ARTICLE

Utilization and Outcomes of Drotrecogin Alfa (Activated) for Sepsis in Critically Ill Patients at a Community Acute Care Hospital

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ABSTRACT

Background: Institutional criteria are in place within the author's institution to optimize and facilitate the use of drotrecogin alfa (activated) (DAA).

Objectives: The primary objective was to evaluate the appropriateness of DAA utilization. The secondary objectives were to characterize the patients and types of infections for which DAA was used and to evaluate mortality in the intensive care unit (ICU), mortality at 28 days, serious bleeding events during the infusion, and wastage of this agent in clinical practice at the author's institution.

Methods: Charts of patients who received DAA from the time it was first marketed in Canada in 2003 until April 2007 in a 9-bed medical–surgical ICU in a community acute care hospital were evaluated retrospectively.

Results: Of the 27 patients who received DAA, the therapy was appropriate for 26 (96%). The mean score (± standard deviation) for the Acute Physiology and Chronic Health Evaluation (APACHE II) was 28 ± 4, and the mean number of dysfunctional organs or systems was 3 ± 0.9. The mortality rate in the ICU was 44%, and the 28-day mortality rate was 60%. Serious bleeding during the infusion occurred in 2 (7%) of the patients. Wastage of DAA totalled 145 mg for 10 (37%) of the patients. Half of the wastage (70 mg, at a total cost of about $4700) occurred because fresh DAA supplies were prepared by the pharmacy before completion of the current bag.

Conclusions: Use of a preprinted order facilitated appropriate DAA utilization. Mortality and bleeding rates were higher than those in randomized controlled trials. Wastage could be minimized by not preparing supplies of DAA before the current bag is finished. This study illustrates the importance of drug-use evaluations and institutional guidelines to facilitate appropriate utilization of DAA.

Key words: drotrecogin alfa (activated), sepsis, drug utilization, wastage

RÉSUMÉ

Contexte : L'établissement de l'auteure a des critères mis en place pour optimiser et faciliter l'emploi de drotrécogine alpha (activée) (DAA).

Objectifs : Le principal objectif était d'évaluer la pertinence de l'emploi de la DAA. Les objectifs secondaires étaient, d'une part, de caractériser les patients ainsi que les types d'infections pour lesquels ont avait recours à la DAA, et, d'autre part, d'évaluer le taux de mortalité à l'unité de soins intensifs (USI) et à 28 jours, le taux d'hémorragies graves pendant la perfusion, et le gaspillage de cet agent en pratique clinique à l'établissement où exerce l'auteure.

Méthodes : Les dossiers médicaux des patients de l'USI médico-chirurgicale de 9 lits d'un hôpital communautaire de soins de courte durée, qui ont reçu de la DAA depuis sa mise en marché au Canada en 2003 jusqu'en avril 2007, ont été évalués.

Résultats : Chez les 27 patients qui ont reçu de la DAA, le traitement était pertinent pour 26 (96 %) d'entre eux. Le score moyen (± l'écart-type) à l'indice APACHE II (Acute Physiology and Chronic Health Evaluation) était de 28 ± 4, et le nombre moyen d'organes ou de systèmes en défaillance était de 3 ± 0,9. Le taux de mortalité à l'USI était de 44 %, et celui à 28 jours, de 60 %. Des hémorragies graves sont survenues durant la perfusion chez 2 (7 %) des patients. Le gaspillage de DAA a été de 145 mg pour 10 (37 %) patients. La moitié de cette quantité (70 mg, pour un coût total d'environ 4700 $) a été gaspillée parce que le pharmacien avait préparé un approvisionnement de DAA frais avant que ne soit épuisé le sac en cours d'utilisation.

Conclusions : Le recours à un système d'ordonnances préimprimées a facilité l'emploi pertinent de la DAA. Les taux de mortalité et d'hémorragies étaient supérieurs à ceux observés dans les études comparatives aléatoires. Le gaspillage pourrait être réduit en ne préparant pas d'approvisionnement de DAA avant que ne soit épuisé le sac en cours d'utilisation. Cette étude montre l'importance de l'évaluation de l'utilisation des médicaments et des lignes directrices de l'établissement pour faciliter l'emploi pertinent de DAA.

