Unraveling Severe Sepsis: Why Did OPTIMIST Fail and What’s Next?

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Why Did OPTIMIST Fail and What's Next?

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In this issue of The Journal, Abraham and colleagues report the results of an international, multicenter randomized controlled trial (optimized phase 3 ticafogin in multicenter international sepsis trial [OPTIMIST]) that compared a 96-hour infusion of recombinant tissue factor pathway inhibitor (TFPI) with placebo in 1754 critically ill patients with sepsis and mild coagulopathy (international normalized ratio [INR] ≥1.2). Tissue factor pathway inhibitor, a naturally occurring anticoagulant, modulated the coagulation cascade but did not impact the mortality rate.

Perhaps the most surprising observation in this trial is the pattern of survival. A planned interim analysis of the first 722 patients demonstrated a large difference in the mortality rate favoring patients assigned to receive TFPI (38.9% vs 29.1%, P = .006). However, the survival difference was not large enough to activate the predefined stopping rules and the study continued. Subsequently, survival in patients assigned to receive TFPI declined precipitously and, at the time of final analysis, there was no evidence of a survival advantage in patients who received TFPI.

Another observation was that concomitant low-dose heparin therapy, prescribed for other reasons, may have influenced survival. Cautious inferences from this observation are warranted because patients were not randomly allocated to heparin. Although mortality was similar in patients who received TFPI whether they received concomitant heparin or not (34.6% vs 34.0%), patients in the placebo group who received heparin had a much lower mortality rate than those who did not (29.8% vs 42.7%).

Moreover, this trial was designed to recruit patients who not only had severe sepsis but also had mild coagulopathy. However, a small parallel cohort of 201 patients with low INR (<1.2) were also recruited. In this subgroup, a trend suggested that patients who received TFPI were less likely to die (12% vs 23%).

These observations prompt 4 important questions: (1) Why study anticoagulants in sepsis? (2) Why was this trial limited to patients with mild coagulopathy? (3) Why was there such a large discrepancy between the survival rates in the interim and final analysis? and (4) What are the implications for the future study of agents to treat sepsis?

Why Should Anticoagulants Be Studied in Severe Sepsis? Coagulopathy is one of the hallmarks of sepsis, arising as a result of both direct activation of coagulation by infecting organisms and as a result of diffuse endothelial injury. Although thrombosis can complicate this coagulopathy, its principal clinical manifestation is bleeding due to uncontrolled consumption of coagulation factors. Microvascular thrombosis and hemorrhage may not only complicate the clinical course but may also contribute to the end-organ damage that ultimately leads to death. These observations led to the suggestion that anticoagulant therapy may benefit patients with sepsis and coagulopathy.

Physiological regulation of coagulation relies on 3 natural anticoagulant proteins: antithrombin, activated protein C, and TFPI. Antithrombin acts as an anticoagulant by binding to and inactivating activated coagulation factors II, IX, X, and XI, a reaction accelerated about 1000-fold by heparin. Activated protein C acts as an anticoagulant by cleaving and inactivating factors Va and VIIIa, which are necessary cofactors for coagulation. Thus, antithrombin and activated protein C act as anticoagulants by interfering with coagulation during its amplification phase, rather than preventing activation of coagulation. Tissue factor pathway inhibitor blocks coagulation at its earliest stages, further reducing factor consumption and treating coagulopathy.

Interest in the use of natural anticoagulants to treat sepsis arises from knowledge of their mechanism of action, bolstered by experimental models and small controlled and uncontrolled studies in humans, which suggests that antithrombin, activated protein C, and TFPI reduce mortality. However, treatment of severe sepsis with physiological anticoagulants has met with mixed results. A large phase 3 multicenter trial demonstrated that antithrombin infusion did not reduce mortality in patients with sepsis.

See also p 238.
Low-dose heparin was also thought to confound this study. As in the OPTIMIST trial, the subset of patients in the placebo group who received heparin had a lower mortality than those who did not. However, in those patients randomized to antithrombin, mortality was higher when the patients also received heparin. One must be cautious interpreting these observations because allocation to heparin was not random. In another large multicenter trial, activated protein C was demonstrated to favorably impact survival, with a 6% absolute mortality rate reduction. Although this trial was successful, the mortality benefit may be mediated not through activated protein C anticoagulant properties, but through modulating other components of the innate immune response. Despite the large mortality decrease and studies suggesting appropriate use of activated protein C is cost-effective, adoption of activated protein C into practice has been slow. Possible reasons include concerns regarding mid trial changes to the study protocol and drug preparation, high acquisition costs, and bleeding.

Although there is strong biological rationale for the use of anticoagulants in sepsis, of the 3 naturally occurring proteins, only activated protein C appears effective. Heparin, the most widely available, least expensive, and most easily used anticoagulant, has not been rigorously tested for the treatment of sepsis.

