ORIGINAL ARTICLE

Gut and Liver, Vol. 12, No. 4, July 2018, pp. 471-477

Clinical Impact of Recombinant Soluble Thrombomodulin for Disseminated Intravascular Coagulation Associated with Severe Acute Cholangitis

Atsushi Okuda, Takeshi Ogura, Miyuki Imanishi, Akira Miyano, Nobu Nishioka, and Kazuhide Higuchi

Second Department of Internal Medicine, Osaka Medical College, Takatsuki, Japan

Background/Aims: Recently, recombinant human soluble thrombomodulin (rTM) has been developed as a new drug for disseminated intravascular coagulation (DIC). This study aims to evaluate the clinical benefit of rTM in patients with sepsis-induced DIC caused by acute cholangitis who underwent biliary drainage. **Methods:** Patients were divided into two groups: the rTM therapy group and the non-rTM therapy group. The primary outcome was the DIC resolution rate at 7 days, and the secondary outcome was 28-day mortality rate. **Results:** Thirty-five patients were treated by rTM, and 36 patients were treated without rTM for DIC. The rate of resolution of DIC at day 7 was significantly higher in the rTM group than in the non-rTM group (82.9% vs 55.6%, p=0.0012). Compared with the non-rTM group, the 28-day survival rate of the r-TM group was significantly higher (rTM vs non-rTM, 91.4% vs 69.4%, p=0.014). According to multivariate analysis, non-rTM (hazard ratio [HR], 2.681) and CRP (HR, 2.370) were factors related to decreased survival. **Conclusions:** rTM treatment may have a positive impact on improving DIC and survival rates in patients with severe acute cholangitis. **(Gut Liver 2018;12:471-477)**

Key Words: Recombinant soluble thrombomodulin; Disseminated intravascular coagulation; Acute cholangitis; Thrombosis

INTRODUCTION

Disseminated intravascular coagulation (DIC) is a well-known condition of thrombotic occlusion of microvessels, with a mortality rate of 30% to 40%,[1,2] that occurs due to systemic activation of the coagulation pathway.[3,4] Therefore, various organs can fail in DIC patients. DIC can also occur in association with several conditions, such as trauma, infection, sepsis, organ failure, malignancy, or collagen disease.[1-5]

On the other hand, acute cholangitis is sometimes a critical systemic condition due to infection of bile juice[6] that can lead to sepsis. The mortality rate of acute cholangitis has been reported to range from 2.7% to 10%.[7-9] According to the Tokyo guideline (TG13), endoscopic biliary drainage (EBD) is recommended for mild or severe acute cholangitis.[10] However, when DIC occurs with acute cholangitis, clinical treatment for this condition may sometimes be challenging even with EBD.

Recently, recombinant human soluble thrombomodulin (rTM) has been developed as a new drug for DIC. This novel drug can improve the mortality rate and respiratory failure associated with severe sepsis.[11,12] To date, several studies of rTM for DIC with various diseases, such as acute pancreatitis[13] or hematological diseases,[14,15] have been reported. However, there have been a few reports of a clinical evaluation of rTM focused only on sepsis-induced DIC caused by acute cholangitis.[16] rTM has been available in our hospital from May, 2010. In this retrospective study, the clinical benefit of rTM for patients with sepsis-induced DIC caused by acute cholangitis was evaluated.

MATERIALS AND METHODS

This retrospective study was carried out at the Second Department of Internal Medicine of Osaka Medical College between May 2008 and May 2016. Patients provided their written, informed consent for all procedures associated with the study. This study was approved by the our Hospital's Institutional Review Board for human research. All consecutive patients underwent noninvasive imaging, such as computed tomography (CT) and endoscopic ultrasound (EUS), and were diagnosed as having severe acute cholangitis on the admission day.

Correspondence to: Takeshi Ogura
Second Department of Internal Medicine, Osaka Medical College, 2-7 Daigakuchou, Takatsuki 569-8686, Japan
Tel: +81-726831221, Fax: +81-726846532, E-mail: oguratakeshi0411@yahoo.co.jp
Received on November 2, 2017. Revised on December 13, 2017. Accepted on December 14, 2017. Published online April 27, 2018
pISSN 1976-2283 eISSN 2005-1212 https://doi.org/10.5009/gnl17489

1. Diagnosis and treatment for cholangitis

Cholangitis was diagnosed according to the criteria of the TG13 guideline.[17] Severe acute cholangitis was diagnosed with onset of dysfunction of at least one of any of the following organs/systems: (1) cardiovascular system dysfunction (hypotension requiring ≥5 μg/kg per minute, or any dose of norepinephrine); (2) neurological dysfunction (disturbance of consciousness); (3) respiratory dysfunction (PaO_2/FiO_2 ratio <300); (4) renal dysfunction (oliguria, serum creatinine >2.0 mg/dL); (5) hepatic dysfunction (prothrombin time-international normalized ratio [PT-INR] >1.5); or (6) hematological dysfunction (platelet count $<10^{10}$/μL).

