. control: 71.8 ± 13.9 vs. 59.8 ± 15.3 years for age, 10.7 ± 3.5 vs. 8.0 ± 4.4 for Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and 3.3 ± 1.8 vs. 2.2 ± 1.8 for sequential organ failure assessment (SOFA) score ($p < 0.05$). We found no significant differences on the admission day in rate of pancreatic necrosis/ischemia between patients treated by rTM and controls (58.3% vs. 63.3%, $p = 0.71$). Nevertheless, the proportion of patients developing WON was significantly lower among those administered rTM than in those not administered rTM {29.2% (7/24 patients) vs. 56.7% (17/30 patients), $p < 0.05$}.
Conclusion: Treatment of SAP patients treated by rTM may prevent progression from pancreatic necrosis/ischemia to WON.

Introduction

Severe acute pancreatitis (SAP) is a potentially high mortality disease. Organ failure (OF) is among the major reasons for this high mortality. Pancreatitis-related OFs are either local or systemic. In general, local OF can be divided into three stages: pancreatic ischemia, pancreatic necrosis, and walled-off necrosis (WON) [1]. Pancreatic necrosis is caused by pancreatic ischemia, which leads to WON. Systemic OF, including shock states, respiratory failure, renal failure, and heart failure, is the common origin of patient instability [2–5]. Both local and systemic OFs can be caused by abnormal coagulability, which causes from the endovascular damage caused by pancreatitis.

Some articles report that endovascular damage in acute pancreatitis patients is related to the development of disseminated intravascular coagulation (DIC). Other studies indicate that a high proportion of acute pancreatitis patients with early DIC may develop OFs. Importantly, acute pancreatitis with DIC is associated with high mortality [5–8]. In the light of these reports, controlling DIC in the early stage of acute pancreatitis may help prevent the development of local and systemic OFs, thereby reducing mortality. However, to the best of our knowledge, no effective treatment

* Corresponding author. Tel.: +81 06 6372 0333; fax: +81 06 6372 8739.
E-mail address: egugu0515@yahoo.co.jp (A. Okada).

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exists with sufficient documented efficacy against both DIC and acute pancreatitis. For example, in recent pancreatitis and DIC practical guidelines deprecate the usefulness of heparin or similar anti-coagulant drugs [9–11]. Evidence for the efficacy of activated recombinant protein C or anti-thrombin III also remains insufficient [12–16].

Recently, recombinant human soluble thrombomodulin (rTM) has been used to treat patients with DIC in Japan, and a phase III clinical trial evaluating the efficacy of rTM in severe sepsis patients with DIC is now ongoing in the USA, South America, Asia, Australia, European Union, and other countries [17–23]. Several studies report that rTM has anti-coagulation effects, resulting in improvements in septic DIC [20–28]. However, the clinical effectiveness of rTM for acute pancreatitis patients with DIC has not been assessed.

This study investigates whether rTM prevents local and/or systemic OFs in acute pancreatitis patients.

Patients and methods

Patients

This study was approved by the institutional review board of Osaka Saiseikai Nakatsu Hospital. From January 2006 to December 2013, we reviewed all pancreatitis patients data in our hospital, retrospectively. Then, >18 years old patients with SAP diagnosed by Japanese criteria were enrolled in this study. Also, patients with cancer related pancreatitis and/or immunosuppressed patients were excluded. Thereby, 54 patients with SAP were enrolled in this study. All patient data was gathered from an electronic database. Age, gender, and etiology were recorded from chart reviews. A diagnosis of acute pancreatitis was made based on 2 of 3 of the following symptoms: abdominal pain, abnormal elevation of amylase and/or lipase, and pancreatic inflammation indicated by computed tomography (CT) imaging [6,29]. SAP was diagnosed using Japanese severity scoring system. The study enrolled patients with SAP whose treatment began within 48 h of onset.

