

# Comparison of Protective Effects of Recombinant Antithrombin Gamma and Plasma-Derived Antithrombin on Sepsis-Induced Disseminated Intravascular Coagulation and Multiple Organ Failure

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## Abstract

In Japan, the dose of the new recombinant antithrombin III concentrate (rAT-gamma) is titrated according to patient body weight (BW), while conventional plasma-derived antithrombin concentrates (AT) are administered as a fixed dose. Therefore, it is anticipated that rAT-gamma could produce better treatment effects than AT. The aim of this study was to compare the organ protective effects of doses of rAT-gamma and AT administered in clinical practice for septic disseminated intravascular coagulation (DIC) and multiple organ failure. This study was performed at a single university hospital in Japan. A total of 49 patients with antithrombin deficiency secondary to septic DIC who were administered either rAT-gamma (n = 26) or AT (n = 23) were retrospectively analyzed to assess the dose of supplemental antithrombin concentrates, plasma antithrombin activity, Japanese Association for Acute Medicine (JAAM)-DIC score, and modified Sequential Organ Failure Assessment (SOFA) score on days 0, 3 and 6. The AT-equivalent dose per kg BW of rAT-gamma (equal to the initial rAT-gamma dose per kg BW divided by 1.2) was significantly higher than the dose per kg BW of AT (AT  $23.4 \pm 5.1$  vs. rAT  $28.9 \pm 3.9$  IU/kg/day;  $P < 0.001$ ). Consequently, serial increases in plasma antithrombin levels occurred more rapidly in the rAT-gamma group ( $P = 0.036$ ). JAAM DIC and modified SOFA scores revealed significantly greater improvement in the rAT versus the AT group (JAAM DIC score:  $P = 0.042$ , mSOFA score:  $P = 0.005$ ). The results of this study suggest that AT supplementation adjusted for patient BW might further improve septic DIC and multiple organ failure.

## Keywords

antithrombin III, sepsis, disseminated intravascular coagulation, recombinant antithrombin gamma, sequential organ failure assessment score

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## Introduction

Sepsis is a disproportionate systemic immune response to infection. The exaggerated inflammation causes coagulopathy, followed by multiple organ failure.<sup>1-3</sup> Both inflammation and coagulopathy are capable of synergistically aggravating each other.<sup>4</sup> Thrombin, which is a sepsis-derived proinflammatory mediator, is a vital trigger in the amplification of intravascular coagulation. Along with activation of the natural anticoagulation pathway, the damaged coagulation system also somehow retains its function.<sup>5</sup> Antithrombin (AT) plays a major anticoagulant role in inhibiting thrombin and the related coagulation factors; it has also been shown to exert anti-inflammatory effects during sepsis.<sup>6,7</sup> In addition, AT decreases the release

of inflammatory cytokines through inhibition of factor Xa and factor VIIa. It might also reduce endothelial vascular damage.<sup>6,7</sup> Furthermore, it is known that AT promotes vascular endothelial cell release of prostacyclin, which hinders activation and aggregation of platelets.<sup>6,7</sup> AT also inhibits

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inflammatory leukocyte adherence to endothelial cells and decreases microvascular permeability.<sup>6,7</sup> These various properties might help to improve the coagulopathy and organ dysfunction. On the other hand, the exaggerated inflammatory reactions of sepsis produce thrombin-antithrombin complexes.<sup>6,7</sup> Sepsis also promotes endothelial antithrombin leakage, as well as leakage of albumin from the intravascular to the interstitial space.<sup>8,9</sup> These 2 mechanisms lead to a decrease in plasma AT levels in sepsis. Therefore, it is supposed that AT supplementation will neutralize excessive thrombin and decrease microvascular leakage. However, the appropriate dose of AT products that should be administered to treat sepsis-associated AT deficiency remains unclear.