Cholangitis was treated by appropriate intravenous antibiotics, and EBD was performed. In our hospital, the first line of EBD was under endoscopic retrograde cholangiopancreatography (ERCP) guidance. If patients had duodenal obstruction or surgical anatomy such as the R-Y procedure or failed ERCP, the second line of EBD was under EUS guidance such as EUS-guided hepaticogastrostomy or EUS-guided choledochoduodenostomy, as described previously.[18,19] If patients had not only bile duct obstruction but also bile duct stones, only stent placement was performed, and stone removal was performed after treatment for DIC and cholangitis.

2. Diagnosis and treatment for DIC

DIC due to severe acute cholangitis was diagnosed by fulfilling the criteria of the Japanese Association for Acute Medicine (JAAM).[20] In the JAAM criteria, 1 DIC point was assigned to patients for each of: a systemic inflammatory response syndrome (SIRS) score ≥3;[21] mild thrombocytopenia (platelet count ≥8.0 and $<12.0\times10^{10}$/L, or >30% decrease within 24 hours from admission); prolongation of the PT-INR (≥1.2); and mild elevation of fibrin/fibrinogen degradation products (FDP) values (≥10 and <25 μg/mL). In addition, 3 DIC points were assigned for each of severe thrombocytopenia ($<8.0\times10^{10}$/L or >50% decrease within 24 hours) and severe elevation of FDP values (≥25 μg/mL). DIC with cholangitis was treated using rTM (Recomodulin Injection; Asahi® Kasei Pharma Corp., Tokyo, Japan) (380 or 130 U/kg/day) with gabexate mesilate. The rTM treatment was performed until DIC scores improved to ≤3 according to the JAAM score. rTM was given from admission day to the day of resolution of DIC.

3. Definitions and statistical analysis

Patients were divided into two groups: the rTM therapy group, in which DIC was treated by rTM with gabexate mesilate;

Table 1. Patient Characteristics

Characteristic	rTM group (n=35)	non-rTM group (n=36)	p-value
Age, yr	71 (36–94)	75 (36–87)	0.325
Sex, male:female	14:21	13:23	0.809
Etiology of cholangitis			0.149
Benign disease	17	11	
Malignant disease	18	25	
Heat failure	12	16	0.461
Renal failure	7	3	0.189
Diabetes	8	3	0.111
DIC score	5 (4–8)	5 (4–8)	0.370
SIRS	27	28	1.000
FDP, μg/mL	25.0 (6.5–143.7)	26.8 (5.1–166.5)	0.359
PLT, $\times10^3$/L	11.2 (0.9–47.8)	9.5 (1.4–42.8)	0.09
PT-INR	1.61 (1.03–2.98)	1.50 (1.06–3.39)	0.08
WBC, /μL	13,750 (5,390–42,310)	12,605 (1,710–34,360)	0.372
CRP, mg/dL	14.6 (1.79–42.29)	12.5 (0.65–28.76)	0.890
T-bil, mg/dL	5.51 (0.4–34.0)	3.7 (0.6–17.2)	0.20
AST, U/L	140 (14 –834)	136 (26–473)	0.71
ALT, U/L	109 (14–447)	147 (15–374)	0.46
Post-ERCP pancreatitis	4	2	0.404

Data are presented as median (range) or number.
rTM, recombinant human soluble thrombomodulin; DIC, disseminated intravascular coagulation; SIRS, systemic inflammatory response syndrome; FDP, fibrin degradation products; PLT, platelet; PT-INR, prothrombin time-international normalized ratio; WBC, white blood cell; CRP, C-reactive protein; T-bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ERCP, endoscopic retrograde cholangiopancreatography.