Assessment of severity

To evaluate the severity of acute pancreatitis, C-reactive protein (CRP) [2], number of patients with Blood Urea Nitrogen (BUN) ≥20 mg/dl [30], Acute Physiology and Chronic Health Evaluation II (APACHE II) score [31,32], Systemic Inflammatory Response Syndrome (SIRS) score [33], Sequential Organ Failure Assessment (SOFA) score [34], and Japanese severity score [35] were calculated before treatment (admission day = day 0) and after the start of treatment (day 3 and 7), based on retrospective reviews of medical charts. A diagnosis of pancreatic necrosis (or ischemia) based on conventional contrast-enhanced CT (CECT) was recorded. Also, patients with acute necrotizing collection (ANC) ≥6 cm (maximum transverse diameter) (n = 20) was measured based on CT or magnetic resonance imaging (MRI) image.

We defined organ failure as the followings: renal failure: serum creatinine >1.9 mg/dL; respiratory failure: PaO_2/FiO_2 ratio <300 mmHg; central nervous system failure: Glasgow coma score <13; coagulopathy: platelet count ≤8.0×10^{10}/L; and cardiovascular failure: systolic blood pressure ≤90 mmHg despite fluid replacement [36]. We defined persistent organ failure (POF) as organ failure persisting for at least 48 h.

Clinical outcomes

Length of hospital stay, need for Intensive Care Unit (ICU) care, length of ICU stay, development of WON and/or POF, and mortality were recorded. WON was diagnosed according to revised Atlanta criteria [37] and previous study [38], using CT or MRI obtained at 4 weeks or later after admission. Single board certificated radiologist, who had 20 years over experience as abdominal image, reviewed blindly all of images.

Treatment strategy for early stage acute pancreatitis

Enrolled patients were treated based on the strategy recommended in the Japanese guidelines for early stage acute pancreatitis [39–42]: in brief, fasting, aggressive fluid therapy, and administration of a protease inhibitor (nafamostat mesilate: 0.06–0.20 mg/kg/hours infused continuously; gabexate mesilate: 20–39 mg/kg/day). Continuous regional arterial infusion of the protease inhibitor (nafamostat mesilate) and prophylactic antibiotics (CRAI) [43–45] was undertaken for patients with ischemic or necrotizing pancreatitis [46,47]. Intravenous antibiotics were admitted for patients suspected to have sepsis (high fever with shock-like states).

Recombinant human soluble thrombomodulin

All patients with DIC were treated using recombinant human soluble thrombomodulin (rTM) (Recomodulin® Injection, Asahi Kasei Pharma Corporation, Tokyo, Japan) (380 U/kg/day or 130 U/kg/day for patients on hemodialysis) [18]. DIC was diagnosed based on a JAAM criteria score of 4 points or higher [18,48]. JAAM criteria assign 1 point for cases involving SIRS, mild thrombopenia (platelet count ≥8.0 and <12.0×10^{10}/L, or >30% decrease within 24 h from admission), and prolongation of prothrombin time-international normalized ratio (≥1.2) and mild elevation of fibrin/fibrinogen degradation products (FDP) values (≥10 and <25 μg/mL). JAAM criteria also assign 3 points for severe thrombopenia (<8.0×10^{10}/L or >50% decrease within 24 h), severe elevation of FDP values (≥25 μg/mL). The rTM treatment was maintained until DIC scores improved to a JAAM score of ≤3.

Changes involving severity, coagulation abnormality and inflammatory response

We investigated patient severity (CRP, SOFA score, APACHE II score, JPN score) on day 0, day 3, and day 7. At the same timing of the severity evaluations, we also measured platelet count, FDP, plasma thrombin–antithrombin III complex (TAT), D-dimer, Interleukin-6 (IL-6), and high morbidity group box 1 (HMGB-1).

Clinical outcomes patients with and without development of WON

We finally investigated length of hospital stay, need for ICU care, length of ICU stay, number and cost of follow-up CT/MRI within 1 year from onset, POF, and mortality, according to patients with and without development of WON.

Statistical analysis

Of the 54 patients, 24 (44.4%) developed DIC and were treated by rTM. The patients were divided into two groups, based on whether rTM was administered or not administered: rTM(+) (rTM group, n = 24) and rTM(−) (control group, n = 30). Then, outcomes, and involving severity coagulation abnormality and inflammatory response were compared between rTM group and control group.