In Japan, AT products are administered for congenital or acquired AT deficiency. Generally, Japanese health insurance covers a dose of 1,500 units of plasma-derived AT (AT) products per day, with no consideration for patient body weight, for up to 3 consecutive days. However, Iba et al. reported the superiority of administration of 3,000 units of AT compared with the conventional dose of 1,500 units for the AT deficiency of septic disseminated intravascular coagulation (DIC).<sup>10,11</sup> This suggests that the conventional dose exhibits insufficient efficacy. Recently, a new recombinant AT product, antithrombin gamma (ACOALAN<sup>®</sup>; Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan) (rAT-gamma) was approved in Japan. Noticeably, rAT-gamma lacks core fucose, which could weaken its affinity for anticoagulants,<sup>12,13</sup> providing biological similarity with AT. A study in healthy male volunteers has shown that the pharmacokinetics of rAT-gamma are very similar to those of AT.<sup>14</sup> The most remarkable clinical difference lies in the dose administered according to the health insurance standards in Japan; the dose of rAT-gamma depends on patient body weight (given at a dose of 36 IU/kg body weight), which is equivalent to 30 IU/kg of AT (data on file, Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan). On the other hand, AT is usually administered as a fixed dose of 1,500 IU/day irrespective of body weight, resulting in an insufficient dose in heavier patients. Thus, we focused our attention on the effects of the difference in the dose of rAT-gamma and AT administered. We hypothesized that rAT-gamma supplementation would achieve a more desirable effect than AT administration. Therefore, the aim of this study was to compare the efficacy of rAT-gamma versus that of AT on organ failure and DIC in patients with septic DIC.

## Materials and Methods

### Ethics Statement

This study was approved by the Institutional Review Board of Sapporo Medical University Hospital (302-135), which waived the requirement for informed patient consent because of the anonymous nature of the data.

### Patient Enrollment

This study was a single-center, retrospective observational study that was performed at a medical and surgical ICU of

Sapporo Medical University Hospital in Japan. Inclusion criteria were as follows: patients 18 years of age and older to whom AT products were administered for antithrombin insufficiency due to sepsis-induced DIC between January 2015 and October 2018. Sepsis was diagnosed based on the Sepsis-3 definition, as organ dysfunction due to infection, with an increase in the Sequential Organ Failure Assessment (SOFA) score by 2 points or more.<sup>15</sup>

Patients who met the following criteria were excluded from the study: 1) AT products administered before intensive care unit (ICU) admission, 2) AT products administered as an alternate-day regimen, 3) concomitant implementation of a venovenous or venoarterial extracorporeal life support system, and 4) death within 6 days after initiation of AT administration.

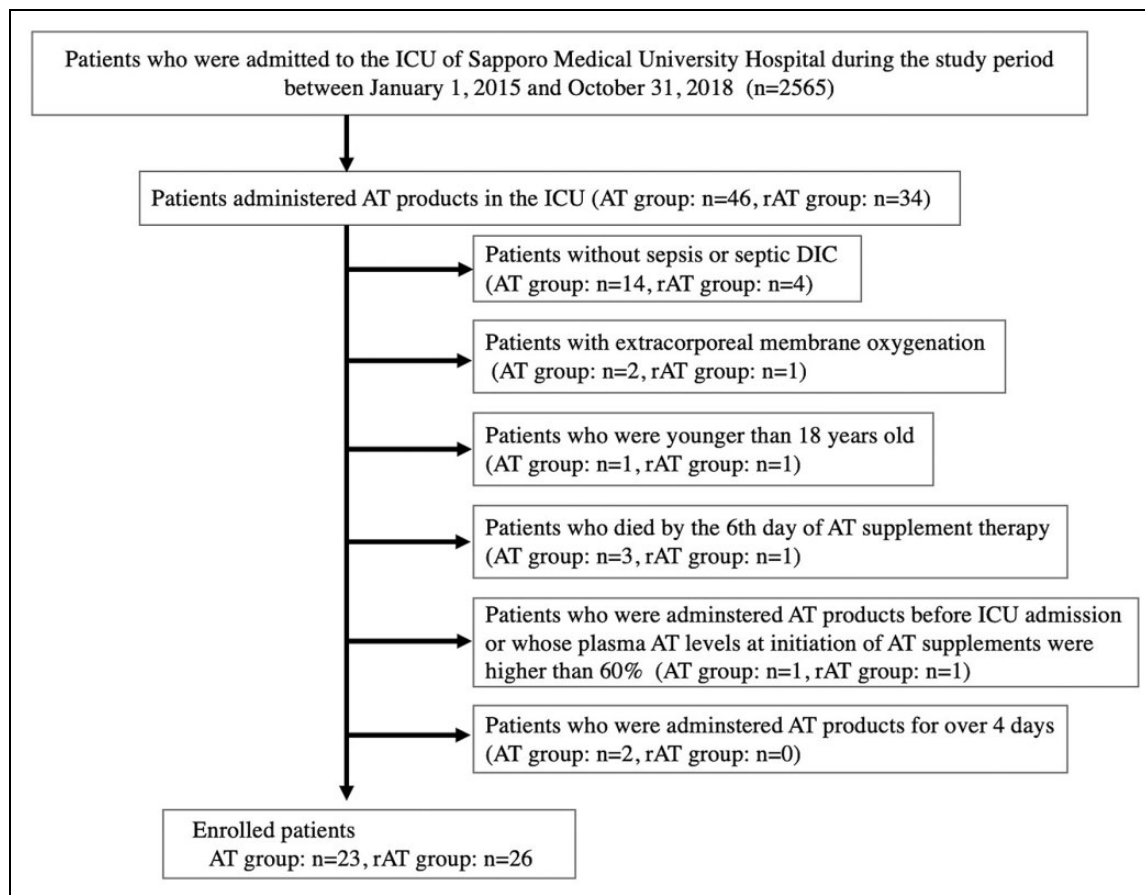
All patients were divided into 2 groups based on the type of AT they received: the rAT group and the AT group. The rAT group was administered rAT-gamma (ACOALAN<sup>®</sup>, Kyowa Hakko Kirin, Tokyo, Japan) and the AT group was administered human plasma-derived antithrombin freeze-dried concentrates (Neuart<sup>®</sup> I.V.; Japan Blood Products Organization, Tokyo, Japan).

