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Benefit Profile of Thrombomodulin Alfa Combined with Antithrombin Concentrate in Patients with Sepsis-Induced Disseminated Intravascular Coagulation

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Abstract

Thrombomodulin alfa (TM-α, recombinant human soluble thrombomodulin) and antithrombin (AT) concentrate are anticoagulant agents for the treatment of disseminated intravascular coagulation (DIC). A post hoc analysis using data from 1198 patients with infection-induced DIC from the post-marketing surveillance of TM-α was conducted. To identify subgroups that benefit from combination therapy, the patients were a priori stratified into four groups by a platelet (Plt) count of $50 \times 10^3/\mu L$ and plasma AT level of 50% (groups 1, 2, 3, and 4, with high Plt/high AT, high Plt/low AT, low Plt/high AT, and low Plt/low AT, respectively). Kaplan-Meier survival analysis showed significantly worse survival in groups 2 and 4 had than in group 1 ($p = 0.0480$, $p < 0.0001$, respectively), and multivariate analysis showed that concomitant AT concentrate was independently correlated with reduced 28-day mortality only in group 4 (hazard ratio 0.6193; 95% confidence interval, 0.3912-0.9805). The adverse drug reactions (ADRs) and bleeding ADRs were not different among the groups. Patients with both severe thrombocytopenia and AT deficiency are candidates for combined anticoagulant therapy with TM-α and AT concentrate.

Keywords

disseminated intravascular coagulation, thrombocytopenia, anticoagulants, antithrombins, thrombomodulin, infections

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Introduction

Infection induces activation of neutrophils that produce thrombosis as a host defense mechanism, which is known as immunothrombosis,[1] but in patients with sepsis, excessive immunothrombosis attacks endothelial cells causing endothelial dysfunction that further activates the coagulation system, resulting in sepsis-induced disseminated intravascular coagulation (DIC).[2]

Thrombomodulin alfa (TM-α, recombinant human soluble thrombomodulin) binds to thrombin, and then the thrombin-TM-α complex activates protein C (PC) to activated PC (APC) that cleaves coagulation factors Va and VIIIa and directly activates thrombin activatable fibrinolytic inhibitor (TAFI), which inhibits complement components C3a and C5a.[3] Antithrombin (AT) binds mainly to thrombin and coagulation factor Xa and eliminates their activity.[4] These factors also have an anti-inflammatory function.[3,4] In view of these mechanisms, both TM-α and AT concentrate have been expected to improve prognosis in patients with sepsis-induced DIC, and further, the possibility that novel modulators of coagulation pathways such as TM-α may have an adjunctive role in treating critically ill patients even with coronavirus disease 2019 (COVID-19) has arisen.[5,6] TM-α and/or AT concentrate are in wide clinical use for treating DIC in Japan, and their combined administration was reported in 20%-40% of cases of

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sepsis-induced DIC.[7–9] Some retrospective analyses from a single center and post-marketing surveillance (PMS) data for AT concentrate showed a beneficial effect of combined therapy versus AT concentrate alone.[10–12] On the other hand, the retrospective analysis from the intensive care unit group showed no further benefits from the combined administration of both agents over those from AT concentrate or TM-α alone.[9] Unfortunately, it has not been possible to narrow down the specific subgroups most likely to benefit from the combination therapy. We thought that the severity of sepsis-induced DIC should be assessed by coagulation factors themselves in view of the pathophysiology and that the increase of coagulation activity and/or the severity of DIC should be evaluated to adjust anticoagulant therapy. Antithrombin deficiency and thrombocytopenia are common in patients with sepsis.[13–22] Some papers have suggested that thrombocytopenia and severe antithrombin deficiency may be associated with the prognosis of septic patients.[16–22] In these papers, the cutoff points for prediction of mortality were approximately 50% for the AT level[16–18] and approximately 50×10^9/L for the platelet count.[19–22] In the present study, patients were a priori stratified into four groups according to a platelet (Plt) count of $50 \times 10^3/\mu L$ and plasma AT level of 50%, and the benefit profile of TM-α and AT concentrate in patients with sepsis-induced DIC was investigated.

Materials and Methods

Study Population

A post hoc analysis of patients with infection-associated DIC in the PMS data for TM-α was conducted. Data were obtained from the original PMS, which was an open-label, multicentre, non-interventional, prospective, observational study of DIC patients who received TM-α from May 2008 to April 2010.[23] The PMS study was not a randomized cohort study and was conducted in accordance with the guidelines for Good Post-Marketing Surveillance Practices as required by the Japanese Ministry of Health, Labour and Welfare. Personal data anonymization was carried out on data collection. Therefore, approval of this surveillance study by ethics committees and institutional review boards and informed consent of the patients were not necessary. All patients who received TM-α were consecutively registered at the start of drug administration by documenting the patient demographics using a central registration system. Patients were followed until day 28 after the last TM-α administration. Patients received TM-α for the treatment of DIC according to the package insert. The standard dose of TM-α was 380 U/kg/day, and the dose of TM-α administered to subjects with renal dysfunction was reduced to 130 U/kg body/day.[23] All patients were treated

