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REVIEW ARTICLE

Drotrecogin Alfa Activated in Clinical Practice and the Current Evidences*

O Uso da Drotrecogina Alfa Ativada na Prática Clínica e as Atuais Evidências

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SUMMARY

BACKGROUND AND OBJECTIVES: The debate on efficacy and patient safety related to the use of drotrecogin alfa (DrotAA) is timely, principally due to the negative results observed in clinical studies performed after the PROWESS study, and the economic cost-related impact of the drug on the healthcare system. The aim of this study was to review the main studies on the use of DrotAA in patients with severe sepsis. The focus was on drug efficacy-and patient safety-related issues.

CONTENTS: Articles were selected by a MedLine search for studies on the use of DrotAA in patients with sepsis using the following key words: activated protein C; drotrecogin alfa; sepsis; septic shock; Xigris®. Additional references were retrieved from the studies initially selected.

CONCLUSIONS: Mortality and bleeding complications associated with the use of DrotAA were more frequent in large observational studies than those reported in randomized trials. In the light of the current knowledge, routine use of DrotAA should be reevaluated until well-designed confirmatory clinical trials can clarify the true efficacy and safety of the drug and help identify the subgroup of patients that can benefit from use of DrotAA. Physicians should be cautious with the rapid transfer of evidences not well-documented, to the guidelines and recommendations practiced in the care and treatment of patients with severe sepsis.

Key Words: activated protein C, drotrecogin alfa, mortality, sepsis, septic shock

RESUMO

JUSTIFICATIVA E OBJETIVOS: O debate sobre a segurança e eficácia da drotrecogina alfa (DrotAA) encontra-se na ordem do dia, principalmente, em função dos resultados negativos observados em ensaios clínicos subseqüentes ao PROWESS e do impacto econômico no sistema de saúde relacionado ao custo elevado do fármaco. O objetivo deste estudo foi rever os principais estudos sobre a utilização da DrotAA em pacientes com sepse grave, com ênfase nas questões ligadas a sua eficácia e segurança.

CONTEÚDO: Foram selecionados artigos sobre a utilização da DrotAA em pacientes com sepse publicados nos últimos dez anos no MedLine. Os seguintes uniter-

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mos foram utilizados: *activated protein C; drotrecogin alfa; sepsis; septic shock; Xigris®.* Estudos referenciados nos artigos selecionados na busca também foram utilizados.
CONCLUSÕES: As taxas de letalidades e as complicações hemorrágicas associadas com o uso do fármaco foram maiores em grandes estudos observacionais do que aquelas descritas previamente nos ensaios clínicos. A luz dos resultados atualmente disponíveis, o uso da DrotAA deve ser reconsiderado até que novos ensaios clínicos possam subsidiar com informações adicionais sobre eficácia, segurança e na identificação dos subgrupos de pacientes com sepse grave que porventura possam ter benefício com o uso deste medicamento. A DrotAA deve servir de exemplo para que haja maior cautela com a rápida transposição de evidências ainda em construção para recomendações e diretrizes de tratamento de pacientes com sepse grave.
Unitermos: choque séptico, drotrecogina alfa ativada, proteína-C ativada, sepse.

INTRODUCTION

Sepsis is one of the main causes of admission to intensive care units (ICU) and, despite improvements in the care of patients followed-up in the last years; it is still associated to high mortality[1-4]. After a sequence of negative results in clinical trials using specific treatments, the PROWESS study showed a significant reduction of mortality by using drotregogin alfa activated (DrotAA) in patients with severe sepsis[5]. Based upon results of this phase 3 trial study the FDA (Food and Drug Administration) and various regulatory agencies sanctioned, under special circumstances, release of this drug for patients with sepsis and high risk of death (e.g. presence of multiple organ dysfunction or APACHE II $\geq$ 25 points). Notwithstanding the initial enthusiasm, debate on the safety and efficacy of DrotAA is timely, primarily because of the negative outcomes in subsequent clinical trials and economic impact on the health system due to its high cost [6-12].
This study intended to review the leading studies on the utilization of DrotAA in patients with severe sepsis, stressing issues related to its efficacy and safety.
Articles on the use of DrotAA in patients with sepsis published in MedLine - PubMed (www.pubmed.gov) during the last ten years were selected. The following keywords were used: activated protein C; drotrecogin alfa*;* sepsis; septic shock; Xigris®. Studies mentioned in the articles selected were also used.