### Treatment of DIC

Although our standard criterion for AT administration in septic DIC is plasma AT activity of approximately 50% or less, AT administration was started after careful consideration of the number of organs that had failed and the Japanese Association for Acute Medicine formulated DIC score (JAAM-DIC score),<sup>16</sup> and the administration was continued for almost 3 days. In some cases, AT administration was discontinued in less than 3 days if plasma AT activity increased to more than 100%. Selection of the AT product used was at the discretion of the ICU physician. Concurrent administration of recombinant human soluble thrombomodulin-alpha (rTM) (Recomodulin<sup>®</sup>, Asahi Kasei Pharma, Tokyo, Japan) was initiated in consideration of a daily decrease in platelet counts and the risk of bleeding. At our institution, concomitant heparin administration is avoided in principle. However, in exceptional circumstances, patients with certain comorbidities, such as chronic atrial fibrillation, were given heparin as required. In addition, the fundamental management of sepsis was performed according to Surviving Sepsis Campaign guidelines.<sup>17,18</sup>

### Data Collection

The following data were obtained from the patients' electronic medical records: age, sex, body weight, primary disease that was the reason for ICU admission, comorbidities, infection sources, concomitant rTM administration, methods of organ support used, ICU outcome, and 28-day outcome. Acute physiology and chronic health evaluation II (APACHE II) score and SOFA score at the time of ICU admission were calculated. In addition, plasma ATIII levels were assessed on Days 0-4 and 6. Simultaneously, prothrombin time ratio, concentration of fibrin/fibrinogen degradation products (FDP) and items of the



**Figure 1.** Patient enrollment in this study. AT: antithrombin, AT group: plasma-derived antithrombin group, rAT group: recombinant antithrombin gamma group, DIC: disseminated intravascular coagulation.

diagnostic criteria of systemic inflammatory response syndrome were assessed, records of platelet counts on Days 0, 3 and 6 were obtained, JAAM-DIC score and modified SOFA (mSOFA) score were calculated, and the number of organ supports used, as mentioned above, was evaluated on Days 0, 3 and 6 (Day 0 was defined as the day of commencement of AT administration). The mSOFA score was calculated as the sum of the score for all organs except central nervous system score, because of the various levels of sedation in individual patients depending on the treatment they were receiving. Furthermore, an additional one point for coagulation was added to the SOFA score when platelet concentrates were transfused on the day before commencement of AT administration.

### Efficacy Evaluation

The following variables were compared between the 2 groups: the temporal changes in mSOFA score, JAAM-DIC score, and DIC recovery on Day 3 and Day 6. DIC recovery was defined based on a JAAM-DIC score of <4. Additionally, maximum plasma AT levels and cumulative plasma AT levels from Day 0 to Day 4 were compared. Cumulative plasma AT level was calculated using the area under the daily plasma AT level curve to reduce underestimation due to missing values. Clinical

outcomes included 28-day ICU-free days to compare the duration of ICU stay, ICU survival and 28-day survival.