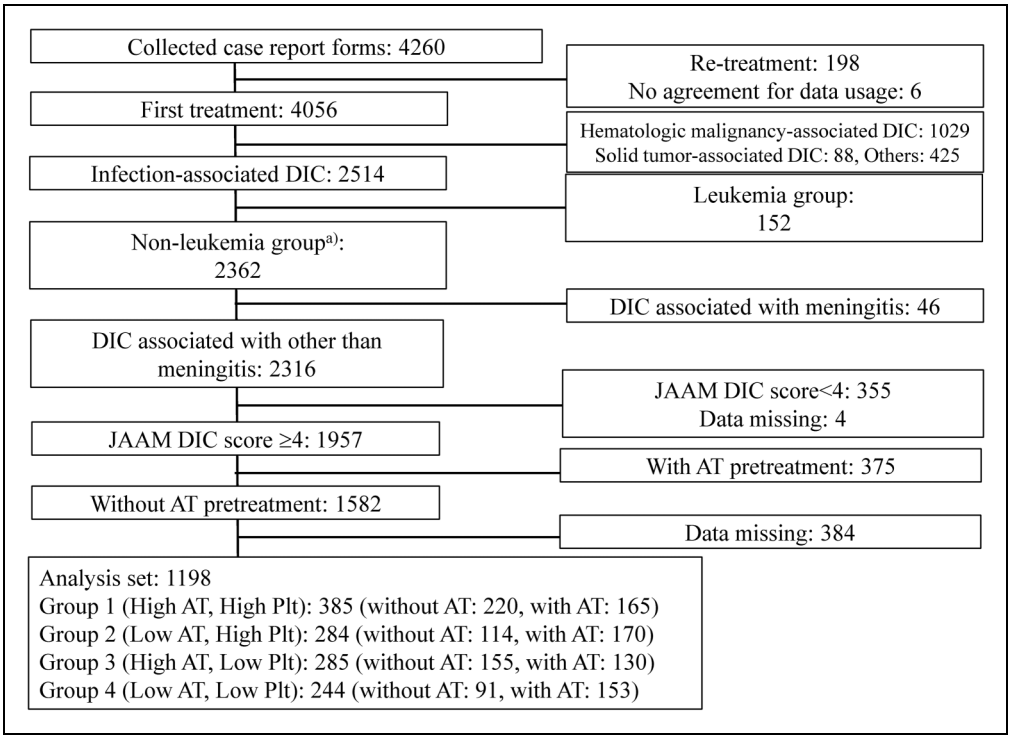

Figure 1. Patient disposition. a, Classification into two groups (leukemia or non-leukemia) according to the Japanese Ministry of Health, Labour and Welfare DIC criteria when the direct cause of DIC is infection. (i) When there were no treatments or complications accompanying a decrease in the platelet count (administration of anticancer agents, hematological malignancy, or aplastic anemia), patients were classified to the non-leukemia group. (ii) When there were treatments or complications accompanying a decrease in platelet count (administration of anticancer agents, hematological malignancy, or aplastic anemia), patients were classified to the two groups (leukemia or non-leukemia) according to predefined procedures in the protocol. The classification was made taking into account the causes of the decrease in platelet count. DIC, disseminated intravascular coagulation; JAAM, Japanese Association for Acute Medicine; Plt, platelet; AT, antithrombin.

Table 1. Patients' Baseline Demographics and Characteristics.

Characteristic	Group 1: High AT, High Plt	Group 2: Low AT, High Plt	Group 3: High AT, Low Plt	Group 4: Low AT, Low Plt	p
No. of patients n	385	284	285	244	
Sex (male/female) n	216/169	159/125	155/130	147/97	0.5794
Age (y) median (IQR)	72.0 (61.0, 80.0)	74.0 (66.0, 81.0)	66.0 (54.0, 76.0)	70.0 (61.0, 78.0)	0.0260[a], 0.0004[b], 0.6291[c]
Sites of infection n (%)					
Respiratory	119 (30.9)	73 (25.7)	62 (21.8)	50 (20.5)	<0.0001
Abdominal	39 (10.1)	74 (26.1)	31 (10.9)	42 (17.2)	
Hepato-biliary/Pancreatic	24 (6.2)	29 (10.2)	21 (7.4)	25 (10.2)	
Urinary/Genital	70 (18.2)	23 (8.1)	34 (11.9)	25 (10.2)	
Soft tissue/Bone	11 (2.9)	22 (7.7)	11 (3.9)	13 (5.3)	
Central nervous system	4 (1.0)	5 (1.8)	2 (0.7)	0 (0.0)	
Cardiovascular	6 (1.6)	2 (0.7)	13 (4.6)	5 (2.0)	
Focus-unknown	106 (27.5)	56 (19.7)	108 (37.9)	82 (33.6)	
Others	6 (1.6)	0 (0.0)	3 (1.1)	2 (0.8)	
Therapeutic intervention n (%)					
Plt concentrate transfusion	49 (12.7)	34 (12.0)	97 (34.0)	94 (38.5)	<0.0001
Flesh frozen plasma transfusion	55 (14.3)	69 (24.3)	62 (21.8)	76 (31.1)	<0.0001
Red blood cell transfusion	83 (21.6)	68 (23.9)	72 (25.3)	79 (32.4)	0.0222
Mechanical ventilation	146 (37.9)	118 (41.5)	95 (33.3)	106 (43.4)	0.0775
CRRT	98 (25.5)	78 (27.5)	81 (28.4)	80 (32.8)	0.0775
PMX-DHP	36 (9.4)	32 (11.3)	36 (12.6)	27 (11.1)	0.5996
Severity score median (IQR), n					
SOFA score	8.0 (6.0, 11.5), 256	10.0 (8.0, 13.0), 176	10.0 (7.0, 13.0), 179	12.0 (10.0, 15.0), 153	<0.0001[a], <0.0001[b], <0.0001[c]
JAAM DIC score	5.0 (4.0, 6.0), 385	6.0 (5.0, 6.0), 284	6.0 (5.0, 7.0), 285	6.0 (5.0, 8.0), 244	0.0646[a], <0.0001[b], <0.0001[c]
ISTH overt-DIC score	4.0 (3.0, 5.0), 385	4.0 (4.0, 5.0), 284	5.0 (4.0, 6.0), 285	6.0 (5.0, 6.0), 244	0.0047[a], <0.0001[b], <0.0001[c]
TM-α treatment					
Dose (U/day) median (IQR)	375.5 (200, 380)	366.3 (136.2, 380)	369.2 (193.9, 380)	365.7 (162, 380)	0.8224[a], 0.9793[b], 0.8173[c]
Period (days) median (IQR)	6 (4, 6)	6 (4, 6)	6 (4, 6)	6 (4, 6)	0.4599[a], 0.1061[b], 0.5146[c]