Descriptive statistics are presented as mean ± standard deviation (SD) or a number (percent). Between the two groups, values were compared using the chi-square test or Mann–Whitney U test with Bonferroni corrections. A p-value of <0.05 was deemed to

Table 1
Background of enrolled patients.

	Total n = 54	rTM group n = 24	Control group n = 30
Age (years)	65.1 ± 15.8	71.8 ± 13.9*	59.8 ± 15.3
Male/Female	35/19	16/8	19/11
Etiology			
Alcohol	20	9	11
Gallstone	9	1	8
Other	25	14	11

rTM: recombinant human soluble thrombomodulin.
*p < 0.05, comparing rTM group to control.

Table 3
Outcomes compared for rTM and control groups.

	Total n = 54	rTM group n = 24	Control group n = 30
Length of hospital stay (days)	35.6 ± 31.1	33.8 ± 21.7	37.0 ± 37.2
Need for ICU care	36 (66.6%)	18 (75%)	18 (60.0%)
Length of ICU stay (days)	6.6 ± 6.0	7.1 ± 6.9	6.0 ± 4.5
Walled-off necrosis	24 (44.4%)	7 (29.2%)*	17 (56.7%)
POF	5 (9.3%)	3 (12.5%)	2 (6.7%)
Mortality rate	4 (7.4%)	2 (8.3%)	2 (6.7%)

ICU: Intensive Care Unit; POF: Persistent Organ Failure.
*p < 0.05, comparing rTM group to control.

indicate statistical significance. All statistical analyses were performed using SPSS Statistics version 20 (IBM Corp, NY, US).

Results

Background of enrolled patients

Table 1 provides a summary of the background information for the enrolled patients. Average age and ratio of male/female for all enrolled patients were 65.1 ± 15.8 years and 35/19, respectively. Etiologies of acute pancreatitis patients were as follows: alcohol in 20 patients, gallstones in 9, and other in 25. Of the background factors for the control group and the rTM group, only average age differed significantly (71.8 ± 13.9 vs. 59.8 ± 15.3 years, $p < 0.05$).

Severity of enrolled patients on admission day

The condition of patients treated by rTM were significantly more severe than that of those in the control group {patients with BUN ≥20 mg/dl: 58.3% (14/24 patients) vs. 23.3% (7/30 patients), APACHE II score: 10.7 ± 3.5 vs. 8.0 ± 4.4; SOFA score: 3.3 ± 1.8 vs. 2.2 ± 1.8; ratio of SAP on JPN criteria: 62.5 vs. 26.7 [%], $p < 0.05$} (Table 2). We found no significant differences in CRP value, ratio of SIRS, ratio of pancreatic necrosis/ischemia, patients with ANC ≥ 6 cm, or organ failure on admission between the rTM and control groups.

Comparison of outcomes between the rTM and control groups

The rate of development of WON in patients treated by rTM was significantly lower than those in the control group {29.2% (7/24 patients) vs. 56.7% (17/30 patients), $p < 0.05$}. On the other hand, we found no significant differences in outcome factors between the rTM and control groups (length of hospital stay, need for ICU, length of ICU stay, POF, or mortality), between the rTM and control groups (Table 3).

Differences in early treatment among enrolled patients with acute pancreatitis

rTM administration aside, there were no significant differences in early treatment between patients treated by rTM and the control group (Table 4).

Changes in severity, coagulation abnormality, and inflammatory response

Fig. 1 shows a summary of changes in patient severity. On day 0 (day of admission), scores for SOFA, APACHE II, and JPN scores for patients treated by rTM were significantly higher than for those in the control group ($p < 0.05$). Such significant differences were not found in CRP values between the rTM and control groups on day 0. Although all scores declined on day 3 and 7, significant differences on day 7 between the rTM and control groups disappeared only for SOFA scores.