### Statistical Analysis

Data were presented as the mean  $\pm$  standard deviation if they were normally distributed, and as the median  $\pm$  quartile if they did not have a normal Gaussian distribution. We used the Student's t-test and Mann-Whitney U test for comparison of continuous variables, Fisher's exact test for categorical variables, and 2-way repeated-measures analysis of variance to evaluate within-group effects of longitudinal data. A p-value of less than 0.05 was considered statistically significant. We used IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) for statistical analyses.

### Results

A flow chart of patient enrollment in this study is shown in Figure 1. Although 80 patients received AT products in the ICU during the study period, 31 patients were excluded according to the exclusion criteria. Finally, 49 patients were analyzed in the study, including 23 patients in the AT group and 26 patients in the rAT group. The main reason for exclusion was either a non-

**Table 1.** Baseline Characteristics of the Enrolled Patients.

		AT group n = 23	rAT group n = 26	P value
Age*	years	61.6 ± 18.6	66.1 ± 10.2	0.307
Sex, male	n (%)	17 (73.9)	15 (57.7)	0.367
Body weight*	kg	65.1 ± 9.2	67.2 ± 16.1	0.573
Plasma AT level on day 0#*	%	38.7 ± 8.2	42.0 ± 6.4	0.116
APACHE II score at ICU admission*		24.7 ± 6.4	24.3 ± 5.9	0.791
SOFA score at ICU admission*		9.1 ± 3.1	9.6 ± 4.3	0.627
Infection source				0.261
Lung/Chest	n (%)	1 (4.3)	6 (23.0)	
Abdomen	n (%)	13 (56.5)	9 (34.6)	
Urinary tract	n (%)	4 (17.4)	7 (26.9)	
Soft tissue	n (%)	1 (4.3)	2 (7.7)	
Central nervous system	n (%)	1 (4.3)	0 (0.0)	
Unknown	n (%)	3 (13.0)	2 (7.7)	
Positive blood culture	n (%)	8 (34.8)	11 (42.3)	0.770
Comorbidity				0.614
Congestive heart failure	n (%)	1 (4.3)	1 (3.8)	
Severe diabetes mellitus	n (%)	4 (17.4)	3 (11.5)	
Neurological disorder	n (%)	1 (4.3)	0 (0.0)	
Chronic kidney disease	n (%)	1 (4.3)	1 (3.8)	
Hematologic tumor	n (%)	3 (13.0)	3 (11.5)	
Metastatic tumor	n (%)	4 (17.4)	1 (3.8)	
Immunosuppression	n (%)	6 (26.0)	10 (38.5)	
None	n (%)	3 (13.0)	7 (26.9)	
Concomitant treatment				
rTM supplement	n (%)	15 (65.2)	14 (53.8)	0.562
Heparin	n (%)	4 (17.4)	3 (11.5)	0.692
IVIG	n (%)	5 (21.7)	9 (34.6)	0.360
RRT	n (%)	16 (69.6)	18 (69.2)	1.000
PMX-DHP	n (%)	7 (30.4)	6 (23.1)	0.747

# Day 0 was defined as the day of commencement of antithrombin (AT) administration.

APACHE: acute physiology and chronic health evaluation, SOFA: sequential organ failure assessment, rTM: recombinant thrombomodulin, IVIG: intravenous immunoglobulin, RRT: renal replacement therapy, PMX-DHP: direct hemoperfusion using polymyxin-B immobilized fiber columns.

\*: Mean ± SD.

**Table 2.** Bleeding Complications and Clinical Outcomes.

		AT group, n = 23	rAT group, n = 26	P value
Bleeding complications during days 0-6	n (%)	4 (17.4)	4 (15.4)	1.000
Digestive tract	n (%)	2 (50.0)	2 (50.0)	
Wound	n (%)	2 (50.0)	2 (50.0)	
28-day ventilator-free days*	days	17.8 ± 9.6	18.8 ± 9.1	0.714
28-day ICU-free days*	days	12.3 ± 8.3	15.0 ± 8.8	0.285
ICU survival	n (%)	19 (82.6)	25 (96.2)	0.173
28-day survival	n (%)	18 (78.3)	24 (92.3)	0.230

\*: Mean ± SD.

septic etiology or non-DIC cases, most of which had postoperative antithrombin deficiency secondary to extended hepatectomy.