Categorical variables were compared between groups using the Chi-squared test. Continuous variables were compared between groups using the Mann-Whitney test.
[a]group 2 vs. group 1; [b] group 3 vs. group 1; [c] group 4 vs. group 1.
AT, antithrombin; Plt, platelet; TM-α, thrombomodulin alfa; CRRT, continuous renal replacement therapy; PMX-DHP, direct hemoperfusion with polymyxin B immobilized fiber; SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation; ISTH, International Society of Thrombosis and Haemostasis.

Table 2. Patients' Baseline Laboratory Data by Group.

Biomarker median (IQR), n	Group 1: High AT, High Plt	Group 2: Low AT, High Plt	Group 3: High AT, Low Plt	Group 4: Low AT, Low Plt	p
Plt count, $\times 10^4$ /μL	7.8 (6.3, 11.0), 385	7.3 (6.1, 9.4), 284	3.2 (2.0, 4.1), 285	3.1 (1.9, 3.8), 244	0.0170[a], <0.0001[b], <0.0001[c]
PT-INR	1.34 (1.19, 1.58), 374	1.51 (1.33, 1.82), 281	1.32 (1.14, 1.57), 274	1.50 (1.34, 1.80), 234	<0.0001[a], 0.6111[b], <0.0001[c]
APTT, sec	40.45 (33.4, 53.1), 358	48.9 (40.3, 65.2), 258	44.7 (35.1, 59.8), 265	53.9 (42.5, 72.6), 206	<0.0001[a], 0.0100[b], <0.0001[c]
Fibrinogen, mg/dL	390 (268, 497), 365	303 (216, 464), 257	397.2 (267, 536), 264	273 (171, 415), 223	0.0003[a], 0.7694[b], <0.0001[c]
FDP, μg/mL	38.2 (20.5, 80.0), 328	28.8 (16.0, 50.0), 239	28.0 (13.7, 58.8), 243	26.9 (14.4, 52.6), 206	0.0001[a], 0.0011[b], 0.0001[c]
D-dimer, ng/mL	18.75 (7.64, 37.68), 338	15.21 (4.7, 24.16), 214	12.0 (5.88, 27.95), 240	12.91 (5.67, 24.5), 191	0.0008[a], 0.0032[b], 0.0015[c]
Antithrombin, %	66.0 (57.0, 76.8), 385	39.4 (31.0, 46.0), 284	64.6 (57.0, 78.0), 285	37.0 (30.0, 44.0), 244	<0.0001[a], 0.9998[b], <0.0001[c]
WBC count, $\times 10^4$/μL	1.15 (0.671, 1.69), 385	1.073 (0.53, 1.78), 281	1.068 (0.46, 1.67), 285	1.168 (0.6, 1.72), 242	0.8933[a], 0.1944[b], 0.9799[c]
Serum albumin, g/dL	2.5 (2.1, 3.0), 343	2.4 (2.0, 2.7), 259	2.5 (2.1, 2.9), 244	2.3 (1.9, 2.7), 208	0.0001[a], 0.5417[b], <0.0001[c]
CRP, mg/dL	15.7 (7.73, 22.8), 377	16.9 (9.43, 23.08), 275	16.12 (7.8, 23.37), 270	15.645 (9.35, 23.8), 236	0.5054[a], 0.9328[b], 0.8677[c]

Categorical variables were compared between groups using the Chi-squared test. Continuous variables were compared between groups using the Mann-Whitney test.
[a]group 2 vs. group 1; [b] group 3 vs. group 1; [c] group 4 vs. group 1.
AT, antithrombin; Plt, platelet; TM-α, thrombomodulin alfa; FDP, fibrin and fibrinogen degradation products; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; WBC, white blood cells; CRP, C-reactive protein.

according to the attending physicians' decisions, and no limitations were placed on the concomitant use of other anticoagulants or medicine for the treatment of underlying diseases and complications. AT concentrate was administered to an AT level of less than 70%, which is used clinically in Japan.

Data Collection and Definitions

The following data were collected from PMS data: age, sex, TM-α treatment (dose, period), sites of infection (respiratory, abdominal, urogenital, hepato-biliary-pancreatic, surgical site/soft tissue/bone, central nervous system, cardiovascular, focus unknown and others, therapeutic intervention, Plt count, prothrombin time-international normalized ratio (PT-INR), activated partial thromboplastin time (APTT), fibrinogen, fibrin/fibrinogen degradation products (FDP), D-dimer, AT level, protein C, white blood cell (WBC) count, serum albumin, C-reactive protein (CRP), total bilirubin, thrombin-antithrombin complex (TAT), and plasmin-$\alpha_2$plasmin inhibitor complex (PIC), fibrin monomer, as well as SOFA, systemic inflammatory response syndrome (SIRS), JAAM DIC, and International Society of Thrombosis and Haemostasis (ISTH) overt-DIC scores.