We also compared changes in activated coagulation (platelet count, FDP, TAT, D-dimer) and inflammatory response (IL-6 and HMGB-1) between the rTM and control groups on day 0, day 3, and day 7 (Fig. 2). We found significant differences in average platelet count, FDP, TAT, and D-dimer between patients treated by rTM and those in the control group on day 0 (rTM vs. control: 15.3 ± 8.6 vs. 18.8 ± 7.6 × 10^{10}/L for platelet count; 40.6 ± 23.2 vs. 18.2 ± 16.7 μg/mL for FDP; 16.8 ± 13.6 vs. 6.9 ± 3.7 μg/L for TAT; 10.8 ± 7.0 vs. 5.2 ± 5.1 μg/mL for D-dimer; $p < 0.05$). Levels of FDP, TAT, and D-dimer for patients treated by rTM fell and platelet counts increased on day 7. Thereby, the significant differences in platelet count, FDP, TAT, and D-dimer observed on day 0 disappeared by day 7.

Table 2
Severity of enrolled patients at the time of admission.

	Total n = 54	rTM group n = 24	Control group n = 30
CRP (mg/dL)	9.9 ± 8.3	12.0 ± 8.7	8.3 ± 7.8
BUN ≥20 mg/dl	21 (38.8%)	14 (58.3%)*	7 (23.3%)
APACHE II score	9.2 ± 4.2	10.7 ± 3.5 *	8.0 ± 4.4
SIRS	2.2 ± 1.1	2.3 ± 1.0	2.2 ± 1.1
SOFA score	2.7 ± 1.9	3.3 ± 1.8*	2.2 ± 1.8
Severe acute pancreatitis (JPN score ≥3)	23 (42.6%)	15 (62.5%)*	8 (26.7%)
Pancreatic necrosis/Ischemia	33 (61.1%)	14 (58.3%)	19 (63.3%)
ANC ≥6 cm	20/33 (60.6%)	8/14 (57.1%)	12/19 (63.1%)
Organ failure	7 (12.9%)	5 (20.8%)	2 (6.7%)

CRP: C-reactive protein; APACHE II score: Acute Physiology and Chronic Health Evaluation II score; SIRS score: Systemic Inflammatory Response Syndrome score; SOFA score: Sequential Organ Failure Assessment score; JPN score: score under Japanese severity scoring system; BUN: Blood Urea Nitrogen; ANC: Acute Necrotizing Collection.
*p < 0.05, comparing rTM group to control.

Table 4
Differences in treatment for enrolled patients with acute pancreatitis.

	Total n = 54	rTM group n = 24	Control group n = 30
Duration of fast (days)	16.4 ± 13.4	16.4 ± 14.7	16.4 ± 12.6
Amount of fluid on the day of admission (mL)	4432.2 ± 1155.4	4425.0 ± 1269.6	4441.3 ± 1021.5
CRAI	11 (20.4%)	4 (16.7%)	7 (23.3%)
Intravenous protease inhibitor	54 (100%)	24 (100%)	30 (100.0%)
Duration of rTM therapy (days)	–	9.4 ± 10.2	–

CRAI: Continuous Regional Arterial Infusion.

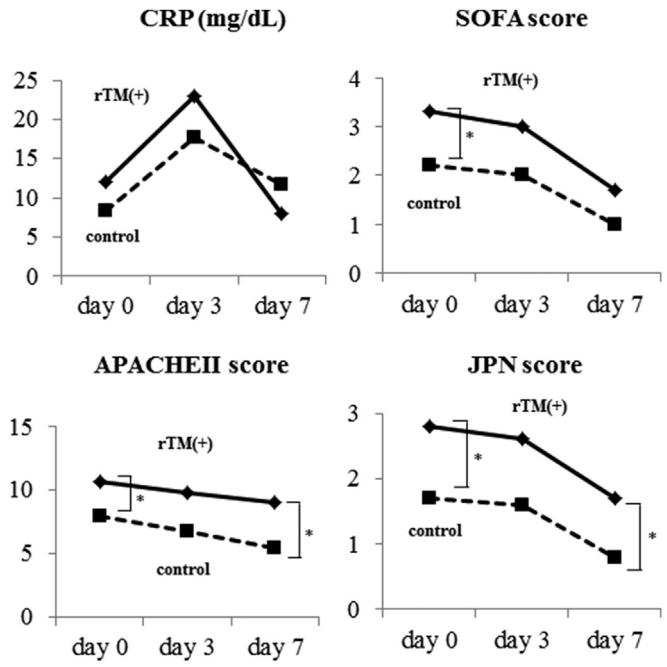

Fig. 1. Comparison of the mean values of the change in severity. CRP: C-reactive protein; APACHE II score: Acute Physiology and Chronic Health Evaluation II score; SIRS score; Systemic Inflammatory Response Syndrome score; SOFA score: Sequential Organ Failure Assessment score; JPN score: score under Japanese severity scoring system. *p < 0.05, comparing rTM group to control.

