Controversies regarding the use of antithrombin for sepsis-associated disseminated intravascular coagulation: an update of the evidence

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Dear Sir,

I enjoyed reading the review article by Liumbruno et al.1 and fully agreed with their opinions that the cornerstone for managing sepsis-associated disseminated intravascular coagulation (DIC) is the management of the underlying infection and that further evidence is required to support the use of the anticoagulants. Since the International Society on Thrombosis and Haemostasis (ISTH) 2014 meeting has just finished, and I introduced the current status of Japanese strategies for the management of septic DIC2 in the Scientific and Standardisation Committee (SSC), I would like to update the latest evidence regarding this issue. As mentioned in Liumbruno's review1, some anticoagulant therapies, including antithrombin supplementation are rated as "potentially effective" in the current "Guidance for diagnosis and treatment of DIC"3 released by the ISTH/SSC. As a matter of fact, "potentially effective" means "needs further evidence" and we all knew that pharmacological doses of activated protein C, high-dose antithrombin, and tissue factor pathway inhibitor failed to demonstrate a benefit for survival in severe sepsis in large-scale, randomised controlled trials. I do not, however, think that conclusions on the usefulness of the anticoagulant therapies can be drawn yet. Some subgroup analyses in subjects with sepsis-associated DIC in the above randomised controlled trials did demonstrate effects on mortality. Furthermore, the Japanese Association for Acute Medicine conducted a small-sized but well-qualified randomised controlled trial and found that a supplemental dose of antithrombin (30 IU/kg/day for 3 days) induced better resolution of DIC compared to the placebo control4. Following this report, Tagami et al.5 analysed the Japanese nationwide administrative database and reported that, compared to treatment without antithrombin, standard antithrombin supplementation (1,500-3,000 IU/day for 3 days) reduced the mortality rate by approximately 10% in patients with pneumonia and DIC and that the odds ratio for 28-day mortality was around 0.87. In addition, we recently reported that antithrombin supplementation, which helps antithrombin activity to return to the normal range (antithrombin activity >80%), significantly improved the rates of survival as well as the recovery from DIC without an increased risk of bleeding in patients with sepsis-associated DIC (Critical Care in press). Based on these pieces of evidence, I think that supplemental doses of antithrombin might be effective to the patients with sepsis-associated DIC. However, to confirm this, adequately robust randomised controlled trials will be required. Finally, I would like to repeat that I agree with the opinions of Liumbruno et al.1 that we must keep on searching for the best target, the right timing, and the sufficient dose of antithrombin.

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References


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