In this study, the patients who had never been treated with TM-α and had DIC associated with infection were included. Patients with hematopoietic malignancy or concomitant treatment with antitumor drugs were excluded. Patients with meningitis were excluded, because the central nervous system SOFA sub-score might not be able to be determined accurately. Patients with DIC were identified as having the Japanese Association for Acute Medicine (JAAM) DIC criteria (DIC score ≥4) before TM-α administration. Patients previously administered AT concentrate before TM-α administration were excluded.

Patients with infection-associated DIC were a priori stratified into four groups according to the Plt count ($<50 \times 10^3$/μL, $\geq 50 \times 10^3$/μL) and AT level (<50%, ≥50%) before TM-α administration: group 1 (high AT and high Plt); group 2 (low AT and high Plt); group 3 (high AT and low Plt); and group 4 (low AT and low Plt). Patients with no recorded AT activity or no recorded Plt count before TM-α administration were excluded.

Outcomes

The outcomes at 28 days after each group started TM-α administration were evaluated. In addition, changes in the following markers and scores from before to after TM-α administration were examined in each group: FDP, D-dimer, Plt count, fibrinogen, PT-INR, APTT, AT, TAT, PC, WBC, CRP, serum albumin, and SIRS, SOFA, JAAM DIC, and ISTH-overt DIC scores. In each group, the outcome 28 days after the start of TM-α administration was evaluated according to the presence or absence of AT concentrate.

Safety data and definitions of adverse drug reactions (ADRs) were described previously.[15] The safety evaluation included bleeding ADRs and all ADRs observed until 28 days after the last TM-α administration.

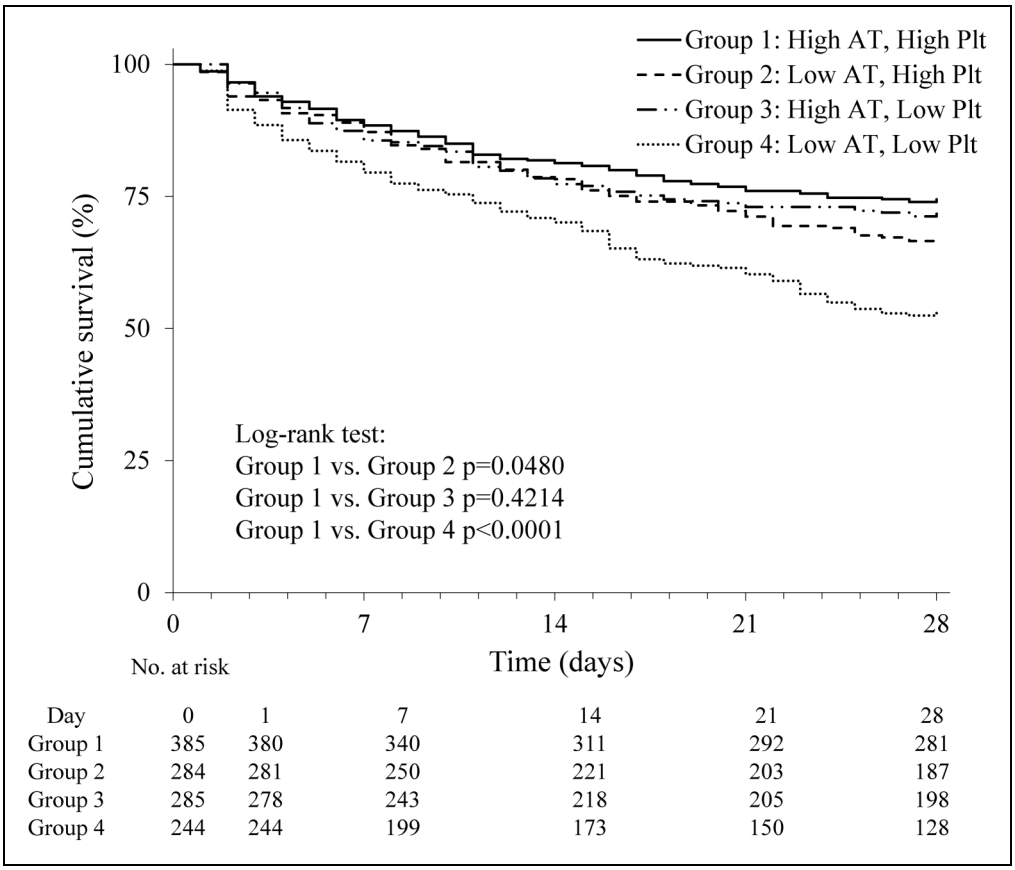

Figure 2. Kaplan-Meier curves of 28-day survival for the combinations of AT with Plt. AT, antithrombin; Plt, platelet count.