and the non-rTM therapy group, in which DIC was treated by rTM with gabexate mesilate. rTM can be used from May 2010 in our hospital, therefore, non-rTM group was enrolled from May 2008 to April 2010, and rTM group was also enrolled from May 2010 to May 2016. We compared with these groups. In this study, the primary outcome was the DIC resolution rate at 7 days after starting treatment. The DIC score and the resolution rate at 0 days and 3 days were also evaluated. Also, adverse events associated with treating DIC using rTM, such as intestinal bleeding, as previously described was evaluated.[22] As secondary outcome, the 28-day mortality rate was evaluated using survival curves estimated by the Kaplan-Meier method. The Mann-Whitney U-test, Wilcoxon signed rank test, and Fisher exact test were used to compare patients' characteristics, DIC scores, and laboratory data between the two groups. The stratified log-rank test was used to compare survival curves, and censored data were taken into account. Univariate and multivariate analyses with a Cox proportional hazards model were used to determine the most significant variables contributing to patients' survival. Acute pancreatitis associated with EBD (post-ERCP pancreatitis), which was graded according to the American Society for Gastrointestinal Endoscopy lexicon's severity grading system,[23] was also evaluated. Differences with a p-value less than 0.05 were considered significant. Finally, continuous variables are expressed as mean values. All analyses were mainly performed with SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Patients' characteristics

A total of 71 patients were enrolled. All patients had severe acute cholangitis complicated with sepsis-induced DIC. The patients' characteristics are shown in Table 1. Among them, 35 patients (median age, 71 years; range, 36 to 94 years; 14 male) were treated by rTM, and 36 patients (median age, 75 years; range, 36 to 87 years; 13 male) were treated without rTM for DIC. Mean days of r-TM treatment was 6.16±1.67 (range, 4 to 10 days). Reasons for acute cholangitis in the rTM group were: benign lesions such as common bile duct stone (n=11); and malignant diseases, such as cholangiocarcinoma (n=25). This result was not significantly different from that in the non-rTM group (p=0.149). In addition, other organ failure was not significantly different between the groups. Various laboratory data associated with DIC scoring, inflammation of acute cholangitis, or transaminases, such as fibrin degradation products (FDP), blood platelet (PLT) count, PT-INR, white blood cell count, C-reactive protein (CRP), total bilirubin, aspartate aminotransferase, and alanine aminotransferase, were also not significantly different between the groups. Finally, post-ERCP pancreatitis was seen in four patients in the rTM group, and two in the non-rTM group

