ORIGINAL ARTICLE

Assessment of utilization and outcomes of drotrecogin alpha (activated) for critically ill patients with sepsis at a government acute care hospital: a retrospective study

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ABSTRACT

Objectives: Several quality improvement projects have documented the positive outcome of protocol-driven sepsis care. Drotrecogin Alpha Activated (DAA) (recombinant human activated protein C) has been advocated and used in the treatment of septic shock in suitable patients. The primary objective of this retrospective study was to evaluate the utilization of DAA guidelines at our institution, and the financial impact of inappropriate use of this agent due to any cause. The secondary objectives were to assess outcome in terms of mortality at 28-days and the incidence of serious bleeding events during the infusion.

Methodology: A retrospective analysis using electronic database for patients who received DAA from June 2008 until April 2011 was conducted at our 20-bed intensive care unit (ICU) at a government hospital as a part of continued Medication-Use Evaluation (MUE) process.

Results: Among the 41 patients who received DAA, the indication was appropriate for 32 (78%). For those patients, the mean score for the Acute Physiology And Chronic Health Evaluation-II (APACHE II) was 27±4 and the mean number of dysfunctional organs was 3±0.5. The 28-day mortality was 56% (23/41). Of the patients who died, 39% (9/23) had poor prognosis thus were not eligible for DAA. The APACHE II score was higher than 25 in 93% (38/41) of patients. The other 3 patients had an APACHE II score of less than 25 (7%). Inappropriate use of DAA occurred in 8 (20%) and totaled 385 mg at a cost of $25755. The rate of serious bleeding during the infusion was 10% (4/41).

Conclusion: The results showed that DAA protocol was not strictly followed at our institution, which had a huge financial burden. Mortality and bleeding rates were higher than those reported by randomized clinical trials, but due to the study design, results need further validation.

Key Words: Drotrecogin alpha; Outcome; Sepsis; Medication-use evaluation; APACHE II

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INTRODUCTION

One of the most important challenges in the management of patients with sepsis is to define the most appropriate treatment strategies, and to identify patients who would benefit most from such therapies. The effective implementation of guidelines will help in effective utilization of agents.

Drotrecogin alfa (activated) (Xigris®, Eli Lilly and Co.), the recombinant formulation of human activated protein C, received FDA approval for management of patients

with severe sepsis in November 2001. It has been associated with a high risk of bleeding. Due to this fact and the high cost of drug (96-h course of treatment with DAA for a 70-kg patient is about $11 000), DAA use protocol was developed at our institution to optimize and facilitate its use for better patient's outcomes.

The main purpose of our retrospective study was to assess the utilization of Activated protein C based on our institution's protocol. Secondary objectives were to assess the rate of bleeding and 28-day mortality as outcome measures in patients who received the medication.

METHODOLOGY

The study was approved by the Institutional Board Review at our hospital. Based on our electronic hospital's information database, we retrospectively evaluated the patients who received DAA from June 2008 until April 2011. Patients included in the study were adults (age >18 years) who were diagnosed with severe sepsis based on systemic inflammatory response syndrome (SIRS) criteria. These patients' relevant data were also collected to evaluate the appropriateness of DAA utilization according to the institution's protocol and the financial impact of giving this agent to patients who were not eligible to receive it. There was no attempt to identify patients who were candidates for DAA but did not receive it. The secondary objectives were evaluating 28-day mortality in the ICU and serious bleeding events during the infusion. Serious bleeding events were defined according to 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 screened from physician's notes and blood transfusion records.

RESULTS

Based on our retrospective analysis, 41 patients received DAA. With reference to our institution's protocol, 32 patients (78%) of those who received DAA were considered to be eligible. The mean APACHE II score was 27±4 and the mean number of dysfunctional organs was 3±0.5 (Table 1). The blood [20 patients(49%)] and lungs [20 patients (49%)] were the most common sites of infection. The planned 96-hour infusion of DAA was completed for 29(71%) of the 41 patients. Among the 12 patients whose entire course of treatment was not completed, the reasons were death 9(75%), gastrointestinal bleed 1(8%), and thrombocytopenia that developed after starting therapy in 2(17%) patients. The mean duration of infusion of DAA for all patients was 88±21 hours.