Mots clés : drotrécogine alpha (activée), état septique, utilisation des médicaments, gaspillage

[Traduction par l'éditeur]

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INTRODUCTION

In the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study,[1] mortality at 28 days after initiation of treatment was lower among adult patients with severe sepsis (associated with acute organ dysfunction) who were treated with drotrecogin alfa (activated) (DAA) than among those treated with placebo (absolute risk reduction 6.1%). In that study, the rate of serious bleeding associated with DAA was higher than that associated with placebo, but the difference was not significant (3.5% and 2.0%, $p = 0.06$)[1]; however, the risk of serious bleeding with DAA during clinical use has subsequently been reported to be higher.[2-4] The cost associated with a 96-h course of treatment with DAA for a 70-kg patient is about $11 000. Given the high cost of the drug, the risk of serious bleeding, and the fact that the greatest benefit of DAA appears to be for patients with a higher risk of death (defined as an Acute Physiology and Chronic Health Evaluation [APACHE] II score of 25 or more[5]), preprinted orders were developed at the author's institution, with criteria to optimize and facilitate the use of DAA.[6] The institution is a 246-bed community acute care hospital in North Vancouver, British Columbia, and the intensive care unit (ICU) is a 9-bed medical–surgical unit. The institutional criteria require that patients have at least 3 of the 4 criteria for systemic inflammatory response syndromes associated with severe sepsis, at least 2 dysfunctional organs or systems (and the time from first organ or system dysfunction must be no more than 48 h before DAA is started), an APACHE II score of at least 25, and no contraindications to therapy. The preprinted order must be completed and signed by an intensivist before the pharmacy department dispenses the DAA. The hospital has intensivist coverage 24 h/day, but when the ICU pharmacist is available, he or she assists in the evaluation of patients for eligibility of DAA use, including completion of APACHE II scoring. Outside the pharmacy's usual hours of operation, a distribution pharmacist is available for call-back to dispense DAA for eligible patients.

The objective of the study reported here was to evaluate the utilization and outcomes associated with DAA in clinical practice at this institution.

MATERIALS AND METHODS

The health records of all patients in the ICU who received DAA from May 2003, when it was first used at this institution, until April 2007 were retrospectively evaluated. Patients who had received DAA were identified by searching the database of medication orders of the hospital's information system. The health records of patients who had received DAA were reviewed by a pharmacist (Z.K.), and relevant data were collected using a predefined data collection tool. The primary objective was to evaluate the appropriateness of DAA utilization according to the institution's criteria. Appropriateness was evaluated for all patients who had received DAA, but there was no attempt to identify patients who could have received DAA but did not. The secondary objectives were to characterize, for this institution, the patients and types of infections for which DAA was used and to evaluate mortality in the ICU, 28-day mortality, serious bleeding events during the infusion, and wastage of this agent. Serious bleeding was defined, in accordance with the PROWESS study, as any intracranial hemorrhage, life-threatening bleeding, bleeding event classified as serious by the investigator, or bleeding that required the administration of 3 units of packed red cells on 2 consecutive days.[1] Bleeding events were captured by screening the physician's notes and transfusion records. Wastage was determined by counting the number of completely or partially unused bags of DAA that were returned to the pharmacy and the number of bags of DAA that were prepared by the pharmacy but not dispensed.

RESULTS

Twenty-seven patients received DAA in the study period. With reference to the institution's criteria for utilization, 26 (96%) of the patients who received DAA were eligible for this type of therapy.

The mean APACHE II score (± standard deviation) was 28 ± 4, and the mean number of dysfunctional organs or systems, according to the criteria in the PROWESS study,[1] was 3 ± 0.9 (Table 1). The lungs (12 patients [44%]) and the abdomen (11 patients [41%]) were the most common sites of infection. There was a greater incidence of gram-positive (12 patients [44%]) than gram-negative (6 patients [22%]) infections, and a significant number of culture results were negative (11 patients [41%]).

The planned 96-h infusion of DAA was completed for 16 (59%) of the 27 patients. Among the 11 patients whose entire course of therapy was not completed, the reasons were death (6 patients [55%]), transfer to another institution for dialysis (2 patients [18%]), adverse effect (2 patients [18%]), and contraindication discovered after starting therapy (1 patient [9%]). The mean duration of DAA infusion for all patients was 65 ± 40 h.

