

Drotrecogin alfa (activated) falls amid continuing enthusiasm to normalise physiology in ICU patients

TO THE EDITOR: It has been a fascinating decade for sepsis management. It all started with a promising but controversial drug, drotrecogin alfa (activated) (DrotAA; which is recombinant human activated protein C, trade name Xigris), approved for clinical use in late 2001. Further studies then failed to replicate the benefits seen in the initial study conducted by the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group.¹ The recently published PROWESS-SHOCK² study brought closure to the DrotAA saga and marked the end of an era.

DrotAA transcended medicine like a Hollywood starlet whose radiance burned bright until a well publicised fall from grace, and front-page headlines became yesterday's news. A blockbuster debut and the generous marketing³ that followed generated a love-hate relationship with the drug among intensivists.

DrotAA was an expensive innovation that emerged at a time when the face of intensive care was rapidly changing. Some have opined that the bundle of interventions incorporated in the controversial Surviving Sepsis Campaign⁴ may have negated the benefits demonstrated in the PROWESS study. With all its imperfections, the campaign still managed to generate awareness and, to an extent, standardised sepsis management worldwide.

As we bid adieu to DrotAA, manufacturers and clinical prescribers can breathe a sigh of relief knowing that, while DrotAA didn't live up to its promise, it was not the most harmful intervention ever attempted in intensive care.⁵ Clinicians who observed the "magic of DrotAA" in cases of extreme microvascular failure and shock, as in fulminant meningococcaemia, will continue to wonder if there will ever be a role for this drug again.

Overall, the DrotAA experience added to the predicament intensivists face every time a new intervention,

aimed at correcting the perturbations in critical illness, claims to make a real difference. Critically ill patients will always have relative or absolute excesses and deficiencies in a myriad of biological factors such as protein C, steroids, trace elements, glucose, hormones and vitamins. Yet, is that a case for normalisation? DrotAA provides another salutary lesson for those still keen on normalising interacting factors without a better understanding of sepsis.

Author details

Kiran Shekar, Staff Intensivist,¹ and Deputy Director²

John F Fraser, Senior Staff Intensivist,¹ and Director²

1 Adult Intensive Care Services, The Prince Charles Hospital, Brisbane, QLD, Australia.

2 Critical Care Research Group, The Prince Charles Hospital and University of Queensland, Brisbane, QLD, Australia.

Kiran_shekar@health.qld.gov.au

References

- 1 Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344: 699-709.
- 2 Ranieri VM, Thompson BT, Barie PS, et al; PROWESS-SHOCK Study Group. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012; 366: 2055-64.
- 3 Eichacker PQ, Natanson C, Danner RL. Surviving sepsis: practice guidelines, marketing campaigns, and Eli Lilly. *N Engl J Med* 2006; 355: 1640-2.
- 4 Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36: 296-327.
- 5 Marti-Carvajal AJ, Sola I, Lathyris D, Cardona AF. Human recombinant activated protein C for severe sepsis. *Cochrane Database Syst Rev* 2011; (4): CD004388. □