### Patient Baseline Characteristics and Clinical Outcomes

The characteristics of the patients enrolled in this study are summarized in Table 1. There were no significant differences in age, sex, body weight, severity score at ICU admission,

comorbidities and concomitant treatment between the 2 groups. In particular, concomitant heparin administration was given to a small number of patients in each group (AT: 4 patients vs. rAT: 3 patients;  $P = 0.692$ ). Although plasma AT level on day 0 in the AT group was lower than that in the rAT group, the difference was not significant (AT  $38.7\% \pm 8.2\%$  vs. rAT  $42.0\% \pm 6.4\%$ ;  $P = 0.116$ ). The source of infection in the AT group consisted of a larger number of abdominal infections (AT 56.5% vs. rAT 34.6%), while more infections in the rAT

**Table 3.** Antithrombin Dose and Derived Variables.

		AT group (n = 23)	rAT group (n = 26)	P value
AT dose*	IU/day	1,500[1,500–1,500]	2,400[1,800–2,400]	< 0.001
AT administration days*	days	3[2-3]	3[2-3]	0.990
AT dose / BW**	IU/kg/day	23.4 ± 5.1	34.7 ± 4.7	< 0.001
pAT equivalent AT dose / BW**	IU/kg/day	23.4 ± 5.1	28.9 ± 3.9	< 0.001
Maximum plasma AT levels during days 0-4**	%	82.0 ± 16.2	94.7 ± 20.8	0.022
AUC of plasma AT levels during days 0-4**	%	258.8 ± 48.5	302.9 ± 49.2	0.003

AT: antithrombin, BW: body weight, AUC: area under the curve.

\*: Median [IQR], \*\*: Mean ± SD.

group were from the lung/chest (AT 4.3% vs. rAT 23.0%) or urinary tract (AT 17.4% vs. rAT 26.9%).

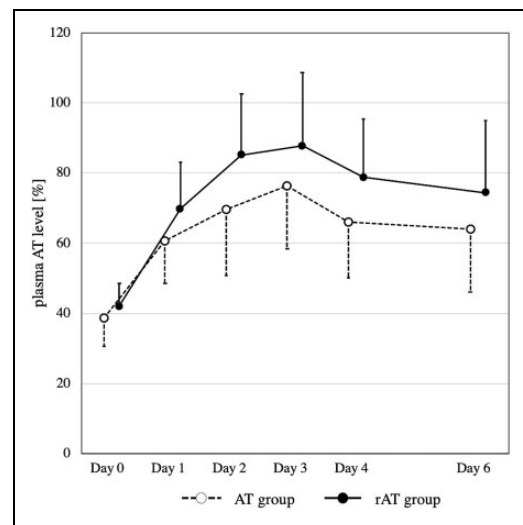
Table 2 shows the outcomes of treatment. The 28-day ICU-free days in the rAT group was statistically comparable to that in the AT group (AT  $12.3 \pm 8.3$  days vs. rAT  $15.0 \pm 8.8$  days;  $P = 0.285$ ). Further, there were no statistically significant differences in ICU and 28-day survival rates between the AT and rAT groups. Bleeding complications were similarly observed in both groups (AT: 4 patients vs. rAT: 4 patients;  $P = 1.000$ ).

### Administration Dose of AT and Time Course of Plasma AT Level

A summary of the data related to AT administration is shown in Table 3. The number of days for which AT was administered was similar in both groups (AT: 3 days [IQR 2-3] vs. rAT: 3 days [IQR 2-3];  $P = 0.990$ ). However, daily AT dose per kg body weight in the rAT group was significantly higher than that in the AT group (AT:  $23.4 \pm 5.1$  IU/kg/day vs. rAT:  $34.7 \pm 4.7$  IU/kg/day;  $P < 0.001$ ). Although the rAT dose is equivalent to 1.2-fold the AT dose, the daily rAT dose divided by 1.2 was also significantly higher than the AT dose (AT:  $23.4 \pm 5.1$  IU/kg/day vs. rAT:  $28.9 \pm 3.9$  IU/kg/day;  $P < 0.001$ ).