Statistical Analysis

In the descriptive analysis of baseline characteristics, numerical data are expressed as means ± standard deviation or medians (Q1-Q3; interquartile range). Statistical analysis was performed to compare values using the chi-squared test and the Wilcoxon signed-rank test. Kaplan-Meier survival curves and the log-rank test were used to compare 28-day outcomes of TM-α administration. In addition, multivariate analysis was performed for mortality-associated covariates using a Cox proportional hazards model to calculate hazard ratios and 95% confidence intervals. The following covariates potentially associated with mortality were examined: sex, age, SOFA score (coagulation and neurological subscores were removed), Charlson comorbidity score, antithrombin level, Plt count, fibrinogen level, PT-INR, and FDP level at baseline, and administration of AT concentrate. Variables missing more than 20% of the values were excluded as candidates, and variance inflation factors (VIFs) were then calculated to quantify the degree of multicollinearity. If multicollinearity between variables was observed (VIF > 10), a variable with a small p value was selected by the backward elimination method. Changes in the severity scores and coagulation markers from baseline to that of the day after the last administration were examined using the Wilcoxon signed-rank test. A value of $p < 0.05$ was considered significant. Multiplicity adjustment was not considered. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) by EPS Corporation (Tokyo, Japan) according to the statistical analysis plan.

Results

Categorization and Patients' Characteristics

A total of 1198 patients with infection-associated DIC were analyzed. The patients were categorized into four groups according to a Plt count of $50 \times 10^3/\mu L$ and plasma AT activity of 50% (Figure 1). The demographic characteristics of the subjects are shown in Table 1. The age of group 1 (median [Q1-Q3]) was significantly younger than that of group 2, but older than that of group 3, but it was not different from that of group 4. Transfusion requirements were significantly different among the four groups, whereas mechanical ventilation, continuous renal replacement therapy, and direct hemoperfusion with polymyxin-immobilized fiber requirements were similar. Regarding severity scores compared to group 1, SOFA and ISTH overt DIC scores were significantly higher in groups 2, 3, and 4, and JAAM DIC scores were higher in groups 3 and 4. The median dose and period of TM-α administration were not different among the groups; therefore, it was possible to evaluate the effect of TM-α among the groups.

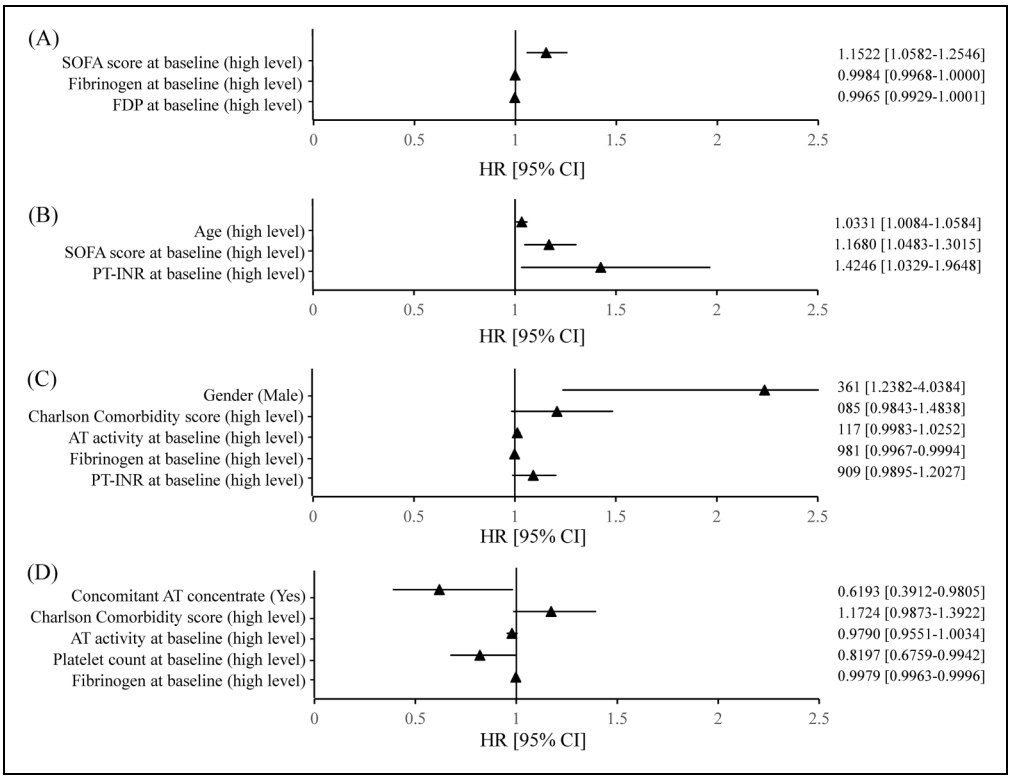

Figure 3. Cox proportional hazards models for the relationships between several explanatory covariates and 28-day mortality. (A), Group 1; (B), Group 2; (C), Group 3; (D), Group 4. Ten independent covariates related to outcome (see Methods section for details) were assessed using a backward elimination covariate selection method in Cox proportional hazards models. HR, hazard ratio; CI, confidence interval; SOFA, sequential organ failure assessment; FDP, fibrin and fibrinogen degradation products; PT-INR, prothrombin time-international normalized ratio.

Table 2 shows the laboratory results for the coagulation and inflammation markers at baseline. Compared with group 1, the serum albumin levels in groups 2 and 4 were significantly lower. The WBC and CRP levels were not significantly different in groups 2, 3, and 4 compared to group 1, but APTT was significantly prolonged in groups 2, 3, and 4 compared to group 1. On the other hand, FDP and D-dimer levels were significantly higher in group 1 than in groups 2, 3, and 4. These data suggest that coagulopathy in groups 2, 3, and 4 seemed to be a typical pathological septic state compared with that in group 1.

