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

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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 rTM 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%, that occurs due to systemic activation of the coagulation pathway. 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. On the other hand, acute cholangitis is sometimes a critical systemic condition due to infection of bile juice that can lead to sepsis. The mortality rate of acute cholangitis has been reported to range from 2.7% to 10%. According to the Tokyo guideline (TG13), endoscopic biliary drainage (EBD) is recommended for mild or severe acute cholangitis. 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. To date, several studies of rTM for DIC with various diseases, such as acute pancreatitis or hematological diseases, 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. 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.
1. Diagnosis and treatment for cholangitis

Cholangitis was diagnosed according to the criteria of the TG13 guideline.\textsuperscript{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\textsubscript{2}/FiO\textsubscript{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\textsuperscript{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.\textsuperscript{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).\textsuperscript{20} In the JAAM criteria, 1 DIC point was assigned to patients for each of: a systemic inflammatory response syndrome (SIRS) score ≥3;\textsuperscript{21} mild thrombocytopenia (platelet count ≥8.0 \times 10\textsuperscript{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 \times 10\textsuperscript{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\textsuperscript{®} 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, ×10\textsuperscript{3}/L |           | 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)        | 0.72    |
| 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.
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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. 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, 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.

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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=0.13]). rTM, recombinant human soluble thrombomodulin.
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 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=0.61) 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.

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).

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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; 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.

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

| Factor           | Univariate HR (95% CI) | p-value | Multivariate 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 (<8x10^9/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.

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 and 10% to 30% in 1981 to 1990s, compared with 2.7% to 10% after 2000. 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. 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 neutroph 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. 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, 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, 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 DCl did not decrease the short-term mortality. 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 severe 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. 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. 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.

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