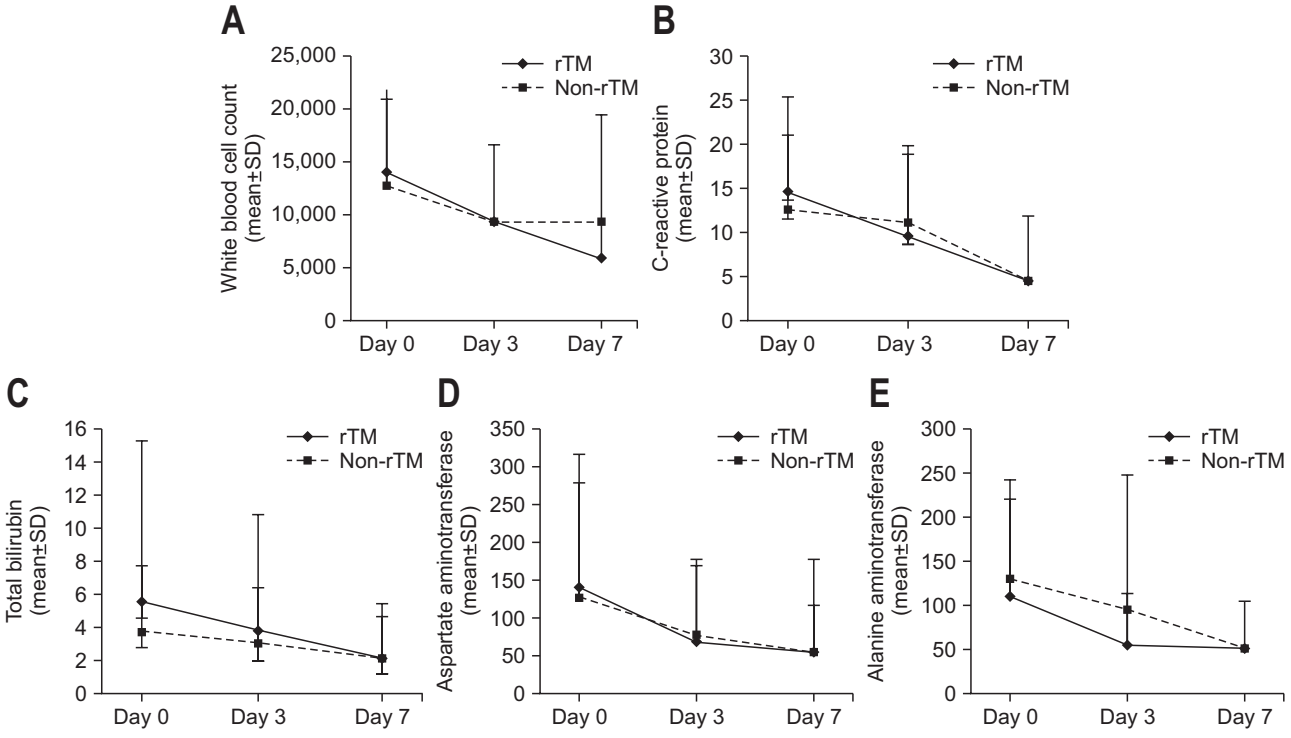

Fig. 1. Summary of mean inflammatory data and changes in transaminase levels. (A) White blood cell count (WBC), (B) C-reactive protein (CRP), (C) total bilirubin (T-bil). (D) Aspartate aminotransferase (AST) and (E) alanine aminotransferase (ALT). Inflammatory data did not differ significantly (rTM vs non-rTM: WBC, day 3 [p=0.33], day 7 [p=0.64]; CRP, day 3 [p=0.05], day 7 [p=0.73]), nor did transaminase makers (rTM vs non-rTM: T-bil, day 3 [p=0.06], day 7 [p=0.20]; AST, day 3 [p=0.764], day 7 [p=0.60]; ALT, day 3 [p=0.22], day 7 [p=0.33]).
rTM, recombinant human soluble thrombomodulin.