The time course of plasma AT levels in both groups showed similar trends, demonstrating peaking of plasma AT levels on day 3, followed by their gradual decline (Figure 2). However, the increase in plasma AT level was more remarkable in the rAT group compared with that in the AT group ( $P = 0.036$ ). Maximum plasma AT level in the rAT group was significantly higher than that in the AT group (AT:  $82.0\% \pm 16.2\%$  vs. rAT:  $94.7\% \pm 20.8\%$ ;  $P = 0.022$ ), and cumulative plasma AT level, represented as the area under the curve in Table 3, in the rAT group was significantly higher than that in the AT group (AT:  $258.8\% \pm 48.5\%$  vs. rAT:  $302.9\% \pm 49.2\%$ ;  $P = 0.003$ ).

Regarding the total cost of AT therapy for 3 days, the rAT group paid almost twice as much for the AT product as the AT group (cost of 1500 IU/day AT for 3 days: €1407 vs. cost of 2400 IU/day rAT for 3 days: €2812). If it is administered at an appropriate dose per body weight such as AT 30 IU/kg/day or rAT 36 IU/kg/day, the per day drug cost for rAT-gamma increased by €162 for every 10 kg of patient body weight, while that of AT increased by €112.



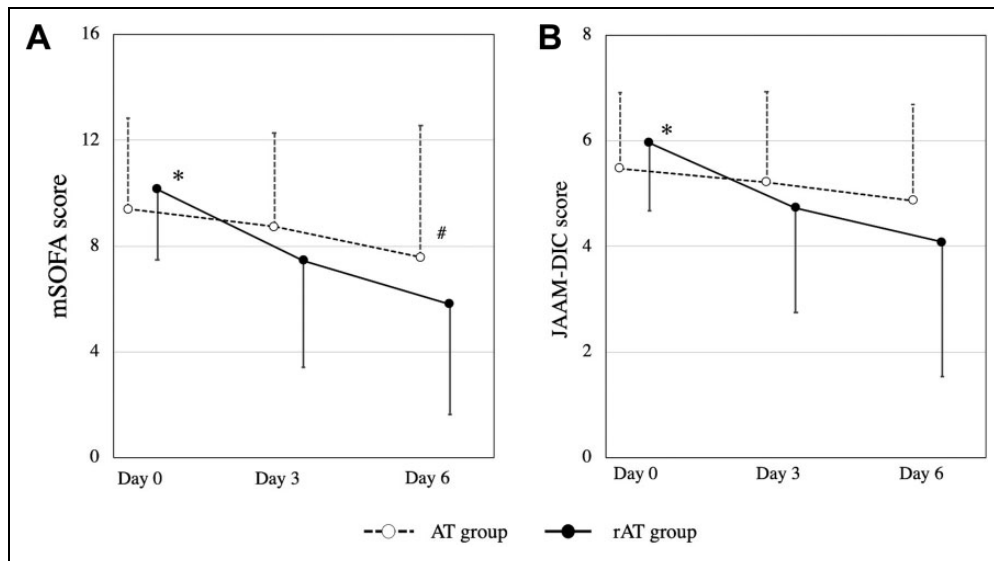
**Figure 2.** Changes in plasma antithrombin levels during the observation period. Baseline plasma AT levels were approximately 40% in the 2 groups. However, the increment with supplementation in the rAT group was significantly larger than that in the AT group ( $P = 0.036$ ), as was the maximum plasma AT level and the area under the curve of plasma AT level from day 0 to day 4 ( $P = 0.022$ ,  $P = 0.003$ , respectively). AT: antithrombin, AT group: plasma-derived antithrombin group, rAT group: recombinant antithrombin gamma group.

### Effects of AT and rAT on Improvement in Organ Failure in Patients With Septic DIC

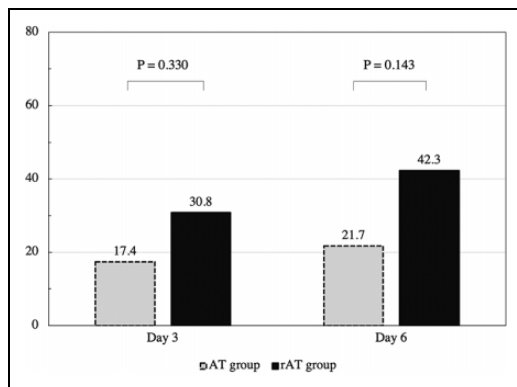
Changes in mSOFA score and JAAM-DIC score following AT treatment in the 2 groups are shown in Figure 3. The degree of improvement in mSOFA scores between the 2 groups was significantly different ( $P = 0.005$ ). The decrease in JAAM-DIC score in the rAT group was significantly greater than that in the AT group ( $P = 0.042$ ). However, DIC recovery rates on day 3 and day 6 were not statistically significantly different between the 2 groups (day 3:  $P = 0.33$ , day 6:  $P = 0.143$ ) (Figure 4).