The ICU mortality rate was 44% (12/27). Of these 12 patients, 6 (50%) died within an average of 8 ± 7 h after DAA was started. In this subgroup, the mean APACHE II score was 32 ± 4 and the mean number of dysfunctional organs or systems was 3.5 ± 1.0. For 2 patients (7%), status at 28 days was unknown because they had been transferred to another institution. The 28-day mortality rate of the remaining patients was 60% (15/25).

The rate of serious bleeding during the infusion was 7% (2/27). One of these patients had a significant episode of gastrointestinal bleeding, and the other had serious hemorrhagic purpura of the left buttock in conjunction with a platelet

Table 1. Characteristics of Patients Who Received Drotrecogin Alfa (Activated) for Sepsis and Sites and Causes of infection

Characteristic	No. (%) of Patients* (*n* = 27)
Age (yr), mean ± SD	60 ± 20
Sex, males	15 (56)
Weight (kg), mean ± SD	74 ± 16
APACHE II score, mean ± SD	28 ± 4
Dysfunctional organ or system	
Mean no. ± SD	3 ± 0.9
Cardiovascular	25 (93)
Respiratory	21 (78)
Renal	13 (48)
Metabolic	11 (41)
Hematologic	4 (15)
Site of infection	
Lung	12 (44)
Abdomen	11 (41)
Urinary tract	2 (7)
Central nervous system	1 (4)
Skin and soft tissue	1 (4)
Type of organism†	
Gram-positive	12 (44)
Methicillin-sensitive *Staphylococcus aureus*	3 (11)
Methicillin-resistant *Staphylococcus aureus*	2 (7)
Streptococcus pneumoniae	3 (11)
Other *Streptococcus* species	2 (7)
Enterococcus faecalis	2 (7)
Gram-negative	6 (22)
Klebsiella spp.	2 (7)
Escherichia coli	1 (4)
Neisseria meningitidis	1 (4)
Morganella morganii	1 (4)
Pseudomonas aeruginosa	1 (4)
Culture-negative	11 (41)

SD = standard deviation, APACHE = Acute Physiology and Chronic Health Evaluation (for which scores of 25 or higher indicate an increased risk of death).
*Unless indicated otherwise.
†For some patients, more than one organism was cultured.

count of 23 × 10^9/L. In both cases, the DAA therapy was stopped because of the adverse event, and the course of therapy was not completed. Both of the patients who experienced serious bleeding died.

Wastage of DAA occurred with 10 (37%) of the 27 patients. A total of about 145 mg of DAA was wasted at a cost of $9700. Among the patients for whom wastage occurred, the average wastage was 0.9 ± 0.7 bags or 14.5 ± 8.3 mg of drug. Reasons for wastage included patient death, expiry of prepared supply secondary to interruptions in therapy, and discontinuation of therapy because a contraindication was discovered. About half of the wastage (70 mg) occurred because additional supplies of DAA had been prepared before completion of the current bag. The cost associated with this form of wastage was about $4700. Of this wastage, 50 mg (71%) was potentially preventable because the extra bags of DAA had been prepared during regular pharmacy hours. The cost associated with this potentially preventable wastage was $3350.

DISCUSSION

This drug-use evaluation was performed to evaluate the utilization and outcomes associated with DAA in a real-life clinical setting and to compare the results with those reported from clinical trials.

The preprinted order appeared to be facilitating the appropriate utilization of DAA at this institution. The single case in which the use of DAA did not meet established institutional criteria involved a young man for whom the physician felt that the drug should be used, despite the patient having only 1 dysfunctional organ and an APACHE II score of 19. There were no serious bleeding events during the infusion, and the patient survived. The use of DAA in this patient occurred before publication of the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) trial,[7] which showed no mortality benefit but an increased risk of serious bleeding associated with the use of DAA in patients with severe sepsis but low risk of death (APACHE II score less than 25). We did not evaluate appropriateness of utilization from the perspective of patients who had an indication for use of this drug but did not receive it.

