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Drotrecogin alfa (activated) in clinical practice and current evidences

Reply to the comments of Doctors Büchele and Janiszewski

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Re: We thank Doctors Büchele and Janiszewski for their interest and comments on our article.¹ Every “non-systematic” review, above all, portrays the authors’ position in relation to a specific subject in view of current knowledge and often, because of the limitations imposed by the journal’s format, it is impossible to address all actual studies. In our opinion, results of the three studies pointed out do not significantly change our conclusions. To affirm that use of drotrecogin alfa activated (DrotAA) must be considered, as stated in our conclusion cannot be understood as a recommendation to suspend use of the drug in the treatment of sepsis, but must be interpreted as a need for readjustment. After the great euphoria in the early years of 2000, with publications of studies demonstrating the benefit of some interventions for the treatments of patients with sepsis and related complications, DrotAA is only one among the other interventions (such as low- dose corticosteroids, strict glycemic control and early-goal directed therapy) whose efficacy and safety have also been questioned.

We emphasize that every observational study is subject to problems and difficulties in the statistical analysis and interpretation of results, liable to bias of the effect assessment in an unpredictable manner.² In the observational studies about utilization of DrotAA, some additional methodological concerns arise: observations are subject to selection bias because the opinion of intensivists on risk of death is more accurate than the predictive scores³ which invalidate *a posteriori* comparisons, especially when the economic factor may affect decision making.^{4,5} Stated in another way, the physician’s opinion on risk of death, as well as on the patients’ life prognosis, with or without treatment, bears a direct influence on the choice or not of using an intervention, especially if this has a significant economic impact. That is why, there is a natural tendency (and beneficial!) in the selection of patients with a better prognosis, for utilization of DrotAA, which cannot possibly be subjected to statistical treatment.

Another serious issue in observational studies is the tendency to group interventions in patients that are being treated by the same team⁶ whose statistical treatment rests upon a methodology not used in the cited studies.⁷ It is easy to understand that there are performance differences between the various units and if there is a variation in the use of an intervention by the same units, the effects observed cannot be the outcome of practice, but of better performance among units.⁸

Our comment is aligned with growing concerns of the international scientific and medical communities regarding the merit of the efficacy and safety of DrotAA, basically to identify subgroups of patients who have a real potential to benefit from the drug.⁹⁻¹² DrotAA presents an interesting phys-

iopathological rationale for clinical use, but as with any intervention cannot be considered a panacea for all patients with sepsis, a syndrome that encompasses severe forms of infectious diseases, many with a distinct clinical and biological behavior.¹³ All these factors are further corroborated, even in the review of the *Surviving Sepsis Campaign* guidelines, recently published, in which recommendation for use of DrotAA was reviewed as a “weak recommendation for use” according to the

GRADE System.¹⁴ The need for a set of new evidences to guide the use of DrotAA, brought about a request by FDA and by the European Union regulatory agencies for new studies, such as RESPOND (Phase II) and PROWESS SCHOCK (Phase III) that are now at patient recruitment stage.¹⁵ It is hoped that such studies may aid in the definition of the true role of drotrecogin alfa activated in the treatment of patients with severe sepsis and septic shock.

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