THE USE OF DROTRECOGIN ALFA ACTIVATED IN CLINICAL PRACTICE

Three large observational studies on the utilization of DrotAA in the "real world" were published[13-15]. In the first study, Bertolini et al. monitored the use of DrotAA in Italy, from July 2003 to March 2006, following a resolution of the Italian Health Ministry to carry out a drug-surveillance program[13]. Included were 668 patients from 134 ICUs, corresponding to approximately 80% of the patients who had used the drug in Italy during the period in question.
The control group (n = 1181) was comprised of patients, eligible for DrotAA who were not given the medication, selected from a program of infection surveillance. Mortality in the ICU was significantly higher in the control group than in those treated with DrotAA (55% versus 46.4%, p= 0.0004). However, patients treated with DrotAA were younger and had a higher prevalence of trauma and surgical procedures and in the multivariate analysis, the use of DrotAA did not continue to be associated with survival (p = 0.434). Furthermore, in stratified analysis according to the type of admission, use of DrotAA was associated with higher mortality in patients who underwent elective surgery [OR = 2.79 (IC 95%, 1.31-5.97)]. In the second study, Kanji et al. carried out a retrospective analysis on the use of DrotAA in 261 patients admitted, from March 2003 to February 2004, in 37 ICUs (57% of the total) in the provinces of Ontario and Quebec, Canada[14]. There was no control group in this study and overall mortality was 45%. Use of DrotAA in the first 12h after diagnosis of severe sepsis was associated with reduction of mortality [OR = 0.51 (IC 95%, 0.28-0.92)]. In the third study, Wheeler et al., retrospectively evaluated 274 patients, treated with DrotAA in five American teaching institutions[15]. In this study, also without a control groups, overall hospital mortality was of 42% being significantly lower in patients given the drug on the day of diagnosis of sepsis than in those given it in the following days (33% versus 40% and 52%, p = 0.016). However, it is noteworthy that observations of the last two studies are subject to bias in selection and treatment access (patients who receive DrotAA late, may have had late access to the hospital and ICU and have received other inadequate interventions).
Two findings common to these studies are particularly relevant. The mortality rates (42% or more) were substantially higher than those described in the PROWESS (24.7% and 30.8%)[5], ENHANCE (25.3%)[16], and ADDRESS (20.5% and 20.6%)[7] studies, although the

authors attributed such results to greater severity of their patients, especially a greater number of organ dysfunctions[13-15]. However, these values are similar to those described in various studies with patients having both severe sepsis and septic shock[1-4]. In the BASES and "Sepse Brasil" studies, mortality rates of patients with severe sepsis were 34% and 47% and the patients with septic shock were 52% and 65% respectively[3-4]. However, the most important observation was the higher incidence of severe hemorrhagic events in the three studies (10% in the Canadian, 10.9% in the Italian; 4.4% in the American), almost all during administration of DrotAA. In the PROWESS, ENHANCE and ADDRESS studies, rates of severe hemorrhagic events were of 3.5%, 6.5% and 3.9%, respectively. Likewise, due to greater severity of patients, risk of bleeding might be higher than in the clinical trials. However, bleeding incidence was not influenced by the severity of patients in other studies[17]. This finding agrees with the literature, where a higher number of adverse events are more frequent in the observational than in the randomized studies[18]. In the Canadian study, hospital mortality rate was significantly higher in patients with hemorrhagic events (68% versus 42.7%, p = 0. 015) and use of DrotAA in patients with a contraindication for use was associated with increase of these adverse events [OR = 2.7 (IC 95%, 1.1–6.5)]. In this study, 20% of patients had relative contraindications and 2% had absolute contraindication for DrotAA. In the Italian study a higher mortality was noted in patients presenting with severe bleedings associated to DrotAA, (57.5% *versus* 44.9%, p = 0.041). In this study an extremely relevant finding was the high frequency of off-label use of the drug detected in 19.1% of patients.

