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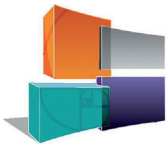

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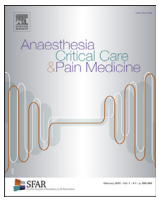

Editorial

Should we continue to test soluble thrombomodulin, or other systemic anticoagulants, as a life-saving therapy for sepsis-induced coagulopathy?

1. The Pro position

The SCARLET study (Sepsis Coagulopathy Asahi Recombinant LE Thrombomodulin) required a herculean effort spanning over 6 years from 159 investigative sites across 26 countries to finish this phase 3 trial, testing a recombinant human form of soluble thrombomodulin in sepsis/septic shock [1]. A total of 800 patients were randomised in this double-blind, placebo-controlled trial. Looking on the bright side, this study confirms that soluble thrombomodulin has an excellent safety record in treating septic patients. This adds further evidence of a low incidence of serious bleeding events or other possible toxicities found in safety studies performed in Japan, where soluble thrombomodulin is already available on the market as a treatment for disseminated intravascular coagulation from sepsis-induced coagulopathy [2].

However, the study results did not reveal any significant differences in the 28-day primary mortality outcome (26.8%-treated vs. 29.4%-placebo control; $P = 0.32$) or other secondary endpoints [1,3]. However, in a sub-group analysis, patients still presenting DIC at the time of drug administration had an apparent survival benefit compared with placebo [1]. Regrettably, these results are not surprising, as essentially all phase 3 sepsis trials over the past 4 decades are disappointing, and fail to meet their primary study outcome measures [4]. The only two exceptions to this long line of repeated failures in phase 2/3 sepsis trials were the first trial with Activated Protein C [5] and the initial Early Goal Directed Therapy trial [6]. Both therapies failed to yield reproducible benefits in subsequent confirmatory clinical trials [3,7–9]. Neither of these initially promising treatment modalities are recommended in the current 2017 international surviving sepsis campaign guidelines [10].

This does not mean we should give up on efforts to improve the outcome of human sepsis. The clinical consequences of sepsis can be devastating. Sepsis is now recognised a major, if not the principal cause of death in intensive care units in high income and low/middle income nations worldwide [3,7–9].

Enormous strides have been made in understanding the basic, molecular pathophysiologic events that underlie sepsis. It is logical to expect that advances in comprehending the basic elements of sepsis will lead to improved therapies and better outcomes. Patients, their families, and society expect new therapies to be deployed and to provide better outcomes. This is not the time to give up and admit that it is just too complicated. We must rethink what we are doing and consider if potential flaws exist in our basic assumptions about sepsis and septic shock.

Few would argue that thrombomodulin was not a logical and promising agent to test in a clinical trial of sepsis-induced coagulopathy. Thrombomodulin possesses a myriad of desirable physiological effects in defending the microcirculation from sepsis-induced coagulopathic effects and the dysfunctional innate immune response [3,7–9]. Thrombomodulin activity is critical in the generation of Activated Protein C to prevent the most severe manifestation of the sepsis-induced coagulopathic state, known as purpura fulminans [11]. Thrombomodulin also possesses histone-binding sites to limit the deleterious effects of extracellular histones as a damage associated molecular pattern molecule in sepsis [12]. Soluble thrombomodulin should be re-evaluated in sepsis-induced coagulopathy providing that the drug is given at an earlier stage of the disease process, using a simplified definition of DIC (INR $>$ 1.4).

2. The Con position

The reason(s) for all these failed clinical sepsis trials is likely attributable to a fundamental issue of human sepsis, intrinsic patient heterogeneity. Consider the remarkable lack of precision in our current definition of sepsis, "a dysregulated host response to infection leading to acute organ dysfunction" [7–10]. There is no single diagnostic test for sepsis [4,7]. It is a clinical diagnosis, induced by systemic infection, and based upon a constellation of rapidly changing haemodynamic, haematologic, immunologic, and host response events. No wonder we have failed to reproduce results from one clinical study to another, even with the most promising of experimental agents. Sepsis is a syndrome, not a disease, and our ability to pick out responsive patients likely to benefit from a novel therapy in large clinical trials remains regrettably insufficient to date [3,4].