Outcome

Figure 2 shows the Kaplan-Meier plots for survival until 28 days after initiation of TM-α administration for each group. The survival time analysis showed significant differences of groups 2 and 4 compared to group 1 ($p = 0.0480$, $p < 0.001$, respectively). The survival time analysis focused on combined administration of TM-α with AT concentrate showed that the patients in group 4 had a significantly lower 28-day cumulative survival rate than those treated with TM-α alone ($p = 0.0310$), but there were no significant differences for the other groups (Supplementary Figure 1). Cox regression analysis showed that concomitant AT concentrate was independently correlated with reduced 28-day mortality (hazard ratio, 0.6193; 95% confidence interval, 0.3912-0.9805) only in group 4 (Figure 3). These findings raise the possibility that combined anticoagulant therapy with TM-α and AT concentrate has a beneficial effect in patients with a Plt count below $50 \times 10^3/\mu L$ and plasma AT activity of 50%.

Changes in JAAM and SOFA scores, Plt counts, and coagulation markers from before to after TM-α administration are shown in Figure 4. All scores and markers were significantly ameliorated after TM-α administration compared with before in each group. WBC counts did not change, except in group 1, whereas CRP levels were significantly decreased in all groups (Supplementary Table 1).

Overall, ADRs were observed in 95 subjects (7.9%), and bleeding ADRs, serious ADRs, and serious bleeding ADRs occurred in 6.3%, 3.3%, and 3.1% of patients, respectively (Supplementary Table 2). The rates of ADRs were not different between the group treated with TM-α alone and the group treated with combined administration of TM-α with AT concentrate (Supplementary Table 3).

Discussion

We previously reported that combined administration of TM-α and AT concentrate was prescribed for 26.6% of patients with sepsis-induced DIC even after administration of TM-α in a PMS analysis of TM-α.[24] In the present study, the patients were categorized into four groups according to a Plt count of 50×

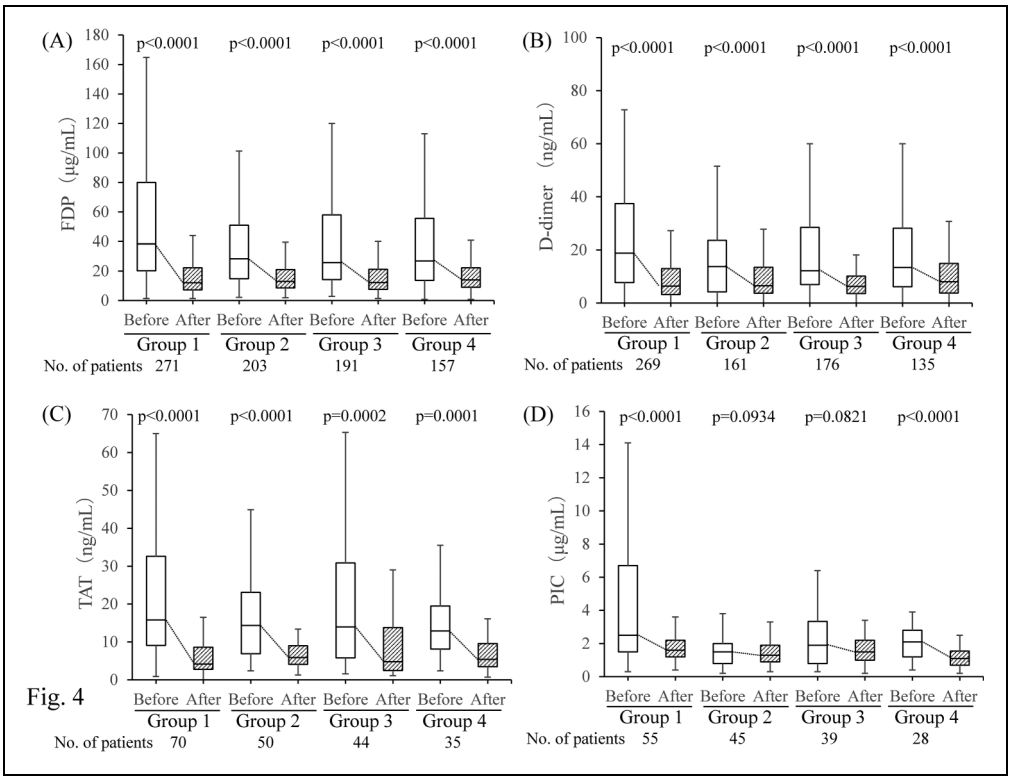

Fig. 4

Figure 4. Changes in coagulation and inflammation markers after TM-α treatment. (A), FDP; (B), D-dimer; (C), TAT; (D), PIC; (E), platelet count; (F), PT-INR; (G), AT; (H), CRP; (I), JAAM DIC score; (J), SOFA score. The box represents the 25th to 75th percentiles (interquartile range, IQR), and the line within the box is the median value. Whiskers indicate minimum and maximum values up to 1.5 times the IQR from the quartiles. Outlying values are not indicated. P values from the Wilcoxon signed-rank test. TM-α, thrombomodulin alfa; FDP, fibrin and fibrinogen degradation products; TAT, thrombin-antithrombin complex; PIC, plasmin α2-plasmin inhibitor complex; PT-INR, prothrombin time-international normalized ratio; AT, antithrombin; CRP, C-reactive protein; JAAM, Japanese Association for Acute Medicine; DIC, disseminated intravascular coagulation; SOFA, sequential organ failure assessment.

