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A Thrombomodulin Alfa Effective for Treatment of Sepsis-Associated Disseminated Intravascular Coagulation

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ABSTRACT

Disseminated intravascular coagulation is a serious complication of sepsis that leads to severe organ dysfunction and high mortality, thus early and effective treatment is essential. While thrombomodulin alfa is known as an effective therapeutic agent for disseminated intravascular coagulation, its optimal plasma level has yet to be established. The present two-phase investigation was conducted to evaluate the relationship between plasma concentration of thrombomodulin alfa and both therapeutic efficacy and safety in patients with sepsis-induced disseminated intravascular coagulation, in order to clarify the optimal concentration. For the first phase, patients were divided into high- and low-concentration groups based on a plasma trough cutoff level of 600 ng/mL, then treatment efficacy and bleeding-related adverse events were compared. For the second phase, receiver operating characteristic curve analysis was performed to determine the cutoff value for plasma trough concentration that significantly affected clinical outcomes. Treatment efficacy was higher with concentrations ≥600 ng/mL, without an increase in bleeding complications. Furthermore, receiver operating characteristic analysis identified a cutoff value of 1010 ng/mL, with the 90-day survival rate significantly higher at that concentration (91.7% vs. 63.4%, $p = 0.017$), while safety was maintained. The present findings suggest that for treatment of sepsis-induced disseminated intravascular coagulation, adjustment of thrombomodulin alfa dose to maintain a plasma trough concentration of at least 1010 ng/mL provides an effective and safe therapeutic strategy.

Introduction

Disseminated intravascular coagulation (DIC) is a systemic coagulation disorder that occurs in conjunction with various underlying conditions, including infection, malignancy, and trauma. In the suppressed-fibrinolytic-type DIC, which occurs in association with sepsis, the fibrinolysis system is suppressed due to increased plasminogen activator inhibitor (PAI) activity, and the blood coagulation system is activated due to excessive thrombin production, resulting in the formation of thrombi in microvessels throughout the body, leading to ischemic organ dysfunction.[1] As a result, the sepsis condition is more likely to become severe, with an extremely high 28-day mortality rate of 30-40%.[2] Thus, septic DIC is a state in which thrombin is overproduced, and controlling thrombin production is key to treatment. Since thrombomodulin (TM) alfa inhibits thrombin generation, it has been suggested that it may prevent the complications and aggravation of organ dysfunction, thereby improving patient outcomes.[3, 4] Patients with sepsis-associated DIC are often affected by abnormal activation of inflammatory and coagulation systems, leading to organ dysfunction and/or bleeding tendency. Although the fundamental treatment strategy is control of the underlying disease, TM alfa given as adjunctive anticoagulant therapy has recently gained attention.

Thrombomodulin is a membrane protein expressed on the surface of endothelial cells and binds to thrombin. That binding results in activation of protein C, which causes inactivation of the coagulation factors Va and VIIIa via activated protein C (APC), resulting in suppression of the coagulation cascade. In addition, both APC and TM possess anti-inflammatory properties, including inhibition of proinflammatory cytokine production and protection of endothelium. Thrombomodulin alfa, a soluble recombinant preparation comprising the extracellular domain of TM, exhibits similar anticoagulant and anti-inflammatory activities in the bloodstream. Furthermore, findings have been presented showing that TM alfa suppresses excessive inflammatory responses in sepsis by neutralizing damage-associated molecular patterns (DAMPs), such as high mobility group box-1 (HMGB1). [5]

In a phase III clinical trial conducted in Japan, administration of TM alfa was found to result in superior improvement in DIC scores as compared with heparin, with fewer bleeding events observed.[6] Moreover, results of retrospective studies and meta-analyses have also indicated that TM alfa treatment tends to provide such advantages as reduced mortality and improvements in organ dysfunction.[7] Based on analysis of such findings, a document issued by the Japanese Society on Thrombosis and Hemostasis, titled “DIC Treatment Guidelines 2024”, presented for management of disseminated intravascular coagulation in Japan, strongly recommends TM alfa as a therapeutic option for sepsis-associated DIC, particularly in patients with a low risk of bleeding.[8]

On the other hand, an international multicenter study termed the SCARLET trial found that administration of TM alfa did not result in significant improvement in 28-day mortality and the primary endpoint was not met.[9] As a result, TM alfa has not been approved for treatment in Europe or the United States, and remains limited to investigational use. Furthermore, international guidelines such as the Surviving Sepsis Campaign[10] do not provide clear recommendations for its use and TM alfa is not currently regarded as a global standard therapy.