The patients who received DAA at this institution had greater severity of illness than those in the PROWESS study, as indicated by mean APACHE II score and number of dysfunctional organs or systems. Given the cost and potential for adverse effects associated with this drug, DAA therapy at the author's institution was limited to patients with at least 2 dysfunctional organs or systems and an APACHE II score of at least 25. In the PROWESS study, about 75% of patients had at least 2 dysfunctional organs or systems at the time of enrollment, and the largest benefit associated with DAA use appeared to be for patients with a higher risk of mortality, as defined by APACHE II score of at least 25.[1,2]

The ICU mortality rate and the 28-day mortality rate in the present study were higher than those reported in the PROWESS study.[1] This difference may be due in part to the higher severity of illness among patients in the current study. The 28-day mortality rate was also higher than the hospital–ICU mortality rate of 45% observed in a previous Canadian study,[3] in which the average APACHE II score was 31 and the mean number of dysfunctional organs was 3.4. Of note, the patients in the earlier Canadian study[3] who had failure of 3 or more organs were at increased risk of death (odds ratio [OR] 3.3, 95% confidence interval [CI] 1.6–7.0, $p = 0.002$). The fact that half of the deaths in the current study occurred within 8 h of initiation of DAA suggests that these patients may have been moribund and therefore not suitable

for DAA therapy. However, the first organ or system dysfunction had to have developed no more than 48 h before DAA therapy was started, so it is unlikely that DAA was being used as a heroic measure in patients for whom conventional therapy was failing and whose first organ failure had developed many days previously.

Rates of serious bleeding associated with DAA use appeared to be higher in clinical practice than those reported in the PROWESS study.[1] A higher incidence of this adverse effect may be expected when a medication is administered on a broader clinical scale than is the case in a study setting.[8,9] The rate of serious bleeding during infusion observed in the current study (7%) was similar to rates reported previously for Canada (7.3%)[3] and Italy (10.9%).[4] At the author's institution, all of the PROWESS exclusion criteria were incorporated in the preprinted order, whereas 20% of patients in the earlier Canadian study[3] had relative contraindications to DAA. Information about contraindications was not published in the Italian study.[4] The use of DAA in patients with a relative contraindication to therapy was associated with a greater risk of a serious bleeding event (OR 2.7, 95% CI 1.1–6.5, $p = 0.028$) in the earlier Canadian study.[3] This illustrates the importance of a risk–benefit assessment for each patient who is considered for therapy with DAA and the potential need to re-evaluate the use of this agent for patients with relative contraindications to therapy.

Wastage of DAA can be minimized by not preparing additional supplies of the drug in advance of completing the current bag. Implementing this recommendation may be difficult in institutions where the drug is prepared in pharmacy dispensaries that are not open 24 h/day; in this situation, it may be necessary to call back pharmacists outside pharmacy hours to prepare the medication, or it may be necessary to prepare additional supplies of the medication in advance of need. The potential risk of inappropriate use of DAA if this medication were to be readily available on the ward (i.e., the risk associated with not ensuring that patients meet all institutional criteria for usage) was felt to outweigh the potential limitations associated with the need for therapy when the pharmacy was closed. In addition, there is a risk of mixing errors if nurses are responsible for mixing the drug, which could lead to negative patient outcomes or further wastage, particularly given that the medication is used infrequently. Most of the potentially preventable wastage identified in this study occurred when the pharmacy was open, which indicates an easily correctable area for improvement. Since completion of the study, pharmacists have been informed of the importance of not preparing additional supplies of DAA in advance of need once therapy has been initiated, and the ICU pharmacist stays in close contact with the dispensary regarding the need for and timing of subsequent supplies of DAA for each patient. The wastage data from this study are unique, as no previous evaluations of wastage associated with DAA use were identified in the literature.

The institution now has information about the patients who receive DAA, as well as information about efficacy, toxicity, and wastage associated with this drug. This drug-use evaluation indicates higher mortality and bleeding rates than originally estimated during randomized controlled trials. Given the retrospective design of the study, these data may be limited because of incomplete data collection or inaccurate reporting of data in patients' health care records. In addition, the sample size was small, despite a lengthy data collection period, because use of this agent is limited. Although there are limitations to the conclusions that can be drawn from single-centre evaluations of the efficacy and safety of DAA, the results of this drug-use evaluation are in keeping with the results from other larger evaluations.[3,4] They illustrate the importance of drug-use evaluations and of institutional guidelines to facilitate appropriate use of DAA. Institutions should also evaluate wastage associated with DAA use, to minimize potentially preventable wastage of this costly drug.

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