Average levels of IL-6 among patients treated by rTM appeared higher than those in the control group on day 0 (rTM vs. control: 556.8 ± 1054.2 vs. 112.9 ± 103.3 pg/mL). However, these differences were not significant at any time point, since SD values were very large. Likewise, average levels of HMGB-1 among patients treated by rTM were higher than those in the control group on day 0, but not significant (rTM vs. control: 24.5 ± 19.1 vs. 17.4 ± 8.5 ng/mL).

Table 5
Clinical outcomes patients with and without development of WON.

	Development of WON	
	(+) n = 24	(−) n = 30
Length of hospital stay (days)	46.5 ± 41.2	20.5 ± 15.3
Need for ICU care	20 (83.3%)*	16 (53.3%)
Length of ICU stay (days)	7.6 ± 4.5*	5.5 ± 6.9
Number of follow up CT/MRI image performing within one year from onset†	6.7 ± 3.2*	4.5 ± 2.4
Costs of follow up CT/MRI image for one year from onset (¥)	87,120 ± 44,470*	57,816 ± 91,156
POF	1 (4.1%)	4 (13.3%)
Mortality late	2 (8.3%)	2 (6.7%)

BUN: Blood Urea Nitrogen; ANC: Acute Necrotizing Collection; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; POF: Persistent Organ Failure.
†: CT/MRI image was performed if patients showed any new additional symptoms.
*p < 0.05, comparing WON (+) group to WON (−) group.

Clinical outcomes patients with and without development of WON

Need for ICU care, length of ICU stay, number and cost of follow-up CT/MRI within 1 year from onset were significant worse than those without {Need for ICU: 83.3% (20/24 patients) vs. 53.3% (16/30 patients), length of ICU stay: 7.6 ± 4.5 vs. 5.5 ± 6.9 days, number of follow-up CT/MRI within 1 year: 6.7 ± 3.2 vs. 4.5 ± 2.4, and cost of follow-up CT/MRI within 1 year: 87,120 ± 44,470 vs. 57,816 ± 91,156 (¥); p < 0.05} (Table 5).

Discussion

On the admission day, the condition of SAP patients treated by rTM was significantly worse than those in the control group. Moreover, the proportion of patients who developed pancreatic necrosis did not differ between those treated by rTM and those not treated by rTM. However, SAP patients treated by rTM developed WON at significantly lower rates than those in the control group,

