Drotrecogin alfa (activated) in clinical practice and current evidences

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To the editor: Soares and colleagues wrote a review on current evidences related to Drotrecogin Alfa (activated)[1] (volume 20, nº 2) and concluded that use of the drug must be reconsidered until new studies provide more information. However, two large multicenter, observational studies were not quoted. One is the Polish observational study by Klüber et al. published in 2008 that observed 3,223 patients with severe sepsis treated throughout the country for two and a half years.[2] Average mortality in the group of 302 patients that used Drotrecogin Alfa (activated) was 38%. With due exception, the comparison made with the control group demonstrated a decrease of relative risk of death of over 30%. More than 75% of patients in the Drotrecogin Alfa (activated) group presented with four organ dysfunctions and at least 50% of them were surgical patients. Another multicenter observational study was published in April 2008.[3] This is the study by Rowan et al. who observed the use of Drotrecogin Alfa (activated) in 112 ICUs in the United Kingdom. Different from most observational studies, this study was evaluated in a prospective manner and previously planned a group of about 1,200 patients using Drotrecogin Alfa (activated) to justify the power of their statistical analyses. Similarly, within the overall group of patients totaling more than 16,000, the control group for comparative analyses was defined by pairing (individual matching and propensity matching). With such methodological strictness, analyses with the "control group" even in observational studies gained a great statistical power. The authors demonstrated that seven from eight paired analyses for risk of death were consistent with the favorable results of the PROWESS study. Only in 2.7% of cases infusion of Drotrecogin Alfa (activated) was discontinued because of adverse hemorrhagic event, not reported necessarily as severe.

Likewise, a large multicenter double-blind and controlled phase III study with use of Drotrecogin Alfa (activated) with or without association of heparin therapy as prophylaxis for deep venous thrombosis was also not cited in the mentioned text. This is a study published in the American Journal of Respiratory and Critical Care Medicine in June 2007 by Levi et al.[4] The authors studied around 2000 patients using Drotrocogin Alfa (activated) randomized to receive low molecular weight heparin or non-fractionated heparin (in prophylactic dose for deep venous thrombosis) and placebo. Primary objective of the study was 28-days mortality. The two arms presented with a similar mortality of about 30% without difference for use or not of prophylactic heparin. There was no difference in the rate of hemorrhagic adverse events.

The indication for Drotrecogin Alfa (activated) has never changed since its launching, "decrease of mortality in severe sepsis at high risk of death". How-

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ever, from the perspective of science's dynamics (especially medical) questioning will always exist. Definition of "patient at high risk of death" is possibly different today than it was eight years ago. In the last few years treatment of severe sepsis has received unconditional support from the intensive care societies and the Surviving Sepsis Campaign is a clear example of intensivists' mobilization for treatment of sepsis. That is why Eli Lilly is further sponsoring researchers of large universities in two extensive multicentric studies. The RESPOND study is directed towards following-up the evolution of plasmatic Protein C activity in patients, thereby adapting doses and infusion time of Drotrecogin Alfa (activated). The PROWESS-SHOCK study, which began just a few months ago, analyses the efficacy and safety of Drotrecogin Alfa (activated) in vasopressor dependent patients with septic shock after adequate volemic resuscitation. The PROWESS-SHOCK study has already started to recruit patients in Europe and the USA and will include fifteen enrolling research centers in Brazil. In addition to various world renowned scientists, as leading investigators, this study reckons with a highly specialized and independent data monitoring committee steered by Dr. Arthur Slutsky MD.

Various literature reviews are available on efficacy and safety of Drotrecogin Alfa (activated) substantiated by the most emblematic opinion leaders in intensive therapy. Due to the epidemiological importance assumed by sepsis, we believe that a drug, unique in its class, indicated for reducing mortality in severe sepsis with high risk of death, by the most significant guidelines of treatment of sepsis published deserves widespread discussion and more careful review of literature.

REFERENCES

01. Soares M, Machado FO, Torres VBL, Salluh JIF, Amaral ACKB. O uso da drotrecogina alfa ativada na prática clínica e as atuais evidências. Rev Bras Ter Intensiva. 2008; 20(2):173-7.
02. Klüber A, Mayzner-Zawadzka E, Durek G, Gaszyński W, Karpel E, Mikaszewska-Sokolewicz M, Majak P. Results of severe sepsis treatment program using recombinant human activated protein C in Poland. Med Sci Monit. 2006; 12(3):CR107-12
03. Rowan KM, Welch CA, North E, Harrison DA. Drotrecogin alfa (activated): real-life use and outcomes for the UK. Crit Care. 2008; 12(2):R58.
04. Levi M, Levy M, Williams MD, Douglas I, Artigas A, Antonelli M, Wyncoll D, Janes J, Booth FV, Wang D, Sundin DP, Macias WL; Xigris and Prophylactic HepaRin Evaluation in Severe Sepsis (XPRESS) Study Group. Prophylactic heparin in patients with severe sepsis treated with drotrecogin alfa (activated). Am J Resp Crit Care Med. 2007;176(5):483-90. Comment in: ACP J Club. 2008; 148(2):32. Am J Respir Crit Care Med. 2008; 177(4):461; author reply 461-2. Am J Respir Crit Care Med. 2008; 177(6):669; author reply 669.