Although TM alfa administration is considered to have a lower risk of bleeding as compared with heparin, caution is needed for patients with severe hepatic dysfunction or bleeding tendency. In addition, evidence regarding optimal patient selection, administration timing, and dose adjustment remains insufficient. The present study focused on plasma concentration of TM alfa, and provides findings useful for evaluation of its efficacy and safety in relation to plasma levels.

Methods

1. PATIENTS

This was a retrospective study of patients with sepsis-associated DIC who were admitted to the intensive care unit of Saiseikai Yokohamashi Tobu Hospital between January 2013 and December 2018, and met the following criteria: a) positive blood culture findings in microbiological testing, b) sepsis diagnosis,[11] c) Japanese Association for Acute Medicine (JAAM) DIC score of ≥4,[12] and d) administration of TM alfa at the same dose for at least three consecutive days. Those younger than 20 years of age, with chronic renal failure requiring maintenance dialysis, showing coagulation disorder primarily attributable to a cause other than sepsis, or whose outcome 90 days after TM alfa administration was unknown were excluded. Patient data collected included age, body weight, TM alfa dosage and duration of administration, creatinine clearance, JAAM-DIC score,[12] Acute Physiology and Chronic Health Evaluation (APACHE) II score,[13] Sequential Organ Failure Assessment (SOFA) score,[14] infection site, and bacterial species identified in blood culture results. Creatinine clearance was calculated using the Cockcroft-Gault formula.[15] In Japan, the approved dose of TM alfa is 380 U/kg/day (0.06 mg/kg/day), which may be reduced to 130 U/kg/day (0.02 mg/kg/day) for patients with severe renal impairment, depending on clinical symptoms.[16]

2. CALCULATION OF PLASMA TM ALFA CONCENTRATION

Results obtained in previous population pharmacokinetic analyses show that plasma TM alfa concentration can be predicted using a one-compartment model, with total clearance and volume of distribution calculated according to formulas ① and ② shown below.[17] Since TM alfa was administered once daily with a 24-hour interval in the present subjects, the plasma trough concentration at 24 hours following the final administration was estimated using formula ④ shown following. For these calculations, the administered dose was converted from units (U) to milligrams (mg), with 6400 U considered equivalent to 1 mg.[16] Endogenous TM cannot be distinguished from exogenous TM alfa, thus plasma TM alfa concentrations were not directly measured in the present study, but rather estimated using the following equations:

$$CL = 0.14 \cdot \left(\frac{BW}{68}\right)^{0.56} \cdot \left(\frac{CCR}{72.6}\right)^{0.27} \quad \cdots ①$$

$$Vd = 5.47 \cdot \left(\frac{BW}{68}\right)^{0.5} \quad \cdots ②$$

$$k = CL/Vd \quad \cdots ③$$

$$C = \frac{D}{Vd} \cdot \left\{\frac{1-e^{-nk\tau}}{1-e^{-k\tau}}\right\} \cdot e^{-k\tau} \cdot 1000 \quad \cdots ④$$

CL: total clearance (L/h), BW: body weight (kg), CCR: creatinine clearance (mL/minute), Vd: volume of distribution (L), C: plasma concentration (ng/mL), D: dose administered (mg), n: number of doses, k: elimination rate constant (h^{-1}), and τ: dosing interval (h).

3. CHANGES IN JAAM-DIC SCORE

The therapeutic efficacy of TM alfa was evaluated based on change in JAAM-DIC score. Using the JAAM-DIC score on day 1 of TM alfa administration as the baseline value, changes in score were calculated for each patient from day 2 through 5. Mean values indicating change for each day for the treatment groups were then compared.

