Letter

Drotrecogin alfa (activated): down and not out, but not really in either

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See related letter by Agarwal and Nath, http://ccforum.com/content/10/4/416,
and related commentary by Friedrich *et al*., http://ccforum.com/content/10/3/145

We read with interest the letter by Agarwal and Nath [1] in response to our commentary [2] analyzing current evidence for drotrecogin alfa (activated) (DrotAA) in the treatment of severe sepsis. Agarwal and Nath argue that our meta-analysis should have used a fixed-effects model, which ignores between-study heterogeneity, rather than a more conservative random-effects model, which includes it. Such a model shows significant benefit for DrotAA in patients with severe sepsis and at a high risk of death defined either by an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 25 or more, or at least two organ dysfunctions.

Agarwal and Nath's letter highlights the surprising degree of statistical heterogeneity that remains between the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) trial [3] and the Recombinant Human Activated Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial [4] results despite minimal methodologic differences between these trials and further minimization of clinical heterogeneity by selecting a more uniform subgroup of patients with severe sepsis and a high risk of death. In particular, for the subgroup with an APACHE II score of 25 or more, I^2 (the percentage of total variation in results across studies that is due to heterogeneity rather than chance [5]) is very high (84%). Given this degree of heterogeneity, we feel that one should account for, rather than ignore, its effects when pooling results.

The APACHE II subgroup effect in PROWESS was one of about 80 prospectively defined subgroup comparisons [6]. Using other definitions of high risk, the difference in treatment effect between high-risk and low-risk subgroups in PROWESS was not statistically significant (for example, patients with multiple organ failure) and in some cases not even directionally consistent (for example, patients requiring mechanical ventilation or vasopressor support) [7]. If the APACHE II high-risk and low-risk subgroup effect in PROWESS is due to chance, then the best estimate of the effect of DrotAA for any patient is the overall pooled result incorporating all patients. Interestingly, although the degree of between-study heterogeneity is significant when the overall data from all four trials presented in Figure 1 [2] are pooled ($I^2 = 59\%$), it disappears if PROWESS is excluded ($I^2 = 0\%$).

Is there a role for DrotAA in severe sepsis? The inconsistent trial results and increased risk of serious bleeding highlight the importance of identifying patients for whom the benefits of DrotAA outweigh the risks. The high variability and very low proportion of patients with severe sepsis receiving DrotAA in many western European countries [8] suggest that many clinicians are having difficulties identifying such patients. We agree with Agarwal and Noth's [1] second point, namely that a meta-analysis using individual patient data and adjusting for baseline covariates would be an important first step to identify appropriate patients for DrotAA. However, such an analysis would be primarily hypothesis generating, and additional trials would still be required to provide definitive guidance on appropriate patient selection. In any case, we believe that evidence for the routine use of DrotAA should be based on consistent clinical trials and should not depend on the use of a

ADDRESS = Administration of Drotrecogin Alfa (Activated) in Early Stage Stage Sepsis; APACHE = Acute Physiology and Chronic Health Evaluation; DrotAA = drotrecogin alfa (activated); PROWESS = Recombinant Human Activated Protein C Worldwide Evaluation of Severe Sepsis.

particular meta-analytic statistical model, particularly one that does not account for between-trial heterogeneity.

Competing interests

The authors declare that they have no competing interests.

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