Mini Review Article

Anticoagulant therapy for septic coagulopathy and disseminated intravascular coagulation: where do KyberSept and SCARLET leave us?

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The use of antithrombin and thrombomodulin to restore impaired anticoagulant pathways in septic coagulopathy has been shown to significantly increase the resolution rate of disseminated intravascular coagulation. In KyberSept and SCARLET, two large, international, randomized controlled trials in patients with sepsis, these anticoagulants have not shown significantly reduced mortality. The aim of this assessment was to compare the heterogeneity in responses to treatment in the two trials according to different patient phenotypes. Results of the KyberSept and SCARLET trials reported in original and post-hoc publications were analyzed and directly compared for treatment effects in various patient subgroups. In both KyberSept and SCARLET, the septic coagulopathy phenotype that benefited most from endogenous anticoagulant supplementation showed markers of excessive activation of coagulation. Interaction between concomitant thromboprophylactic heparin and the endogenous anticoagulants abrogated the efficacy of both antithrombin and thrombomodulin. In both trials, higher disease severity was associated with better treatment outcome. In conclusion, in two landmark studies of endogenous anticoagulants in patients with sepsis, similar findings of beneficial effects in the coagulopathy phenotype and interactions with heparin comedication and disease severity support the potential roles that thrombomodulin and antithrombin might play in treating septic coagulopathy and disseminated intravascular coagulation. Further prospective validation is warranted. Future trial designs to definitively establish the therapeutic relevance of antithrombin and thrombomodulin in septic coagulopathy should focus on involvement of patients characterized by coagulopathy and disease severity as well as interactions between endogenous anticoagulants and exogenous heparin.

Key words: Anticoagulant, antithrombin III, disseminated intravascular coagulation, heparin, sepsis, thrombomodulin

INTRODUCTION

SEPTIC COAGULOPATHY AND disseminated intravascular coagulation (DIC) cause endothelial dysfunction and microvascular thrombosis, which can lead to organ dysfunction and serious adverse outcomes for patients.[1] The use of anticoagulant therapies capable of restoring impaired anticoagulant pathways of septic coagulopathy has been shown to significantly increase the resolution rate of DIC.[2.] However, international, randomized controlled trials (RCTs) of such agents in patients with sepsis have not shown significantly reduced mortality.[3–6] Of note, the majority of patients in these sepsis trials did not have DIC.

Tissue factor pathway inhibitor and drotrecogin alfa (activated), which is a recombinant human activated protein C, are not available for clinical use after landmark sepsis trials failed to determine efficacy and safety.[4–6] Plasma-derived human activated protein C, a drug that is approved in Japan for the treatment of diseases caused by congenital protein C deficiency, has been found to improve DIC more efficiently than heparin, but only in a small RCT.[7] Antithrombin and thrombomodulin are, therefore, the two remaining endogenous anticoagulant drugs on the market currently under clinical development for septic coagulopathy and DIC.[2]

KYBERSEPT TRIAL

REGARDING THE USE of plasmatic antithrombin concentrate, post-hoc subgroup analyses of the landmark

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KyberSept study by Warren *et al.*[3] indicated survival benefits in severe sepsis patients who did not receive concomitant heparin,[8] who were at high risk of death,[9] and who had the most severe coagulopathy.[10] High-quality observational data from Japan also indicated significant benefit in antithrombin-treated patients with sepsis and DIC.[11] These findings need prospective validation.

Thrombomodulin is an endogenous anticoagulant that amplifies formation of activated protein C by forming a complex with thrombin and exerts anti-inflammatory effects.[12] An early RCT from Japan suggested clinical benefit of ART-123, a soluble human recombinant thrombomodulin preparation, in patients with DIC associated with hematologic malignancy or infection,[13] consistent with a subsequent international phase IIb study in patients with sepsis and suspected septic DIC.[14] Observational data from Japan indicated significant benefit also in thrombomodulin-treated patients with sepsis and DIC.[11] Prospective validation of these results in a large, international, phase III RCT of ART-123 in patients with severe sepsis and coagulopathy was recently reported[15] and is discussed here.

SCARLET TRIAL

THE SCARLET (Sepsis Coagulopathy Asahi Recombinant LE Thrombomodulin) phase III trial was designed to determine the impact of ART-123 on 28-day mortality in patients with sepsis-associated coagulopathy.[15] Thus, SCARLET is the first large, international, phase III RCT designed to examine the effects of anticoagulants in coagulopathic patients. Eight hundred and sixteen subjects with cardiovascular or respiratory dysfunction and coagulopathy were enrolled and 800 received either ART-123 or placebo in a randomized fashion. The study's primary efficacy endpoint was 28-day all-cause mortality; other prespecified outcome measures included changes in coagulation parameters from baseline.

There was a trend towards lower 28-day mortality in the ART-123 group, but this difference was not statistically significant and the primary end-point was therefore not met: 2.55% ($P = 0.318$) absolute risk reduction versus placebo (95% confidence interval [CI], −3.68% to 8.77%). The analysis could have been hampered by the sample size, as mortality in the placebo group was lower than anticipated and the CI around the mortality point estimate was wide.