Why Was the Use of TFPI Limited to Patients With Mild Coagulopathy? In the OPTIMIST study, the primary efficacy analysis was limited to patients with increased INR. Although the proposed benefits of TFPI would be expected through stabilization of the consumptive coagulopathy of sepsis, most patients with sepsis have abnormal activation of coagulation, even if the INR is within a normal range. Furthermore, initiation of therapy before the INR increases may be at least as effective as waiting until a more severe coagulopathy develops; therefore, the apparent benefit of TFPI identified among patients with an INR within a normal range underscores this point. The decision to limit trial entry to those patients with an increased INR may have been primarily as a result of the findings of a logistic regression model of 210 patients enrolled in a prior phase 2 study that suggested a possible interaction between TFPI and INR. This decision illustrates the difficulty that investigators face when proceeding to phase 3 trials in sepsis.

With so many failed phase 3 trials in sepsis, investigators need better techniques for interpreting results from the preceding phase 2 trials before embarking on definitive phase 3 studies. The difficulties in extrapolating phase 2 results to phase 3 studies are illustrated by the phase 219,20 and phase 321 Monoclonal Anti-TNF: a Randomized Controlled Sepsis (MONARCS) trials of an antitumor necrosis factor antibody, afelimomab, for severe sepsis. The phase 2 study suggested a larger treatment effect in the subgroup of patients with elevated IL-6 levels. Therefore, although they enrolled 2634 patients into the phase 3 study, the investigators restricted their a priori primary analysis to the subset of 998 patients whose IL-6 level was 1000 pg/mL or higher. The MONARCS trial did show a statistically significant mortality reduction overall, but the benefit was not larger in the subgroup with high IL-6 levels, and the primary analysis, limited to only this subset of patients, failed to achieve statistical significance.21

The recurrent observation that promising phase 2 trials of 200 to 500 patients are poor predictors of success in phase 3 trials is the issue. With the mortality rate as the only reliable end point for phase 3 studies, results of small phase 2 studies make informed decisions about optimal subgroups or drug doses challenging. Instead, crucial design decisions are made based on sometimes tenuous statistical inferences. Although increasing the size of phase 2 studies might provide more reliable data for a phase 3 study design, this strategy may be impractical. Therefore, one approach lies in finding new end points for phase 2 trials that are excellent proxies for mortality. Perhaps a useful analogy is the minimal inhibitory concentrations for antibiotics. The minimal inhibitory concentration correlates well with eradication of infection and thus aids determination of optimal dose, yet it is sensitive enough to provide good power with small sample sizes in phase 2 studies. The best places to evaluate proxy end points are in large successful phase 3 trials and large observational studies. Unfortunately, both are currently rare in sepsis research.

Why Was There Such a Large Discrepancy Between the Survival Rates in the Interim and Final Analysis? Several post-hoc exploratory analyses were unable to explain the changing mortality pattern among patients who received TFPI. There was no evidence that a clerical error resulted in active drug and placebo being confused in the second half of the study. No evidence of a systematic change in TFPI potency as a result of unanticipated alterations in the manufacturing process was identified as time passed. In the absence of a clear explanation for the change in the pattern of mortality, this appears to be due to the play of chance, as unlikely as this might seem. This finding reinforces the importance of large studies, adherence to a prospective analysis plan, and the need for very stringent stopping rules. More lenient stopping rules for this trial would have led to early discontinuation and an erroneous conclusion about the efficacy of the drug.

What Does This Mean for the Future of TFPI and Similar Agents? The completion of the OPTIMIST study marks the end of the recent era of large randomized trials of novel naturally occurring anticoagulants. The one existing anticoagulant that probably should be studied is heparin. Understanding the pathophysiology of sepsis continues to evolve and the list of potential targets for future study, such as high-mobility group B1 protein, microphage, migration inhibitory factor, complement C5a, and apoptosis inhibitors, continues to increase. To maximize the likelihood of successful trials, efforts to conduct more informative studies before the phase 3 evaluations must be redoubled. With what is often
only a single opportunity at a phase 3 trial, it is imperative to make the best possible design decisions regarding dosing and entry criteria. Otherwise, concluding that a potentially effective therapy is ineffective or vice versa is a real risk.

In the meantime, important headway has been made in defining optimal care for the patient with or at risk for severe sepsis. Attention to head tilt in the patient who is ventilated,23 sterile precautions during central venous catheter insertion,24 hand washing,25 and appropriate stress ulcer prophylaxis26 all decrease the risk of developing nosocomial infection and sepsis. Once infection occurs, prompt diagnosis and initiation of appropriate antibiotics,27,28 along with surgical drainage when indicated, promotes optimal resolution of infection. Early goal-directed resuscitation can attenuate the progression of organ dysfunction and reduce mortality.29 Optimal organ support, including low tidal volumes for acute lung injury,30 daily ventilator weaning trials,31 tight blood glucose control,32 and sedation protocols33 all improve outcomes. In appropriately selected patients, manipulation of the innate immune response with activated protein C11 and corticosteroids34 may help to further decrease mortality of this common and frequently lethal condition.35,36

REFERENCES