The lack of reproducibility in the SCARLET study is particularly striking, as it was well designed and should have worked [1]. A previous large phase 2b trial showed promising results in patients treated with ART123 with sepsis-induced coagulopathy [13]. The

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phase 3 study was a biomarker-driven study requiring evidence of ongoing coagulopathy (relative thrombocytopenia $< 150 \times 10^9$/L and prolonged international normalised ratio (INR) > 1.4) before entrance into the trial [1]. Despite its clear therapeutic rationale, the clinical trial failed to demonstrate that soluble thrombomodulin provided significant survival benefits compared with the control group.

Two potential issues may have sabotaged the SCARLET trial: a process issue and an analytic/statistical issue. The process issue is the need to provide some degree of protection against the risk of deep venous thrombosis (DVT) in both treated and control populations. While not clearly demonstrated in the critical care setting, DVT prophylaxis is considered standard of care for critically ill patients with sepsis [8,10]. This generates a challenge in a double-blind study in which one arm (treatment) is a systemic anticoagulant, while the other arm (placebo) has no anticoagulant activity. The investigators and the clinicians caring for the patient are blinded from treatment assignment.

This problem is usually solved by allowing low doses of anticoagulants in both groups. The investigators are hoping that low dose heparin (or other anticoagulants) will be enough to prevent DVT while still allowing the experimental agent to work, thereby improving outcomes without causing increased risk of bleeding by excessive anti-coagulation. This trade-off might not work in an actual clinical trial.

Heparin interactions with circulating antithrombin induce numerous anti-inflammatory effects separate from its anti-coagulant effects [2,8,12–14]. Non-anticoagulant forms of heparin have been described as retaining their anti-inflammatory activities and even protecting animals in experiment studies from septic shock [12]. Unless investigators are willing to rely upon non-heparin strategies, such as venous compression stockings for DVT prophylaxis, potential unwanted interactions between low-dose unfractionated heparin and low molecular weight heparins will continue to complicate efficacy signals when testing a new anticoagulant for treatment of sepsis [11–13].

The analytic/statistical issue that plagues sepsis trials is patient heterogeneity. This issue has been extensively explored in a recent, intriguing study by Seymour et al. [15] Using "big data" from combining electronic medical record information from ten of thousands of septic patients, they analysed their routine clinical, laboratory, and physiologic data within their first 12–24 hours of hospitalisation. This information was subjected to cluster analysis by unsupervised machine learning to search for predictable and consistent patterns of patient sub-groups. Four phenotypes were repeatedly identified, which predicted their cytokine responses and 28-day, all-cause mortality. These phenotypes, denoted as alpha, beta, gamma or delta, would all be acceptable candidates for entry into a clinical sepsis trial using current definitions of sepsis (systemic infection with acute organ dysfunction.).

They then took one step further and analysed the database using Monte Carlo simulations to predict the outcomes of sepsis studies based on phenotype distribution. Adding more patients to a theoretical trial of early goal directed therapy would progressively worsen outcomes, while adding more patients would progressively increase the chance of success to an early goal directed clinical trial [14].

Clearly, we need a better way of defining and classifying patients into sepsis trials that consider phenotypic and genotypic differences in responsiveness to experimental agents [15–19]. The introduction of genomic, metabolomic and transcriptomic endotypes or phenotypes in sepsis studies might provide the necessary clarity to see the next generation of sepsis trials succeed where past efforts have failed.

In the meantime, there is no sense in continuing with soluble thrombomodulin unless the drug gets tested against a restricted heparin dose comparator group with venous graded pressure stockings.

Disclosure of interest

Bruno François report personal fees from AKPA during the conduct of the SCARLET study as advisor and member of the steering committee. Xavier Wittebole, MD, study investigator, Saint Luc University Hospital, Brussels, Belgium (compensation was received by the institution and/or investigators as clinical coordinating center physicians). Pierre-Francois Laterre reported personal fee for participation to one advisory board after the study completion. Steve Opal, Thierry Dugernier, M. Levy declare that they have no competing interest.

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