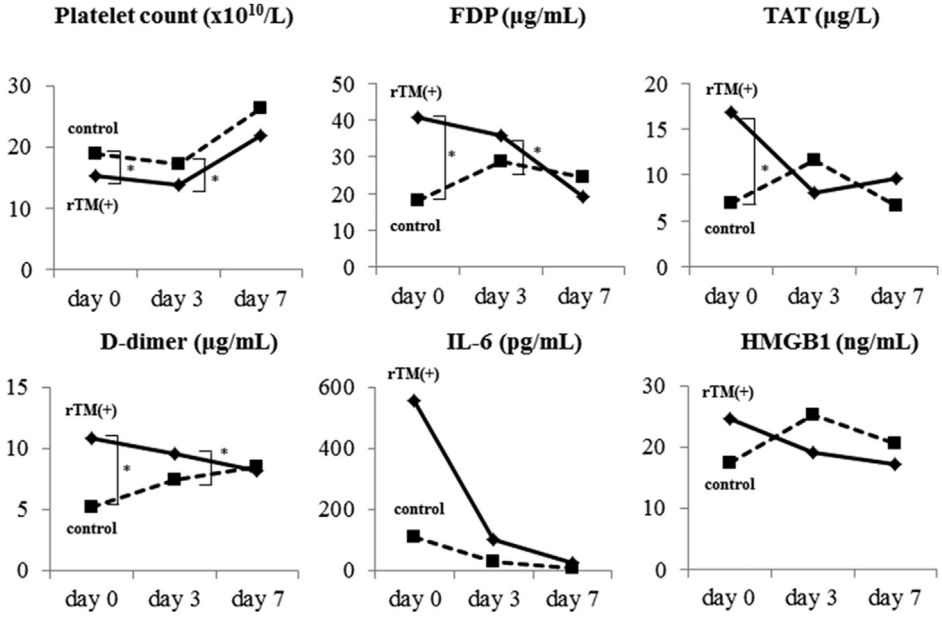

Fig. 2. Comparison of the mean values of the change in coagulation abnormality, and inflammatory response. FDP: fibrin/fibrinogen degradation products; TAT: plasma thrombin–antithrombin III complex; IL-6; Interleukin-6; HMGB-1: high morbidity group box 1. *p < 0.05, comparing rTM group to control.

although treatment strategy did not otherwise differ between the two groups. This suggests that rTM may prevent the development of WON in SAP patients.

DIC is characterized by the systemic activation of blood coagulation due to endovascular damage from cytokines and/or toxic factors (e.g., trypsin). Disturbances in microcirculation pose serious issues for patients with DIC [17,49]. In SAP patients, DIC may affect the progression from pancreatic ischemia to necrosis. In our study, rTM was used to control abnormal coagulation in the early stage of SAP; this may have prevented the development of ischemia into necrosis, thereby reducing the rate of WON. In actual, patients treated by rTM developed WON at a significantly lower rate than those not treated with rTM, in this study.

According to the revised Atlanta classification, WON is a major risk factor for developing SAP [37]. SAP patients with WON are subject to high mortality rates—roughly 30% [50–52]. Also in our study, in patients with WON, ICU stay was more needed and its duration was longer. Moreover, number and costs of follow-up CT/MRI in the patients with WON was significantly higher than those without. Therefore, reduction of ratio of development of WON is important to treat SAP patients. In our study, SAP patients treated by rTM developed WON at a significantly lower rate than those not treated by rTM. Importantly, the severity of patients treated by rTM was significantly worse than non-treated, on admission day. Thereby, their prognosis were expected to be worse. However, this difference of prognosis failed to emerge between the two groups, perhaps due to the lower rate at which WON developed among those treated by rTM. To confirm this hypothesis, prospective randomized study is needed.

Initial levels of HMGB1 in our study among patients treated by rTM was higher than those not treated with rTM. However, this relationship was reversed on day 3: Levels of HMGB1 among patients treated by rTM appeared lower than among those not treated with rTM. HMGB1 is released primarily by necrotic tissue. Thus, changing levels of HMGB1 during hospital stay may support the hypothesis that rTM helps prevent the development of necrosis.

To development of WON, two major pass ways can have important roles; vascular damage and fibrosis. Initially, vascular damage is induced by leakage of activated protease due to pancreatitis resulting in development of pancreatic or peripancreatic necrosis. Importantly, necrotic tissue can stimulate eosinophil and mast cell which can cause fibrotic responses. Thorombomodulin can control abnormal coagulation, moreover, inhibits the activation of eosinophils and mast cells [53,54]. From these regards, thorombomodulin might have reduced ratio of development of WON in our study.

rTM was commonly used for patients with DIC in Japan and the treatment of rTM was approved by Japanese health care insurance system. In actual in this study, no serious adverse event (e.g. bleeding) was seen in the two groups during the study period.

There are some limitations in our study. In our institution, not few SAP patients were triaged from other hospitals. From this reason, number of patients with development of pancreatic necrosis was large. In addition, this study was carried out at a single institution and enrolled relatively few patients. This might cause selection bias. In addition, it was not a randomized controlled trial; we compared two groups retrospectively. Also, in our study, timing of CT to diagnose pancreatic necrosis/ischemia at 3 days or later, since accuracy of conventional CT to diagnose them in the early stage is not enough. If only patients with pancreatic ischemia had been treated with rTM, the proportion of patients developing WON may have been reduced still further. However, for this study, we lacked the information to determine whether pancreatic low density areas identified by CT represented ischemia or necrosis.

In conclusion, this study indicates that treating SAP patients with rTM may prevent the development of WON and alter the prognosis.

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