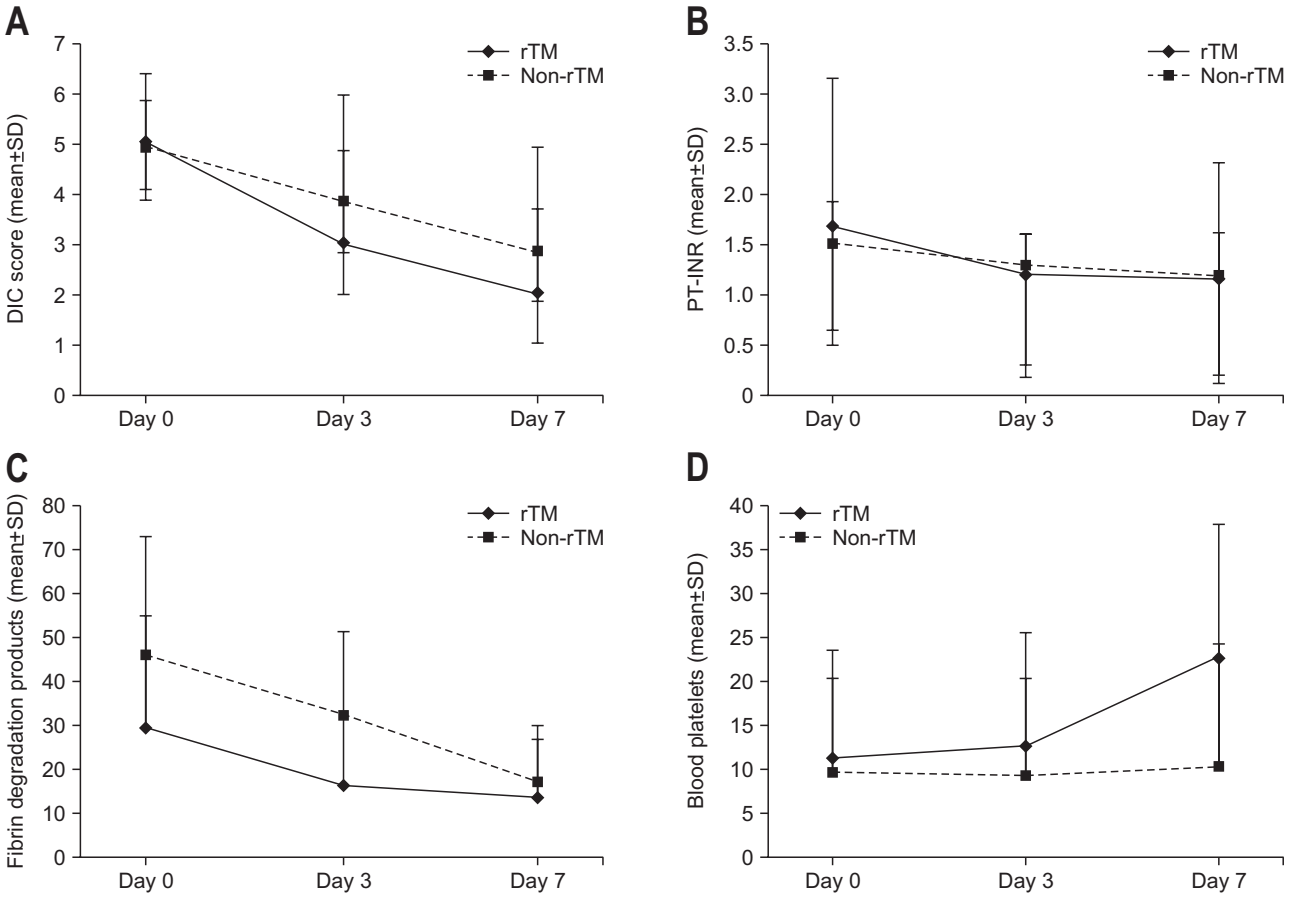

Fig. 2. Summary of disseminated intravascular coagulation (DIC) score changes. (A) DIC score, (B) prothrombin ratio and international normalized ratio (PT-INR), (C) fibrin degradation products (FDP), (D) blood platelets (PLT). Although PT-INR was significantly improved on day 3 (p=0.002), no significant differences in PT-INR were observed between the groups at day 7 (p=0.612) or in FDP (day 3, p=0.09; day 7, p=0.40). PLT counts were significantly higher in the rTM group than in the non-rTM group on day 7 (day 3, p=0.06; day 7, p=0.03). DIC resolution on day 7 was significantly higher in the rTM group than in the non-rTM group (82.9% [29/35], 55.6% [20/36], p=0.0012).
rTM, recombinant human soluble thrombomodulin.

(p=0.404).

2. Changes of acute cholangitis and DIC scoring

Fig. 1 shows a summary of the changes in inflammatory data and transaminase levels. On day 0 (day of admission), day 3, and day 7, there were no significant differences between the groups in inflammatory data and transaminase levels. Therefore, effective drainage was achieved by EBD in all patients.

Fig. 2 shows a summary of changes in DIC scores or coagulation makers. Although there was a significant difference at day 3 in the improvement in PT-INR (p=0.002), no significant differences were seen between the groups in PT-INR at day 7 (p=0.61) and in FDP (day 3, p=0.09; day 7, p=0.40). On the other hand, there was a significantly higher PLT in the rTM group than in the non-rTM group on day 7 (day 3, p=0.06; day 7, p=0.03). Finally, the rate of resolution of DIC at day 7 was significantly higher in the rTM group than in the non-rTM group (82.9% [29/35], 55.6% [20/36], p=0.0012).

Fig. 3 shows the 28-day survival curve of the two groups

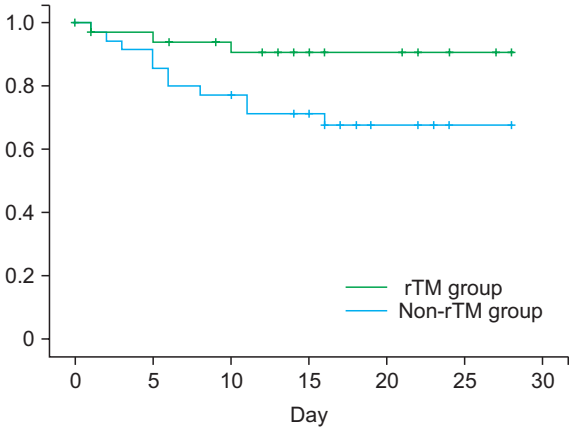

Fig. 3. The 28-day rTM and non-rTM group survival curves using the Kaplan-Meier method showed that the rTM group survived longer (p=0.029).
rTM, recombinant human soluble thrombomodulin.