10^3/μL and plasma AT activity of 50%, and it was found that TM-α with AT concentrate improves mortality in patients with severe thrombocytopenia and low plasma AT activity.

Activation of coagulation is regulated and inhibited by TM-PC and the AT-thrombin system. On the other hand, AT inhibits thrombin-mediated APC generation by the TM-PC pathway. Whether AT concentrate complements the anticoagulant effects of the TM-α-APC axis or counteracts the TM-α-APC axis through inhibition of thrombin-mediated APC generation remains incompletely understood. Therefore, whether the combination of TM-α and AT concentrate can benefit patients with sepsis-induced DIC and what kind of patient population can benefit from combination therapy remain very important clinical questions.

An *in vitro* APC generation assay using human plasma indicated that APC generation was decreased depending on the degree of increase in AT levels.[25] Recently, *in vitro* experiments using lipopolysaccharide (LPS)-stimulated endothelial cells, reflecting the pathophysiology of sepsis, demonstrated that concomitant use of TM-α and recombinant AT showed additive effects and efficiently suppressed thrombin generation on the surface of LPS-stimulated endothelial cells.[6] Anticoagulant therapy in animal models of LPS-induced sepsis showed that it improved coagulopathy and organ damage and lowered the mortality rate.[26]

Some retrospective analyses assessing the efficacy and safety of AT and TM combination therapy in patients with sepsis-induced DIC have been reported.[9–12]

PMS data for AT concentrate showed a beneficial effect of combined therapy versus AT concentrate alone in sepsis-induced DIC patients with AT activity ≤70%.[12] The retrospective analysis of adult patients with sepsis-induced DIC from a nationwide multicenter registry database by the intensive care unit group showed no further benefits from the combined administration of both agents over those from AT concentrate or TM-α alone.[9]

In a single-center study, combined therapy showed significant improvements that were only observed in severely ill patients, such as those with acute physiology and chronic health evaluation (APACHE) II scores > 25 or AT activity levels < 50%.[10] Another single-center study showed that combination therapy with TM-α following AT concentrate was more effective than AT monotherapy in patients with severe sepsis-induced DIC who had lower baseline Plt counts (4.9×10^4/μL).[11]

In the present study, combined anticoagulant therapy with TM-α followed by AT concentrate improved prognosis in

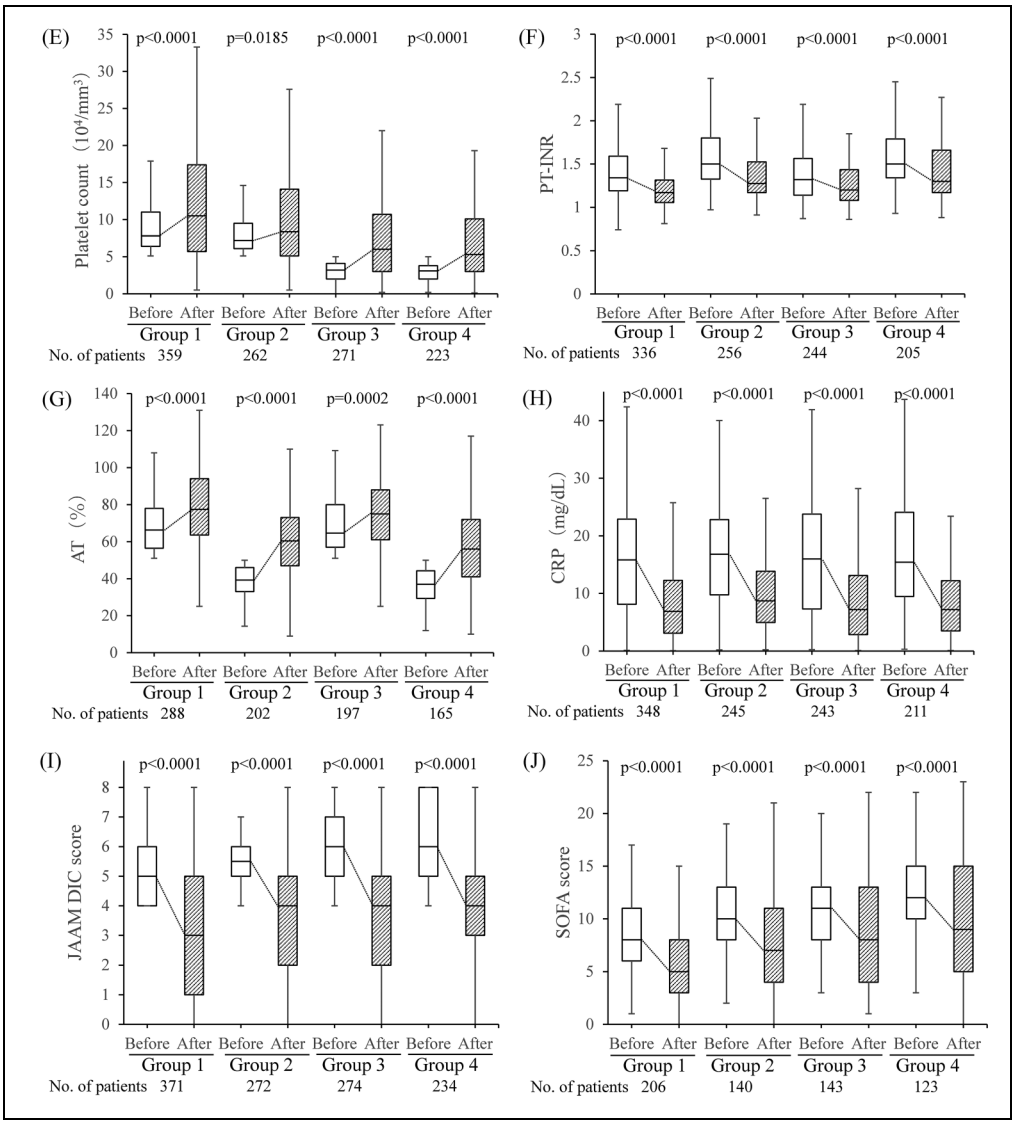

Figure 4. Continued.

patients with both a low Plt count and a low plasma AT level compared with TM-α monotherapy.