4. 90-DAY SURVIVAL

Survival status was assessed for each patient from the first day of TM alfa administration up to 90 days and survival rates were compared between the groups. Patients discharged or transferred within 90 days of treatment initiation, or whose subsequent outcome was unknown were censored at the time of discharge or transfer.

5. HEMORRHAGIC ADVERSE EVENTS

The incidence of intracranial hemorrhage, pulmonary hemorrhage, and gastrointestinal bleeding, conditions classified as serious bleeding in the TM alfa package insert,[16] was investigated and compared between the groups. The follow-up period extended from the start of TM alfa administration to five days after the end of treatment, corresponding to approximately five times the half-life of the drug.

6. PLASMA TROUGH CONCENTRATION CUTOFF

Using data from patients who died within 90 days of TM alfa initiation, receiver operating characteristic (ROC) curve analysis was performed to determine the plasma trough concentration cutoff value with significant influence on patient outcome.

7. EVALUATION OF CUTOFF VALUE UTILITY

Based on the cutoff value derived from ROC curve analysis, patients were categorized according to whether the plasma trough concentration was above or below the cutoff. Therapeutic efficacy was assessed based on 90-day survival, while safety was evaluated according to incidence of hemorrhagic adverse events.

8. STATISTICAL ANALYSIS

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA), with the significance level set at $p < 0.05$. For comparisons between two groups, categorical data were analyzed using a χ^2 test or Fisher's exact test, while continuous data were analyzed using Student's t-test or the Mann-Whitney U test, as appropriate. The cutoff value, area under the ROC curve (AUC), sensitivity, and specificity were calculated using ROC curve analysis. Survival curves were estimated using the Kaplan-Meier method, with differences assessed by a log-rank test. Additionally, Cox regression analysis was performed to calculate hazard ratio (HR) and 95% confidence interval (CI) values.

9. ETHICAL CONSIDERATIONS

This study was conducted following approval from the institutional ethics committee of our hospital (approval numbers: 2018031, 20200143) with due consideration for protection of personal information.

Results

1. FIRST-STAGE STUDY[17]

a) Patients

There were 57 patients treated for sepsis-associated DIC between January 2013 and December 2016, and who met the inclusion criteria for the first-stage study. Of those, eight were subsequently excluded, including two because of a coagulation disorder attributed to a hematologic disease, two affected by cirrhosis, and four due to use of extracorporeal membrane oxygenation (ECMO). The remaining 49 patients were included in the present analysis, among whom 14 had a TM alfa plasma trough concentration < 600 ng/mL (low-concentration group) and 35 had a concentration ≥ 600 ng/mL (high-concentration group). The predicted plasma trough concentration ranged from 325-583 ng/mL in the low-concentration group and 600-1579 ng/mL in the high-concentration group, while peak concentrations ranged from 489-972 ng/mL and 960-2265 ng/mL, respectively. Group assignment was based on plasma concentration, thus administered doses differed significantly between the groups. However, there were no significant differences between the groups for disease severity, as shown by JAAM-DIC, APACHE II, and SOFA scores.

b) Changes in JAAM-DIC score

On day 4 of TM alfa administration, the change in JAAM-DIC score was −0.71 in the low-concentration and −2.06 in the high-concentration group, a statistically significant difference ($p < 0.05$). Furthermore, the change from baseline score for the low-concentration group was consistently lower on all treatment days as compared to that for the high-concentration group.

c) 90-day survival

The 90-day survival rate was 49.0 % in the low-concentration group and 85.4 % in the high-concentration group, representing significantly greater survival in the latter ($p = 0.017$). Furthermore, Cox regression analysis showed a HR of 0.27 (95 % CI: 0.09–0.86), indicating a significantly lower risk of death in the high-concentration as compared with the low-concentration group.

d) Hemorrhagic adverse events

The incidence of severe bleeding, including intracranial, pulmonary, and gastrointestinal hemorrhage, did not differ significantly between the groups (one patient in low-concentration group, three patients in high-

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concentration group). During the TM alfa administration period, one patient in the low-concentration group and one in the high-concentration group had a severe gastrointestinal bleeding event.