Table 2. Univariate and Multivariate Analysis for Decreased 28-Day Survival

Factor	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (>75 yr)	2.258 (0.708–7.203)	0.169		
Male sex	1.288 (0.447–3.712)	0.640		
rTM (–)	3.869 (1.079–13.874)	0.038	2.681 (1.362–5.277)	0.004
Diabetes (+)	1.322 (0.296–5.911)	0.715		
Renal failure (+)	1.311 (0.293–5.857)	0.723		
Heat failure (+)	1.699 (0.533–5.418)	0.371		
SIRS (+)	2.908 (1.009–8.388)	0.048	1.020 (0.447–2.328)	0.962
CRP (>10 mg/dL)	4.212 (1.458–12.171)	0.008	2.370 (1.095–5.129)	0.028
WBC (>12,000/μL)	2.054 (0.712–5.923)	0.183		
DIC score (>5)	1.132 (0.316–4.057)	0.849		
PT-INT (>1.2)	0.799 (0.223–2.864)	0.731		
FDP (≥25 μg/mL)	0.639 (0.214–1.907)	0.422		
PLT (<8×10^3/L)	1.766 (0.592–5.271)	0.308		
Malignancy (+)	0.562 (0.197–1.605)	0.282		

HR, hazard ratio; CI, confidence interval; rTM, recombinant human soluble thrombomodulin; SIRS, systemic inflammatory response syndrome; CRP, C-reactive protein; WBC, white blood cell; DIC, disseminated intravascular coagulation; PT-INR, prothrombin time-international normalized ratio; FDP, fibrin degradation products; PLT, platelet.

using the Kaplan-Meier method showed longer survival in the rTM group (p=0.029).

3. Univariate and multivariate analyses of factors related to lower 28-day survival

The survival rate at day 28 was significantly higher in rTM group compared with non-rTM group (91.4% [32/35] vs 69.4% [25/36], p=0.014). The results of univariate and multivariate analyses for decreased 28-day survival are shown in Table 2. Univariate analysis showed that the factors related to decreased survival were non-rTM (hazard ratio [HR], 3.869; 95% confidence interval [CI], 1.079 to 13.874; p=0.038), SIRS (+) (HR, 2.908; 95% CI, 1.009 to 8.388; p=0.048), and CRP >10 (HR, 4.212; 95% CI, 1.458 to 12.171; p=0.008). On the other hand, non-rTM (HR, 2.681; 95% CI, 1.362 to 5.277; p=0.004) and CRP (HR, 2.370; 95% CI, 1.095 to 5.129; p=0.028) were the factor related to decreased survival on multivariate analysis.

DISCUSSION

Acute cholangitis is a potentially fatal systemic condition characterized by infected bile juice, which can occur due to bile duct obstruction or the presence of bile duct stones. As a result, sepsis may occur due to acute cholangitis. Recently, because of the use of EBD or intravenous antibiotics, the survival rate has also improved. Indeed, the mortality rate of acute cholangitis was higher than 50% before 1980[24] and 10% to 30% in 1981 to 1990s,[25] compared with 2.7% to 10% after 2000.[7,8] However, treatment of severe acute cholangitis may still be challenging even with adequate EBD or intravenous antibiotics, because this disease is sometimes associated with sepsis-induced DIC, which can lead to multiple organ failure (MOF).

DIC is a kind of coagulation disorder with widespread and excessive activation of coagulation within blood vessels that results in thrombotic occlusion of microvessels.[1] During the sepsis-induced DIC process, various factors such as high-mobility group box-1 (HMGB1), which is secreted by activated monocytes and macrophages and necrotic or damaged cells, or neutron extracellular trap, which is released by neutrophils, promoting immune thrombosis, play important roles. Among various factors, HMGB1 promotes up-regulation of tissue factor and down-regulation of thrombomodulin, which is an endothelial anticoagulant cofactor that plays a key role in the regulation of intravascular coagulation, resulting in endothelial cell injury and a microcirculation disorder that results in DIC and MOF.[26] Therefore, rTM has potential benefit for preventing DIC progression.

To date, several studies have reported the use of rTM for treating sepsis-induced DIC. According to a Japanese phase III randomized,[27] double-blind clinical trial that included 227 DIC patients (125 with hematological malignancies and 102 with sepsis) who received rTM or low-dose heparin, sepsis-induced DIC resolved in 66.7% (32/48) in the rTM group, compared with 54.9% (28/51) in the heparin group. In addition, the incidence of bleeding-related adverse events for up to 7 days was lower in the rTM group than in the heparin group (43.1% [50/116] vs 56.5% [65/115], p=0.048). Therefore, they concluded that rTM has clinical impact in the management of various diseases that