## Discussion

This retrospective study compared the dose and efficacy of rAT-gamma and AT products administered at doses guided by insurance standards and clinical guidelines in Japan, in



**Figure 3.** Changes in mSOFA score (A) and JAAM-DIC score (B). The baseline values of both scores were similar between the AT and rAT groups. However, the rAT group achieved significantly larger decrements in both mSOFA and JAAM-DIC scores than the AT group ( $P = 0.005$  and  $P = 0.042$ , respectively). \* $P < 0.01$  versus each score in the rAT group on days 3 and 6. # $P < 0.05$  versus the mSOFA score in the AT group on day 0. mSOFA: modified sequential organ failure assessment, JAAM-DIC: Japanese Association for Acute Medicine-disseminated intravascular coagulation, AT group: plasma-derived antithrombin group, rAT group: recombinant antithrombin gamma group.



**Figure 4.** DIC recovery rate. Although the difference between the 2 groups was not statistically significant, the recovery rate in the rAT group was almost twice that in the AT group on each day. The results are presented as the DIC recovery rate. AT group: plasma-derived antithrombin group, rAT group: recombinant antithrombin gamma group.

septic DIC patients with low AT levels. When the doses were compared after correcting for the difference in dose per kg body weight between the two, the doses in the rAT group were higher. As a result, the plasma AT value was also higher in the rAT group. In addition, our results showed that the rAT group achieved greater improvement in mSOFA and JAAM-DIC scores, although it failed to show a significantly greater increase in DIC recovery rate as compared to the AT group.

To date, only a few clinical studies have compared the clinical efficacy between rAT-gamma and AT. It was previously shown that 36 IU/kg/day of rAT-gamma administration has similar potency and safety in septic DIC as compared to 30 IU/kg/day of AT administration for 5 consecutive days.<sup>19</sup>

However, in Japan, patients with acquired AT deficiency are usually administered 1500 IU/day of AT for 3 days regardless of their weight, since this is the generally accepted maximum amount that is covered by Japanese public health insurance. This practical quantity and duration of AT therapy has also been reported in some retrospective studies.<sup>10,20,21</sup> Since the mean body weight of patients enrolled in the current study was approximately 66 kg, the conventional 1500 IU dose of AT dose did not reach the dose of 30 IU/kg of AT in most patients. Conversely, the dose of rAT-gamma is adjusted according to patient body weight, with the authorized dose being in the range of 36–72 IU/kg. Therefore, our results suggest that adequate AT supplementation by either preparation might result in significant therapeutic effects on septic multiple organ failure.

Our results also suggest that a generous amount of AT supplementation might provide a faster improvement in organ failure. The results of the present study are compatible with Iba et al.'s report, which showed that double dose AT supplementation (AT 3000 IU/day for 3 days) more effectively alleviated coagulation abnormalities in septic DIC patients in comparison with regular doses of AT supplementation (AT 1500 IU/day for 3 days).<sup>10,11</sup> However, with regard to mortality and DIC recovery, our results are not in line with Iba et al.'s results. Several factors could account for this discrepancy. Our study included a very small number of patients, making it difficult to identify significant differences. Also, there is a large dose difference between the 2 studies: the difference between the AT dose and the AT-equivalent rAT-gamma dose was 5 IU/kg/day (AT 23.4 IU/kg/day vs. AT-equivalent rAT-gamma 28.9 IU/kg/day) in our study, indicating an approximately 23% increase in the rAT group compared with the AT group, while the dose difference between the 2 study groups in Iba et al.'s study was almost

100%. In addition, the JAAM-DIC scoring system is established for the early detection of DIC, and the score is not significantly affected by a transition from platelet decrement to increment. Hence, detection of DIC recovery might be delayed by applying the JAAM-DIC score.