In addition, a significant proportion of subjects enrolled in the full analysis set (182/816 patients, 22%) no longer met the criteria used to define coagulopathy (international normalized ratio >1.4 and platelet count $>30 \times 10^9$/L) by the time the first dose was given. In the post-hoc analysis, removal of study participants not maintaining coagulopathy at baseline resulted in a larger absolute risk reduction of 5.40% (95% CI, −1.68% to 12.48%).[15]

For each of the coagulation markers assessed, that is, D-dimer, prothrombin fragment F1.2, and thrombin-antithrombin complex, decreases from baseline values during the 6-day treatment period were significantly greater ($P < 0.05$) with ART-123 versus placebo.[15]

IN SEARCH OF THE SEPTIC DIC PHENOTYPE

SCARLET IS THE second negative large-scale RCT of treating sepsis with an endogenous anticoagulant intervention, after the KyberSept study on the use of human plasmatic antithrombin concentrate in severe sepsis. This is surprising, as SCARLET, in contrast to KyberSept, aimed for inclusion of patients with septic coagulopathy only. To better understand the results of SCARLET, study details and data were directly compared with those of KyberSept, revealing some intriguing similarities.

First, in SCARLET, the difference in 28-day mortality between the ART-123 and placebo groups was −0.87% (95% CI, −9.52% to 7.77%) in subjects who received heparin for thromboprophylaxis ($n = 416$) and was 6.25% (95% CI, −2.72% to 15.22%) in those who did not ($n = 384$).[15] In KyberSept, 2,314 patients with severe sepsis were randomized to receive either antithrombin or placebo, and 1,616 of these patients also received concomitant heparin.[3] Among the 698 patients without concomitant heparin, mortality at day 28 was reduced in the antithrombin group compared with the placebo group (37.8% versus 43.6%; absolute reduction, 5.8%; risk ratio, 0.860; 95% CI, 0.725 to 1.019), a difference which increased as deaths accrued through day 90 (44.9% versus 52.5%; absolute reduction, 7.6%; risk ratio, 0.851; 95% CI, 0.735 to 0.987). No effect of antithrombin on mortality was apparent when analyzing only those patients who had received concomitant heparin.[8] Possibly, heparin can modulate the anti-inflammatory effects of both antithrombin and thrombomodulin through interaction with glycosaminoglycans and high mobility group box 1 with its receptor of advanced glycation end products, respectively.[12,16]

Second, as discussed by Jecko Thachil in greater detail against the perspective of SCARLET,[17] mortality was markedly decreased with ART-123 therapy when patients showed dysfunction in up to three organs, whereas this effect was absent in patients with four organs affected by sepsis.[15] In patients from KyberSept whose predicted mortality, according to the Acute Physiology and Chronic Health Evaluation II score, was 30–60%, survival during the 90 days of follow-up was higher in the group who received antithrombin

in place of placebo, which was not the case in patients with the highest predicted mortality.[9]

Third, in a meta-analysis of five RCTs, including SCARLET, that evaluated ART-123 therapy for sepsis-induced coagulopathy and enrolled a total of 1,762 patients, the primary outcome measure of 28-day all-cause mortality was reduced by approximately 13% with ART-123 versus control, although this difference was not statistically significant (relative risk, 0.87; 95% CI, 0.74 to 1.03; $P = 0.10$; $I^2 = 0\%$).[18] However, by removing the SCARLET results that were derived from the full analysis set ($n = 800$) and replacing them with those for the subgroup of patients who continued to meet the coagulopathy criteria at dosing ($n = 634$), mortality was shown to be significantly decreased by ART-123 treatment (risk ratio, 0.82; 95% CI, 0.69–0.98; $P = 0.03$; $I^2 = 0\%$).[19] Similarly, a recent meta-analysis found no significant survival benefit of antithrombin use in septic DIC but was carried out under the assumption that all 2,314 patients in KyberSept had sepsis and DIC,[20] whereas post-hoc analyses showed this not to be the case.[10] After replacing the mixed sepsis group, which included patients with and without DIC, with only those sepsis patients with confirmed DIC, revised meta-analysis instead indicated a reduction in mortality risk with antithrombin.[21]

Defining septic coagulopathy and timing of ART-123 treatment were additional issues in SCARLET that might have impacted overall trial outcome and, hence, should be carefully selected in future studies.[17,22] Furthermore, in patients with DIC, elevated serum lactate concentration predicted 90-day mortality, a relationship that was not evident in patients without DIC.[23] Disseminated intravascular coagulation status could therefore modify the effect of lactate on mortality in sepsis, and lactate levels might have a role in identifying subgroups of patients who stand to benefit from therapies able to reverse DIC. Finally, in sepsis, patients with liver dysfunction and shock appear to be more inclined to develop coagulopathy or DIC and have a higher mortality rate than patients with other sepsis phenotypes.[24]

CONCLUSIONS

THE RESULTS OF SCARLET add important information to the current understanding of the use of endogenous anticoagulants in the treatment of sepsis and DIC. Intriguing similarities in the findings of landmark studies on thrombomodulin and antithrombin support the important role that endogenous anticoagulants could play in treating septic coagulopathy and DIC.

The DIC phenotype that likely benefits most from endogenous anticoagulant supplementation includes markers of excessive activation of coagulation. Future studies will need to unravel the roles of markers of coagulation together with those of inflammation.[25] Interaction mechanisms between thromboprophylactic heparin and antithrombin have been proposed;[16] however, such interactions between heparin and ART-123 await further study. Treatment benefits of both antithrombin and ART-123 could be modified by disease severity.

Current best evidence suggests that thrombomodulin and antithrombin are effective treatments when coagulation is particularly activated in patients with severe sepsis and DIC. As this conclusion is from post-hoc analyses, prospective validation is warranted. In future studies, in addition to patient selection, end-points other than 28-day mortality, such as improvement in organ failure or DIC scores, could be important as well.[26]

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