2. SECOND-STAGE STUDY[18]

a) Patients

There were 86 patients treated for sepsis-associated DIC between January 2013 and December 2018, and who met the inclusion criteria of the second-stage study. Of those, 21 were subsequently excluded, including two with a coagulation disorder attributed to hematologic disease, three affected by cirrhosis, one due to chemotherapy, nine due to use of ECMO, and six with an unknown outcome 90 days after TM alfa administration. The remaining 65 patients were included in the present analysis. In the non-survivor group, median TM alfa dose and plasma trough concentration were 0.050 mg/kg and 663.3 ng/mL, respectively, while those in the survivor group were 0.057 mg/kg and 847.0 ng/mL, respectively, with significantly higher values for the survivor group. Conversely, indicators of disease severity, including APACHE II score, as well as proportion of patients with pulmonary or thoracic infection were significantly higher in the non-survivor group.

b) Determination of cutoff value for plasma trough concentration

Receiver operating characteristic curve analysis was performed using patients who died within 90 days of TM alfa initiation as event cases, with plasma trough concentration as the variable. The AUC value for the ROC curve was 0.669 (95 % CI: 0.530-0.808). The cutoff value was determined to be 1010 ng/mL, with a sensitivity of 0.458 and specificity of 0.882.

c) Cutoff value evaluation

Patients were divided into two groups based on TM alfa plasma trough concentration above or below the cutoff value of 1010 ng/mL. The 90-day survival rate was significantly higher for patients with a concentration above (91.7 %) as compared with those below (63.4 %) the cutoff ($p = 0.017$). Cox regression analysis revealed a HR of 0.199 (95 % CI: 0.045-0.871).

d) Cutoff value safety evaluation

The incidence of major bleeding events (intracranial, pulmonary, gastrointestinal hemorrhage) did not differ significantly between the groups (four patients in group below cutoff value, one patient in group above cutoff value). During TM alfa administration, two patients in the group below the cutoff value developed gastrointestinal bleeding.

Discussion

Thrombomodulin alfa was approved in Japan in 2008 as a therapeutic agent for DIC, and findings regarding its efficacy and safety for treatment of sepsis-associated DIC have been reported. However, no known study has sufficiently examined the role of plasma concentration in treated patients. For the present analysis, the TM alfa plasma trough concentration was analyzed in patients with sepsis-associated DIC, and its relationship with estimated concentration, therapeutic efficacy, and occurrence of hemorrhagic adverse events evaluated.

The effective plasma concentration of TM alfa for treatment of DIC has been reported to range from 300-900 ng/mL.[20] For the present first-stage study, a cutoff value of 600 ng/mL, the midpoint of that range, was used to divide patients into those with a trough concentration above or below that threshold to evaluate efficacy and safety. At the initiation of TM alfa treatment, there was no significant difference for JAAM-DIC score between the groups. However, by day 4 of treatment, the change in JAAM-DIC score was significantly greater in the high-concentration group, indicating a superior therapeutic efficacy of TM alfa for patients with a higher plasma concentration. Moreover, the high-concentration group showed a significantly higher rate of 90-day survival than the low-concentration group ($p = 0.017$) as well as significantly reduced risk of death (HR: 0.27, 95 % CI: 0.09–0.86). Notably, the incidence of severe bleeding was comparable to that reported by Yamakawa et al.,[21] indicating that the results were reasonable.

For the second-stage study, the cutoff value of plasma trough concentration that had influence on clinical outcome was calculated based on the ROC curve and determined to be 1010 ng/mL. To further evaluate the efficacy and safety of that cutoff value, the patients were divided into two groups, above and below that threshold, and 90-day survival as well as incidence of severe bleeding were compared. For patients with a concentration above the cutoff value, the 90-day survival rate was significantly higher ($p = 0.017$) and the risk of death was also significantly reduced, demonstrating clinical utility (HR: 0.199; 95% CI: 0.045–0.871). There was no significant difference for adverse bleeding incidence between the groups, though that tended to be higher for the group below the cutoff value. The incidence of hemorrhagic adverse events observed in this study was also consistent with the report presented by Yamakawa et al.,[21] thus supporting the validity of the findings. This was thought to be due to the fact that TM alfa inhibits thrombin generation via APC in a concentration-dependent manner, thereby suppressing the activated coagulation system.[22] Furthermore, APC reduces PAI-1 activity, activating the suppressed fibrinolytic system.[23] In other words, the high-concentration group demonstrated a greater therapeutic effect against septic DIC because the coagulation and fibrinolytic systems recovered earlier in the TM alfa administration compared to the low-concentration group. TM alfa also exhibits indirect anti-inflammatory effects through its inhibitory effects on APC-mediated adhesion molecule production and neutrophil activation.[24, 25] Furthermore, TM alfa exhibits direct anti-inflammatory effects by directly adsorbing and neutralizing endotoxin, HMGB-1, and extracellular histones.[26-28] Because inflammatory substances such as endotoxin, HMGB-1, and histones produced in sepsis activate the coagulation system and cause DIC,[29] the anti-inflammatory effects of TM alfa may have had a positive impact on the therapeutic efficacy of septic DIC.

