EDITORIAL VIEW

Drotrecogin Alfa (activated) in severe sepsis and septic shock

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Severe sepsis and septic shock account for considerable morbidity and mortality in critically ill patients. There are complex biological events that lead to organ failure and death. It has been recognized that combined inflammatory component, haemostasis abnormality and endothelial cell injury interplay in pathophysiology of sepsis1.

Under normal physiological conditions, protein C plays a critical part in the maintenance of haemostasis and modulation of inflammation. It is a vitamin K dependant glycoprotein synthesised by the liver and circulates in blood in an inactive form. In the presence of thrombin it is converted to an activated protein C, which has antithrombotic, profibrinolytic properties and also plays a crucial part in maintaining the balance of anti-inflammatory and antiapoptotic system in response to injury. It also has direct anti-inflammatory effect by its ability to inhibit both the production of TNF-α and interleukin-1 by monocytes and the expression of E-selection on endothelial cells, thereby inhibiting leucocytes attachment to the endothelium2.

During sepsis conversion of protein C to its activated form is impaired, therefore patients may be unable to generate sufficient levels of endogenous activated protein C. Low protein C levels have been correlated with poor outcome in patients with severe sepsis as it may lead to widespread activation of coagulation resulting in the intra vascular deposition of fibrin and ultimately thrombotic occlusion of small and medium size vessels, commonly referred to as disseminated intra vascular coagulation-leading to multiorgan failure3.

Drotrecogin alfa (activated) [DrotAA] (Xigris) is a recombinant form of the natural anticoagulant activated protein C (rhAPC). It was approved by the US Food and Drug Administration (FDA) in November 2001 for the treatment of adult patients with severe sepsis at high risk of death (for instance, as indicated by Acute Physiology and Chronic Health Evaluation [APACHE] II score > 25).

In 2002 the European Agency for the Evaluation of Medical Products recommended that its use be restricted to patients with two or more sepsis-induced organ dysfunctions.

DrotAA has properties that address microvascular injury in severe sepsis through its direct effects on endothelial cells and leukocytes, while also having antithrombotic and indirect profibrinolytic proper ties. Sepsis bundle and guideline implementation has been associated with improved survival and includes DrotAA administration in appropriate patients4. The evidence concerning its use in adults is primarily based on two R CTs: PROWESS5 and ADDRESS6. Additional safety information comes from an open-label observational study, ENHANCE7.

PROWESS (the Protein C World-wide Evaluation in Severe Sepsis), the first major multicentre trial in involved 1,690 patients. The trial demonstrated a reduction of 28 days in all cause mortality. Sub group analysis of the study data showed greater benefit in the most severely ill patients; including those with APACHE II score > 25 or multi organ dysfunction. An analysis of secondary end points suggested that the incidence of multi organ dysfunction was lower in patients treated with DrotAA and that the therapy was associated with more rapid recovery of pulmonary and cardiac function5. This observation supported the decision of the FDA to indicate the use of DrotAA for the treatment of patients with severe sepsis at high risk for death.

ADDRESS (Administration of Drotrecogin alfa [activated] in Early stage Severe Sepsis) trial involved 2,613 patients having severe sepsis and at low risk of death at the time of recruitment. (e.g., patients with a baseline APACHE II score < 25 or only one organ dysfunction at baseline). This trial supported the FDA recommendation that DrotAA was not of benefit in patients at the low risk of death6.

In ENHANCE (Extended Evaluation of Recombinant Human Activated Protein C) trial inclusion and exclusion criteria were similar as in PROWESS trial except the time of initiation of DrotAA infusion was up to 48 hours after
the first sepsis-induced organ dysfunction. They found that 28 days all cause mortality for patients treated with DrotAA was similar to that observed in PROWESS. The ENHANCE trial also suggested early administration of DrotAA was associated with better outcomes as there is significantly lower mortality rates in patients treated within 24 hours from their first sepsis-induced organ dysfunction than those treated after 24 hours (22.9 versus 27.4 percent)\textsuperscript{7}.

Serious adverse events did not differ in all the studies with the exception of serious bleeding. Bleeding is more common in DrotAA-treated patients; therefore, a careful assessment of bleeding risk is required. Serious bleeding seen in the patients treated with DrotAA: PROWESS 2% vs. 3.5% (p = 0.06); ADDRESS 2.2% vs 3.9% (p < 0.01); ENHANCE, open label 6.5%. Intracranial hemorrhage (ICH) occurred in all the trials but was not statistically significant in any of the trials. The incidence of serious bleeding was found to be significantly higher among patients with one or more risk factors for bleeding, compared to patients without any risk factors\textsuperscript{8}. Risk factors include platelet count < 30,000/mm\textsuperscript{3}, recent anticoagulant therapy, history of severe trauma and/or coagulation disorders in surgical patients and in those requiring invasive procedures.

Both the RCTs in adult patients (PROWESS & ADDRESS) were methodologically strong and well defined and provided direct evidence regarding death rates. For adult use, there is probable reduction in mortality in patients with high risk of death, having APACHE II >25 or multiple organ failure. No benefit is reported in patients with low risk of death, having APACHE II < 20 or single organ dysfunction. The effect is unclear in patients with more than one organ failure but APACHE II < 25. In such circumstances the clinicians may use clinical assessment of the risk of death and number of organ failures to support the decision.

Treatment of sepsis is expensive. Cost of treatment of patients with sepsis and septic shock is an ongoing concern of practicing intensive care physicians. The mean cost of treating a patient with severe sepsis has been reported as four times that of a non-septic patient\textsuperscript{9} and use of DrotAA can lead to considerable impact on the providers budget as the therapeutic cost for DrotAA appears high.

Then the question arises what to do? One has to balance the care of the patients versus cost. There comes the ethical issue of not using an available therapeutic agent, which has higher chances of decreasing mortality, just because of its cost. Cost-effectiveness of DrotAA versus that of standard care in the treatment of severe sepsis has been assessed in various studies. It has been found that for patients with severe sepsis or septic shock and an APACHE II score \textsuperscript{12}25, DrotAA is a cost-effective therapy as measured in cost per year of life saved\textsuperscript{10,11}.

Although various trials in sepsis research has provided evidence that use of DrotAA can significantly reduce morbidity and mortality but the selection of patient is important in maintaining the highest benefit while reducing the amount of unnecessary treatment. Decision on utilization depends on assessing likelihood of mortality reduction vs. increases in bleeding and cost. Every department should make a guideline according to its circumstances and financial burdens to implement the use of new therapies available and should not unnecessarily treat the patient leading to financial burden.

REFERENCES