Taken together, these reports suggest that combined anticoagulant therapy with TM-α and AT concentrate compared with AT or TM-α monotherapy does not show a beneficial effect in all patients with sepsis-induced DIC, but it does show a beneficial effect in patients with severe sepsis-induced DIC, as an example, based on the presence of thrombocytopenia and plasma AT activity.

Decreased plasma AT levels in patients with DIC were not affected by consumption that depended on coagulation activity and reflected the serum albumin level.[27] Ebina et al. reported that AT supplementation was useful in patients with a serum albumin level less than 2.5 mg/dL.[28] These results, including those of the present study, suggest that combined anticoagulant therapy with TM-α and AT concentrate be prescribed for patients with a serum albumin level less than 2.5 mg/dL, even if plasma AT activity cannot be measured quickly in the clinical setting.

The present study showed that the beneficial effect of AT supplementation was observed only in group 4, where not only the AT level, but also the platelet count was low. Because both TM-α and AT concentrate bind to thrombin, and either TM-α or AT concentrate can be given to control excess thrombin, the beneficial effect of AT supplementation could be observed in group 2, where only the AT level was low. Platelets play an important role in host defense against infection via not only the activation of coagulation, but also the inflammatory response.[1] Pathogen-activated platelets can adhere to the surface of neutrophils to form aggregates and promote the release of neutrophil extracellular traps (NETs) that kill pathogens.[1] Sepsis-induced thrombocytopenia is frequently associated with a dysregulated host response.[19–22,29] In the mouse sepsis model, thrombocytopenia worsened sepsis, leading to increased bacterial growth in the blood and lungs and reducing the survival rate of animals.[30] TM-α inhibits LPS

or histone-induced NET formation *in vitro* and *in vivo*.[31–34] Therefore, TM-α may inhibit progression to abnormally excessive NET formation, maintain platelet counts, and have benefit for septic DIC patients whose platelet counts are low. However, it should also be noted that patients with very severe thrombocytopenia may not fully benefit from TM-α treatment, because the formation of NETs mediated by platelets is low grade.

In septic phenomena, coagulation activation is closely related to inflammation and the complement system, especially in severe thrombocytopenia that is pathophysiologically likely to result in infection-induced secondary thrombotic microangiopathy.[35] In the present study, TM-α significantly lowered CRP and all coagulation markers except fibrinogen. Both TM and AT themselves independently regulate the inflammation system,[3,4] and more, TM inhibits the complement activation components, such as C3a and C5a, regulated by TM-induced TAFI activation.[3] These mechanisms could explain that combined anticoagulant therapy with TM-α and AT concentrate greatly improved inflammation and complement activity, resulting in recovery of severe coagulopathy and multiple organ failure even in patients with serious sepsis-induced DIC with severe thrombocytopenia, and would support the hypothesis for its use in integrated therapy for COVID-19.[36]

There were several limitations in the present PMS post hoc analysis. First, this PMS study was not a randomized cohort study and, therefore, suffered from potential selection and ascertainment biases. Second, this PMS study was performed under daily clinical practice conditions, with restrictions on neither the treatment of underlying diseases nor the usage of other anticoagulants. Finally, the effect and safety of AT concentrate alone or TM-α following AT concentrate cannot be evaluated, because there were no data for AT concentrate alone or TM-α following AT concentrate in this PMS study.

Conclusion

In the patients with sepsis-induced DIC, organ failure and coagulopathy are serious in those with either severe thrombocytopenia or low plasma AT activity. Anticoagulant therapy including TM-α may improve the severity of organ failure and coagulopathy, and combined anticoagulant therapy of TM-α with AT concentrate make an impact on good prognosis restrictedly in patients with both severe thrombocytopenia and low plasma AT activity. Further study is needed.

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Authorship Contribution Statement

Murao A and Kato T planned the study design, interpreted data, drafted the figures and tables, and wrote the manuscript. Honda G planned the study design, analyzed data, drafted the figures and tables, and revised the paper. Eguchi Y oversaw the study and revised the manuscript. Yamane T provided advice on the study design, interpreted data, and revised the manuscript.

Disclosure of Conflicts of Interest

Honda G is an employee of Asahi Kasei Pharma Corporation. Murao A, Kato T, Yamane T, and Eguchi Y received no grants or personal fees. Asahi Kasei Pharma Corporation covered the expenses for the analysis and the English editing of the manuscript.

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Ethical Approval

Our institution does not require ethical approval for reporting individual cases or case series from existing information that has been anonymised prior to its use in the study.

Informed Consent

Informed consent for patient information to be published in this article was not obtained because personal data anonymization was carried out on data collection.

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Supplemental material

Supplemental material for this article is available online.

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