Drugs 2002; 62 (4): 631-632
0012-6667/02/0004-0631/$30.00/0

Drotrecogin Alfa (Activated)

A Viewpoint by Marcel Levi

Department of Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Sepsis is a frequently occurring condition and is a major cause of mortality in the Western world. Sepsis is associated with activation of systemic inflammatory pathways, leading to endothelial cell perturbation and widespread intravascular activation of coagulation. This may result in a systemic microvascular deposition of fibrin thrombi, contributing to multiple organ failure and mortality. In the pathogenesis of microvascular thrombosis during sepsis, there is a central role for dysfunctional physiological anticoagulant pathways, in addition to tissue factor-dependent generation of thrombin and impaired fibrinolysis. One of the most important of these anticoagulant pathways is the protein C system. Activated protein C is formed from circulating protein C by endothelial cell-bound thrombomodulin and is a strong modulator of procoagulant activity. The protein C system is severely compromised in sepsis due to low levels of circulating protein C and downregulation of endothelial thrombomodulin in combination with some other mechanisms. Hence, administration of activated protein C is a rational strategy to restore this physiological anticoagulant system, and should improve organ function in the course of sepsis and the outcome of the patient.

This hypothesis was proven in clinical trials with recombinant human activated protein C [drotrecogin alfa (activated)] in patients with sepsis, thereby rendering this treatment one of the first strategies to reduce mortality from sepsis. In fact, the efficacy of activated protein C in this situation underscores the central role of microvascular thrombosis in organ failure and mortality in patients with sepsis. The question remains, however, whether the beneficial effect of activated protein C is solely due to its ability to overcome endothelial dysfunction and to ameliorate the sepsis-associated coagulopathy, or whether its modulating effect on inflammatory activity, which has been shown *in vitro*, may also play a role. ▲