BIOBUSINESS BRIEFS

TRIAL WATCH

Sepsis study failure highlights need for trial design rethink

The failure of Eisai's eritoran to improve survival in a Phase III trial in patients with severe sepsis (*JAMA* **309**, 1154–1162; 2013) adds to the long list of ineffective experimental treatments for such patients. It also suggests that a complete rethink is needed in the strategies to evaluate novel agents for sepsis.

The trial tested the hypothesis that administering the synthetic Toll-like receptor 4 (TLR4) antagonist eritoran to block the interaction of lipopolysaccharide (LPS) — a component of the cell wall of Gram-negative bacteria and a potent inducer of immune responses — with its receptor MD2-TLR4 could improve survival in patients with severe sepsis, in whom there is a systemic uncontrolled inflammatory response to infection. However, among the 1,961 patients evaluated, who were randomized and treated with either eritoran or placebo within 12 hours of onset of first organ dysfunction, there was no reduction in 28-day mortality in the group receiving eritoran.

Steven Opal, Division of Biology and Medicine, Brown University, Rhode Island, USA, and lead author of the paper, attributes the failure of eritoran largely to the underlying hypothesis being incorrect, and suggests some explanations. “It might be too late to use this kind of therapy once septic shock is underway. Alternatively, there may be redundant inflammatory pathways that lead to continued pathology other than the TLR4 pathway, such as TLR2, TLR9 and complement.”

Mitchell P. Fink, David Geffen School of Medicine, University of California, Los Angeles, USA, agrees. “The trial failure suggests that LPS is not an important upstream trigger for the deleterious manifestations of sepsis, or that inflammatory pathways activated by other pathogen-associated molecular pattern molecules, instead of or in addition to LPS, are important.”

However, he adds: “It is also important to note that patients were not enrolled in the Phase III trial for eritoran on the basis of the presence of LPS in the circulation.” This indicates a key change that is needed in future clinical trials in sepsis if the dismal success rate is to be increased — enrolling only patients who are likely to respond to the drug on the basis of appropriate biochemical screening. “So, for example, if one is seeking to test an antibody to TNF [tumour necrosis factor], one should enrol only patients with pathological circulating levels of TNF,” suggests Fink.

“The old way of doing sepsis studies should be largely abandoned and we should focus on more homogeneous populations with either specific diseases — for example,

community-acquired pneumonia or peritonitis — or specific biomarkers to identify patients who are likely to benefit from the intervention,” agrees Opal. “We have to come up with a strategy to use rapid nucleic acid-based diagnostics and other ‘omics’ approaches to pick out potentially responsive patients with an attributable risk of sepsis mortality, along with immune phenotyping of patients and their likelihood of responding to specific therapies,” he adds.

Such approaches could then be coupled with innovative trial designs incorporating parallel arms with different interventions and/or drug doses. “We need better surrogate markers of survival that can be used in small Phase II studies to screen lots of potential therapeutic strategies for efficacy. Adaptive designs should be used for Phase II and even Phase III registration trials,” says Fink.

In the meantime, the focus turns to sepsis therapies remaining or embarking in clinical trials, which include biologics such as granulocyte-macrophage colony-stimulating factor (to enhance immune responsiveness in selected patients with sepsis and biochemical evidence of immunoparalysis) and soluble human recombinant thrombomodulin (focused on patients with sepsis-induced coagulopathy). New vasopressors, new antibiotics and improved intravenous immunoglobulins are also under evaluation. Non-pharmacological approaches are also in progress: “A well-designed trial of haemofiltration, using a cartridge containing LPS-absorbing fibres, is in progress [ClinicalTrials.gov identifier: NCT01046669], in which only patients with biochemical evidence of endotoxaemia are being enrolled,” says Fink. “In addition, the ‘Cooling And Surviving Septic Shock Study’ [ClinicalTrials.gov identifier: NCT01455116] is studying the effect of moderate induced hypothermia in reducing mortality. Data from a single-centre Phase II trial of this intervention showed encouraging results.”

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