are exacerbated by inflammation-coagulation interactions including sepsis. As a larger study associated with sepsis-induced DIC,[28] Vincent *et al*. evaluated the safety and efficacy of rTM in a randomized, double-blinded, placebo-controlled, phase IIb study. In this study, 371 patients received rTM therapy, and 370 received placebo therapy. The 28-day mortality rate was 17.8% (66 patients) in the rTM group and 21.6% (80 patients) in the placebo group. Although there was no significant difference in the Kaplan-Meier survival curves (p=0.17), a Cochran-Mantel-Haenszel test stratified by baseline DIC and pooled country resulted in a two-sided p-value of 0.273 in favor of the rTM group, which met the predefined statistical test for evidence suggestive of efficacy. Furthermore, the rate of serious adverse events such as bleeding was not significantly different between the rTM group and the placebo group (5.1% vs 4.6%). Therefore, according to this previous study, rTM has clinical benefit in the treatment of sepsis-induced DIC. On the other hand, recent meta-analysis demonstrated that using rTM for the treatment for infection patients with DCI did not decrease the short-term mortality.[29] On the other hand, in our study, survival rate of the rTM group at day 28 was significantly higher than of the non-rTM (rTM vs non-rTM, 91.4% [32/35] vs 69.4% [25/36], p=0.014). In this meta-analysis, various sites of infection, such as the lungs or urinary tract, were included. On the other hand, our study included only sever acute cholangitis patients with DIC were included, and all patients underwent effective biliary drainage. Therefore, heterogeneity of baseline disease may be influenced for difference result between previous reports and our study. Further studies including individual disease may be needed to evaluate benefit of rTM.

To date, there have been a few reports of rTM that focused only on pancreato-biliary disease. Eguchi *et al*.[13] first evaluated the efficacy or rTM in preventing the development of wall-of-necrosis (WON) in severe acute pancreatitis patients. In this study, though the condition of the rTM group was significantly worse than that of the control group, the incidence of WON was significantly lower in the rTM group than in the control group (29.2% [7/24] vs 56.7% [17/30], p<0.05). Further, the need for intensive care unit (ICU) care, length of ICU stay, number and cost of follow-up CT/magnetic resonance imaging examinations within 1 year from onset were significantly worse in those with WON than in those without. In addition, serious adverse events were not seen in any patients. As well, in the present study, the rate of improved DIC at day 7 was significantly higher in the rTM group than in the non-rTM group. Moreover, rTM was an independent factor associated with improved 28-day survival on multivariate analysis. Suetani *et al*.[16] examined factors that contributed to persistent DIC associated with acute cholangitis. In this study, absence of biliary drainage was significantly associated with persistent DIC (p<0.01) on multivariate analysis. In addition, although there were no signify differences, malignant disease (p=0.055) and the non-rTM (p=0.08) had a tendency to be associated with persistent DIC.

Compared with previous studies, our study may have several strengths. First, in our study, biliary drainage was performed in all patients and clinical success was obtained in all patients. To treat DIC caused by severe acute cholangitis, biliary drainage may be most important. Compared with previous reports, our study included only patients who underwent effective biliary drainage. Therefore, clinical role of rTM for DIC caused by acute cholangitis may be able to truly evaluate. Second, DIC was treated using only rTM. These facts may influence the pure effectiveness of rTM for sepsis-induced DIC. However, the present study has several limitations. First, this was not a randomized, controlled trial. Second, the patient population may have been heterogeneous, including cases such as bile duct stone or cholangiocarcinoma. Although there were no significant differences in patients' background characteristics and laboratory data, such as FDP, between the groups, one cannot completely exclude that DIC scoring and the improvement process of the DIC score may have been influenced by cancer-induced DIC. Therefore, to confirm the present results, a comparative prospective evaluation including a large number of patients may be needed based on strict criteria, such as including acute cholangitis caused by benign disease.

In conclusion, rTM treatment was an impact factor associated with improved DIC and survival rates in patients with severe acute cholangitis, with no adverse events associated with rTM treatment. Thus, rTM has clinical benefit for sepsis-induced DIC patients with severe acute cholangitis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Levi M, Ten Cate H. Disseminated intravascular coagulation. N Engl J Med 1999;341:586-592.
2. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation: British Committee for Standards in Haematology. Br J Haematol 2009;145:24-33.
3. Yamakawa K, Ogura H, Fujimi S, et al. Recombinant human soluble thrombomodulin in sepsis-induced disseminated intravascular coagulation: a multicenter propensity score analysis. Intensive Care Med 2013;39:644-652.
4. Ueno H, Hirasawa H, Oda S, Shiga H, Nakanishi K, Matsuda K. Coagulation/fibrinolysis abnormality and vascular endothelial damage in the pathogenesis of thrombocytopenic multiple organ failure. Crit Care Med 2002;30:2242-2248.
5. Frossard JL, Steer ML, Pastor CM. Acute pancreatitis. Lancet 2008;371:143-152.