Regarding bleeding side effects, TM alfa exerts its anticoagulant effect by directly or indirectly inhibiting thrombin generation depending on its concentration. Bleeding is related to the direct inhibition of thrombin generation, which requires high concentration. It has been reported that the risk of adverse events increases sharply

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when the mean plasma concentration of TM alfa exceeds 9.8 μg/mL.[30] Therefore, the main effect of TM alfa when administered clinically is believed to be indirect inhibition of thrombin generation via activation of protein C, and the risk of bleeding is thought to be low.[31] Reanalysis of the present data was performed using mean plasma concentration, which showed a cutoff value of 1515 ng/mL, markedly lower than 9.8 μg/mL. The maximum plasma concentration in the first-stage study population was 2265 ng/mL and in the second-stage study population was 2514 ng/mL, indicating a low risk of bleeding in both. Furthermore, analyses of efficacy and safety using mean plasma concentration yielded results similar to those obtained with use of trough concentration (unpublished data). Although the plasma concentrations of TM alfa observed in this study exceeded the recommended optimal range (300-900 ng/mL), administration was considered to be both safe and effective.

The present results indicate that a plasma trough concentration of 1010 ng/mL is the level at which TM alfa exerts maximal therapeutic efficacy with minimal risk of severe bleeding. For treatment of patients with sepsis-associated DIC, it may be necessary to adjust the dosing regimen to achieve a predicted trough concentration of at least 1010 ng/mL. In addition, they show the potential for individualized TM alfa therapy based on plasma concentration, underscoring the need for further prospective studies.

Conclusions

For treatment of patients with sepsis-associated DIC, a TM alfa plasma trough concentration of at least 1010 ng/mL appears to maximize therapeutic efficacy, while minimizing the risk of hemorrhagic adverse events. Adjustment of the dosing regimen to achieve this target may be an effective and safe clinical treatment strategy.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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References

