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Drotrecogin Alfa (Activated)

A Viewpoint by Derek C. Angus

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This drug, a recombinant form of activated protein C, was recently demonstrated to significantly lower 28-day mortality in a large, multicentre trial of patients with severe sepsis. Endogenous activated protein C appears to play several roles in sepsis, including anti-thrombotic, pro-fibrinolytic, and anti-inflammatory mechanisms. Circulating concentrations of activated protein C appear to fall in most patients with severe sepsis and are often lowest in patients with the worst outcome. However, the exact mechanism of action of drotrecogin alfa (activated) is unclear and does not appear to be due to replacement therapy. In other words, there was no obvious relationship between the magnitude of protein C deficiency and improved clinical outcomes with drotrecogin alfa (activated) therapy. Nevertheless, the results of the clinical trial were impressive: patients treated with drotrecogin alfa (activated) had a 6% absolute and 19% relative reduction in the risk of death. Thus, this therapy could have a profound effect on the care of patients with severe sepsis. There are, however, some caveats.

First, severe sepsis is a syndrome that occurs in a heterogeneous patient population. The clinical benefits or adverse events of drotrecogin alfa (activated) therapy may vary across different patient subgroups. Unfortunately, the recent trial was only adequately powered to find an overall treatment effect; however, the relative risk reduction of 19% appears to be constant across different subgroups. The absolute risk reduction will be less in patients who are less sick and greater in patients who are more sick.

Second, the trial attempted to enrol a specific population of patients who had enough acute physiological derangement to be at significant risk of death yet were not so ill with underlying disease as to be at no chance of survival (even if the sepsis was cured). If the therapy is prescribed for patients who either have less severe sepsis or who are very sick with other underlying or concomitant conditions, the observed benefits may be less than those seen in the trial.

Third, to prescribe this therapy appropriately will require prospective and prompt identification of patients at the time they meet the constellation of clinical and physiological criteria that defines 'severe sepsis'. Ensuring physicians and nurses start identifying severe sepsis promptly and accurately may be a difficult task, yet failure to make the diagnosis properly may either limit use or limit appropriate use.

Fourth, there is limited data on patient-centred outcomes associated with this therapy. Many patients with severe sepsis are old and infirm, prompting speculation that drotrecogin alfa (activated) may improve 28-day mortality, yet may not result in any meaningful long-term gains for the patients. In the recent trial, however, most patients were at home prior to hospital admission; half of the survivors were already at home at day 28 and only 10% were still on mechanical ventilation. Data are pending on duration of survival benefit in long-term follow-up studies.

Finally, drotrecogin alfa (activated) may be expensive. Although it may be cost-effective when compared to other therapies in other diseases, the sheer number of potential candidates for this therapy may make drotrecogin alfa (activated) a 'budget-buster' for many hospital pharmacies. Consequently, clinicians, pharmacists, and hospital administrators may all feel strongly, and perhaps differently, about how best to use this therapy. The key factors that will drive these decisions may be the number of potential candidates, the proposed mechanism for screening and identifying appropriate patients in a timely fashion, the balance of short-term risks and benefits, the drug acquisition costs, and the cost-effectiveness and long-term effects of the therapy.

It appears that drotrecogin alfa (activated), if administered in a fashion similar to that in the recent trial, has the potential to significantly improve survival in this devastating and common clinical condition. Optimal use will require careful patient selection and attention to the other essential components of severe sepsis management: antibiotics, surgery when required, and appropriate monitoring and support of organ dysfunction. ▲