6. Higuchi R, Takada T, Strasberg SM, et al. TG13 miscellaneous etiology of cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci 2013;20:97-105.
7. Pang YY, Chun YA. Predictors for emergency biliary decompression in acute cholangitis. Eur J Gastroenterol Hepatol 2006;18:727-731.
8. Agarwal N, Sharma BC, Sarin SK. Endoscopic management of acute cholangitis in elderly patients. World J Gastroenterol 2006;12:6551-6555.
9. Yeom DH, Oh HJ, Son YW, Kim TH. What are the risk factors for acute suppurative cholangitis caused by common bile duct stones? Gut Liver 2010;4:363-367.
10. Itoi T, Tsuyuguchi T, Takada T, et al. TG13 indications and techniques for biliary drainage in acute cholangitis (with videos). J Hepatobiliary Pancreat Sci 2013;20:71-80.
11. Ogawa Y, Yamakawa K, Ogura H, et al. Recombinant human soluble thrombomodulin improves mortality and respiratory dysfunction in patients with severe sepsis. J Trauma Acute Care Surg 2012;72:1150-1157.
12. Abeyama K, Stern DM, Ito Y, et al. The N-terminal domain of thrombomodulin sequesters high-mobility group-B1 protein, a novel antiinflammatory mechanism. J Clin Invest 2005;115:1267-1274.
13. Eguchi T, Tsuji Y, Yamashita H, et al. Efficacy of recombinant human soluble thrombomodulin in preventing walled-off necrosis in severe acute pancreatitis patients. Pancreatology 2015;15:485-490.
14. Kawano N, Tasaki A, Kuriyama T, et al. Effects of recombinant human soluble thrombomodulin treatment for disseminated intravascular coagulation at a single institution: an analysis of 62 cases caused by infectious diseases and 30 cases caused by hematological diseases. Intern Med 2014;53:205-213.
15. Yokoyama H, Takahashi N, Katsuoka Y, et al. Evaluation of the safety and efficacy of recombinant soluble thrombomodulin for patients with disseminated intravascular coagulation associated with acute leukemia: multicenter prospective study by the Tohoku Hematology Forum. Int J Hematol 2017;105:606-613.
16. Suetani K, Okuse C, Nakahara K, et al. Thrombomodulin in the management of acute cholangitis-induced disseminated intravascular coagulation. World J Gastroenterol 2015;21:533-540.
17. Kiriyama S, Takada T, Strasberg SM, et al. TG13 guidelines for diagnosis and severity grading of acute cholangitis (with videos). J Hepatobiliary Pancreat Sci 2013;20:24-34.
18. Ogura T, Higuchi K. Technical tips of endoscopic ultrasound-guided choledochoduodenostomy. World J Gastroenterol 2015;21:820-828.
19. Ogura T, Higuchi K. Technical tips for endoscopic ultrasound-guided hepaticogastrostomy. World J Gastroenterol 2016;22:3945-3951.
20. Wada H, Asakura H, Okamoto K, et al. Expert consensus for the treatment of disseminated intravascular coagulation in Japan. Thromb Res 2010;125:6-11.
21. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med 2015;372:1629-1638.
22. Aikawa N, Shimazaki S, Yamamoto Y, et al. Thrombomodulin alfa in the treatment of infectious patients complicated by disseminated intravascular coagulation: subanalysis from the phase 3 trial. Shock 2011;35:349-354.
23. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010;71:446-454.
24. Thompson JE Jr, Pitt HA, Doty JE, Coleman J, Irving C. Broad spectrum penicillin as an adequate therapy for acute cholangitis. Surg Gynecol Obstet 1990;171:275-282.
25. Salek J, Livote E, Sideridis K, Bank S. Analysis of risk factors predictive of early mortality and urgent ERCP in acute cholangitis. J Clin Gastroenterol 2009;43:171-175.
26. Okamoto K, Tamura T, Sawatsubashi Y. Sepsis and disseminated intravascular coagulation. J Intensive Care 2016;4:23.
27. Saito H, Maruyama I, Shimazaki S, et al. Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial. J Thromb Haemost 2007;5:31-41.
28. Vincent JL, Ramesh MK, Ernest D, et al. A randomized, double-blind, placebo-controlled, Phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. Crit Care Med 2013;41:2069-2079.
29. Zhang C, Wang H, Yang H, Tong Z. Recombinant human soluble thrombomodulin and short-term mortality of infection patients with DIC: a meta-analysis. Am J Emerg Med 2016;34:1876-1882.