1. Ogura H, Gando S, Iba T, et al. SIRS-associated coagulopathy and organ dysfunction in critically ill patients with thrombocytopenia. *Shock*. 2007; 28: 411-417.
2. Gando S, Saitoh D, Ogura H, et al. Disseminated intravascular coagulation (DIC) diagnosed based on the Japanese Association for Acute Medicine criteria is a dependent continuum to overt DIC in patients with sepsis. *Thromb Res*. 2009; 123: 715-718.
3. Eguchi Y, Gando S, Ishikura H, et al. Post-marketing surveillance data of thrombomodulin alfa: sub-analysis in patients with sepsis-induced disseminated intravascular coagulation. *J Intensive Care*. 2014; 2: 30.
4. Gando S, Shiraishi A, Yamakawa K, et al. Role of disseminated intravascular coagulation in severe sepsis. *Thromb Res*. 2019; 178: 182-188.
5. Abeyama K, Stern DM, Ito Y, et al. The N-terminal domain of thrombomodulin sequesters HMGB1: a novel anti-inflammatory mechanism. *J Clin Invest*. 2005; 115: 1267–1274.
6. Saito H, Maruyama I, Shimazaki S, et al. Efficacy and safety of recombinant human soluble thrombomodulin in disseminated intravascular coagulation: a phase III, randomized, double-blind trial. *Crit Care Med*. 2007; 35: 657–662.
7. Yamakawa K, Aihara M, Ogura H, et al. Recombinant human soluble thrombomodulin in sepsis: a systematic review and meta-analysis. *Crit Care*. 2015; 19: 543.
8. Japanese Society on Thrombosis and Hemostasis. Disseminated intravascular coagulation management guidelines 2024. *Jpn J Thromb Hemost*. 2025; 36: 68-156.
9. Vincent JL, Francois B, Zabolotskikh I, et al. SCARLET trial: recombinant thrombomodulin in sepsis-associated coagulopathy. *N Engl J Med*. 2019; 380: 617–628.
10. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: International Guidelines 2021. *Intensive Care Med*. 2021; 47: 1181–1247.
11. Singer M, Deutschman CS, Seymour CW, et al. The Third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016; 315: 801-810.
12. Gando S, Iba T, Eguchi Y, et al. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. *Crit Care Med*. 2006; 34: 625-631.
13. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985; 13: 818-829.
14. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996; 22: 707-710.
15. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16: 31-41.
16. Recomodulin® Inj, 12800 package insert. Available at: https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/100898_3339401D1027_1_15 [In Japanese]. (accessed August 29, 2025).
17. Imaura M, Tsumori M, Nagase S, et al. Therapeutic and adverse effects of thrombomodulin alfa to treat sepsis-induced disseminated intravascular coagulation. *Shock*. 2020; 54: 50-55.
18. Imaura M, Katagiri F, Nagase S, et al. Optimal plasma concentration of thrombomodulin alfa to treat sepsis-induced disseminated intravascular coagulation. *Shock*. 2023; 60: 221-226.
19. Mouksassi MS, Marier JF, Bax L, et al. Population pharmacokinetic analysis of thrombomodulin alfa to support dosing rationale in patients with renal impairment. *Clin Pharmacol Drug Dev*. 2015; 4: 210-217.
20. Mohri M, Sugimoto E, Sata M, et al. The inhibitory effect of recombinant human soluble thrombomodulin on initiation and extension of coagulation--a comparison with other anticoagulants. *Thromb Haemost*. 1999; 82: 1687-1693.
21. 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.
22. Tawara S, Sakai T, Matsuzaki O. Anti-inflammatory and anti-fibrinolytic effects of thrombomodulin alfa through carboxypeptidase B2 in the presence of thrombin. *Thromb Res*. 2016; 147: 72-79.
23. Sakata Y, Curriden S, Lawrence D, et al. Activated protein C stimulates the fibrinolytic activity of cultured endothelial cells and decreases antiactivator activity. *Proc Natl Acad Sci USA*. 1985; 82: 1121-1125.
24. Macias WL, Yan SB, Williams MD, et al. New insights into the protein C pathway: potential implications for the biological activities of drotrecogin alfa (activated). *Crit Care*. 2005; 9 (Suppl 4): S38-S45.
25. Toltl LJ, Beaudin S, Liaw PS. Activated protein C up-regulates IL-10 and inhibits tissue factor in blood monocytes. *J Immunol*. 2008; 181: 2165-2173.
26. Shi CS, Shi GY, Hsiao HM, et al. Lectin-like domain of thrombomodulin binds to its specific ligand Lewis Y antigen and neutralizes lipopolysaccharide-induced inflammatory response. *Blood*. 2008; 112: 3661-3670.
27. 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.
28. Xu J, Zhang X, Pelayo R, et al. Extracellular histones are major mediators of death in sepsis. *Nat Med*. 2009; 15: 1318-1321.
29. Esmon CT, Taylor Jr FB, Snow TR. Inflammation and coagulation: linked processes potentially regulated through a common pathway mediated by protein C. *Thromb Haemost*. 1991; 66: 160-165.
30. Information to overview of application materials of thrombomodulin alfa 2025. https://www.info.pmda.go.jp/go/interview/1/100898_3339401D1027_1_018_1F.pdf [In Japanese]. (accessed August 29, 2025).
31. Mohri M, Sugimoto E, Sata M, et al. The inhibitory effect of recombinant human soluble thrombomodulin

on initiation and extension of coagulation--a comparison with other anticoagulants. *Thromb Haemost*. 1999; 82: 1687-1693.

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