Meanwhile, there is a negative opinion regarding the ability of high-dose AT therapy in ameliorating septic shock. The KyberSept trial study group demonstrated that high-dose AT therapy (AT 6000 IU loading, followed by 6000 IU/day for 4 days) failed to reduce 28-day mortality in severe sepsis.<sup>22</sup> However, their study population consisted of both DIC and non-DIC patients. Later, Kienast et al. revealed that high-dose AT therapy could have favorable effects in septic DIC patients without concomitant heparin in a stratified-analysis of KyberSept trial data.<sup>23</sup> Although we cannot comment on the effect of heparin based on our study results since the number of patients with concomitant heparin therapy was very small in both groups, it is unlikely that concurrent heparin administration affected our results. However, our study corroborates the results of the previous studies showing that clinically adequate supplemental doses of AT are required for beneficial effects in septic DIC patients.

rAT-gamma seems to be a feasible option in the management of septic DIC cases since it is not associated with the risk of infections inherent to donated blood and there is a stable supply of the product. Plasma-derived AT products are manufactured following multiple inspections of donor blood for infections. However, the risk of infection cannot be completely avoided, as mentioned by Endo et al.<sup>19</sup> Further, an effect of the aging of society might be reduction in the population who are able to donate blood, resulting in a shortage of plasma-derived products. On the other hand, the cost of rAT is currently higher than that of AT. Even if the doses of both AT products are determined based on patient body weight, it is estimated that the drug cost of rAT-gamma increases by €50 per day for every 10 kg of body weight in comparison with AT. Hence, at present, the cost difference is significant. However, rAT could have sufficient benefits as an alternative to AT from the viewpoint of the above-mentioned AT weaknesses, i.e. the infection risk and availability of enough plasma.

Currently, another recombinant AT product, AT alpha (ATryn<sup>®</sup>, GTC Biotherapeutics, Framingham, MA, USA) is also commercially available in the European Union and USA for prevention of venous thromboembolism in patients with hereditary AT deficiency, although the pharmacokinetics and pharmacodynamics of the 2 recombinant AT products, AT alpha and rAT-gamma, are comparatively distinct. In particular, the half-life of AT alpha is excessively short compared with that of AT,<sup>24</sup> making its continuous intravenous injection essential. In contrast, the half-life of rAT-gamma is similar or longer than that of AT (rAT-gamma  $81.8 \pm 50.1$  hours vs. AT  $58.0 \pm 18.5$  hours) (data on file, Kyowa Hakko Kirin Co., Ltd., Tokyo Japan).<sup>20</sup> The differences are attributed to the glycosylation profile of the 2 products. In terms of the glycosylation profile, nonfucosylation plays an important role in heparin-binding activity,<sup>12,13,25</sup> rAT-gamma and AT contain

almost no fucose,<sup>26,27</sup> and AT alpha contains a significant amount. This nonfucosylation could be responsible for the difference in anticoagulant activity and pharmacokinetics between AT alpha and the other substances.<sup>27</sup> Moreover, AT consists of both  $\alpha$  and  $\beta$  isoforms, as does rAT-gamma, with the proportion of the isoforms being similar between them in spite of some heterogeneity in the attached sugar chains. Therefore, unlike AT alpha, rAT-gamma has biological features that are very similar to those of AT.<sup>27</sup>

Our study has several limitations. First, the results were collected from a single surgical/medical ICU in a university hospital, resulting in a small sample size. Second, retrospective data collection inevitably suffers from selection bias. Third, since some patients who did not survive for more than 5 days after AT therapy were excluded, the efficiency of rAT therapy in these patients was not verified. Lastly, since the AT-equivalent rAT-gamma dose in the rAT group significantly differed from the AT dose in the AT group, we were unable to show that rAT per se is more efficacious in cases of septic multiple organ failure than AT at equivalent doses.

## Conclusions

The results of this study led us to conclude that adequate weight-dependent AT supplementation, especially using rAT-gamma, could provide a therapeutic advantage against septic organ failure and septic DIC as compared to the fixed dose regimen of AT, although this observation could be due to the fact that the AT dose administered in this study was inadequate in terms of the required per kg body weight dose. In our opinion, there is a need for a large-scale randomized controlled trial to evaluate the optimal dose of AT for septic organ failure.

## Authors' Note

HK and YM contributed to the conception and design of the study and drafted the article. HK extracted the clinical data, performed the statistical analysis, and interpreted the results. All authors approved the final manuscript. Some of the results of this study were presented at the European Society of Intensive Care Medicine EuroAsia meeting in Hong Kong on 12th April, 2018.

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## Declaration of Conflicting Interests

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