IMPLICATIONS IN THE ASSESSMENT OF EFFICACY, DRUG-SURVEILLANCE AND SAFETY OF PATIENTS

Drug-surveillance and safety of patient related issues must be addressed. Results of the three studies[13-15], together with the two ADDRESS[7] and RESOLVE[6] studies, impose significant considerations about safety and efficiency of DrotAA in patients with sepsis. The ADDRESS study included adult patients with severe sepsis and "low risk of death", that is to say a single organic dysfunction or with APACHE II score < 25 points[7]. However, although the required sample size had been estimated at 11,444 patients, this study was stopped early after interim analysis of 2,640 patients (23% of the planned), for lack of benefit (mortality rates of 20.5% for the placebo group and 20.6% for the group treated with DrotAA, p = 0.98) and by the increased incidence of severe hemorrhagic events (2.2% versus 3.9%, p = 0.01). Although the ADDRESS study was not designed to evaluate use of DrotAA in more severe patients, due to the dual possibility of assessing the severity of the patient, patients with an APACHE II score < 25 points but with more than one organic dysfunction and patients with one organic dysfunction and APACHE II score > 24 were included. In the analyses of these sub-groups of "greater severity" (according to the inclusion criteria for use of the drugs in Europe and in the USA respectively), there were no noticeable differences in the mortality rate of patients receiving placebo or DrotAA. The RESOLVE study evaluated pediatric patients with severe sepsis and was designed to include some 3,000 patients[6]. However this study also was interrupted at the second interim analysis, after inclusion of 477 patients (15.9% of planned), due to lack of benefit (17.5% mortality for the placebo group and 17.2% for the group treated with DrotAA, p = 0.93) and a tendency towards increased risk of bleeding in the central nervous system, in patients with < 60 days (4.6% versus 2.1%, p = 0.13). The PROWESS study, planned to include 2,280 patients was also stopped early after inclusion of 1,690 patients (74% of the planned), but in this case due to benefit , since in the second interim analysis a lower mortality was observed in the group treated with DrotAA (24.7% versus 30.8%, p = 0.006)[5] . However, there was not enough power to properly assess the occurrence of severe bleedings [3.5% (30/850) in the group treated with DrotAA versus 2% (17/840) in the placebo group, p = 0.06] In a simulation, with projection for the initially desired sample size in which frequencies of adverse events in the two groups would be maintained, this difference would become statistically significant [3.5% (40 events in the DrotAA group) versus 2% (23 events in the placebo group), p = 0.04].

The clinical trials stopped early due to benefit, have merited special attention. Montori et al. evaluated the frequency and quality of such clinical trials published in the last years[19]. From a total of 143 studies, 92 (64%) were published in medical journals with the highest impact factor (N Engl J Med, JAMA, Ann Intern Med, Lancet and BMJ). Notwithstanding, the authors noted that these studies: a) are becoming more frequent; b) are usually sponsored by industry; c) often fail to adequately report relevant information about the decision to stop early; d) present implausibly large tre-

atment effects, particularly when the number of events is small; and recommend that clinicians should view the results of such trials with skepticism. In that review, Critical care ranked, fourth in the order of frequency of these studies. The OPTIMIST[20] trial which assessed the response to use of recombinant tissue factor pathway inhibitor (tifacogin) on mortality of patients with severe sepsis is a fair example of the issues related to clinical trials stopped early. In the first interim analysis, a significant decrease of mortality (29% versus 39%, p = 0.006) was observed in patients treated with tifacogin. Yet, the study was continued until the sample reached the planned size. This difference of the endpoint magnitude initially observed, was totally reversed with pursuance of the study and end mortality was similar between groups. Use of tifacogin was associated to a higher rate of bleedings. Similar performances have already been perceived in other areas of Medicine[21,22]. Findings of OPTIMIST associated to the negative outcomes of the ADDRESS and RESOLVE studies suggest the possible influence of chance in the results of the PROWESS study.

DrotAA is one among many examples of treatments incorporated in the practice in Critical Care practice based upon results of a single phase 3 studies. The new flexibilization of drug release policies adopted by the FDA (fast-track) came to meet the needs for treatment of patients with severe diseases when time is the key element, such as antiretrovirals for treatment of the acquired immunodeficiency syndrome (AIDS) and chemotherapy for treatment of advanced tumors. This program consists of accelerating the approval of a new drug based upon results of preliminary studies[23,24]. However, final approval of these drugs has to rely on confirmatory trials (phases 3 or 4) on the benefit and safety of the drug, as well as permit identification of subgroups of patients that would benefit most from the treatment, thereby avoiding costs of inefficient treatments and patient loss of an opportunity for a more appropriate treatment. There are many recent examples of treatments and devices whose efficacy and safety are questionable and many were withdrawn from the market due to subsequent studies[25-29]. Phase 4 studies are especially important for drug-surveillance since a phase 3 study, even with inclusion of 2,000 or 3,000 patients, is not acceptable to identify occurrence of less frequent, although potentially severe or fatal, adverse events[30].

As for DrotAA, it is remarkable that prior to publication of the PROWESS study, there were no publications on pre-clinical studies that suitably described their mechanisms of action. Indeed DrotAA's anticoagulant and anti-inflammatory roles[31] as well as the prognostic impact of protein C levels in patients with severe sepsis and ISRS were clarified only recently[32-34].

CONCLUSIONS

The rush to transfer evidences still being gathered, for recommendation and treatment guidelines of patients with severe sepsis, is a matter of concern that has been subject of intense debate[35-38]. In the light of the current evidence, the use of DrotAA must be reconsidered until new clinical trials contribute with additional information on the efficacy, safety and identification of subgroups of patients with severe sepsis that may possibly benefit from use of this drug. This statement must be underscored because various questionings about the possible biases and failures in the method of the PROWESS study have not yet been adequately answered[30,40].

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