The ICU mortality was 56% (23/41) and the 28-day mortality was 83% (19/23). Of the 23 patients who died, 39% (9/23) had poor prognosis, one had an APACHE II score of less than 25 and one started DAA after 24 hours of multi-organ failure. When those patients are excluded, the ICU mortality becomes 29% (11/41) and the 28-day mortality becomes 35% (8/23). In addition, of the 23 patients who died, 5(22%) died within 24 hours of starting DAA infusion, and 2(9%) died within 48 hours of starting DAA.

A subgroup analysis of patients who died showed a mean APACHE II score of 27±2 and the mean number of dysfunctional organs was 3±0.4.

Table 1: Characteristics of patients who received DAA and sites and causes of infection

Patient characteristics	
Number of patients	41
Age (yr), mean±SD	51±18
Male:Female	28:13 (68:32%)
Weight (kg), mean±SD	76±18
APACHE II score, mean±SD	27±4
Dysfunctional organ or system, mean±SD	
Cardiovascular	35(85)
Respiratory	30(73)
Renal	32(78)
Metabolic	15(36)
Site of infecti	
Blood	20(49)
Lung	20(49)
Abdomen	15(37)
Urinary tract	5(12)

SD = standard deviation, APACHE = Acute Physiology and Chronic Health

Three (7%) patients who were candidates for DAA received it after 24 hours, but all survived. Of the 41 patients evaluated, 3(7%) had an APACHE II score of less than 25, and one patient of these (4%) died. This patient's DAA was discontinued due to severe thrombocytopenia of less than 30K.

The rate of serious bleeding during the infusion was 10% (4/41) which is close to that reported in a Canadian study

(7.3%)5 and an Italian (10.9%)6 study. One of these patients had a serious gastrointestinal bleeding and DAA infusion was stopped due to this adverse events. The other three had an unknown cause for the drop in their hemoglobin level, but DAA was continued and patients were transfused with more than 3 units of PRBCs. One of the patients who experienced serious bleeding died.

Wastage of the drug was suggested in 8(20%) of the 41 patients who received DAA. A total of about 385 mg of DAA was wasted at a cost of $25755. Reasons for wastage were mainly due to inappropriate prescription of DAA to patients due to poor prognosis (300 mg {78%}). In this group interruption of therapy was due to one incidence of gastrointestinal bleed, and low platelets in two other cases. No wastage was due to extra DAA bags mixed in the pharmacy.

DISCUSSION

The intent of this retrospective study was to assess the utilization and outcome of DAA as a part of MUE. The advantage of such analysis is to evaluate DAA in a real-life clinical setting and to compare with results deri ved from clinical trials. In order to be eligible for DAA, patients must have a known infection or a suspected infection based on certain criteria, at least 3 of the 4 criteria for systemic inflammatory response syndromes (SIRS) associated with severe sepsis, at least one dysfunctional organ or system (and the time from first organ or system dysfunction must be no more than 24 hours before D AA is star ted), an APACHE II score of at least 25, and no contraindication to the therapy1. The preprinted eligibility protocol must be completed and signed by an intensivist dispensed by pharmacy.

The FDA approval of DAA was based on the data from the PROWESS (recombinant human activated Protein C Worldwide Evaluation of Severe Sepsis) trial1; a randomized, double-blind, placebo-controlled, multicenter efficacy and safety study. In this study, 1690 patients were randomized to 96-hour continuous infusion of 24 mcg/kg/hour of DAA or placebo.[1-3]

Based on PROWESS, mortality at 28 days was lower in patients who were treated with D AA for sev ere sepsis versus placebo (unadjusted 6.1% absolute mor tality reduction). In that study, the rate of serious bleeding was higher in DAA arm, but the difference was not significant (3.5% and 2.0%, p = 0.06), and the number needed to treat (NNT) to save one life was 16.1 Unfortunately, the risk of serious bleeding with D AA was re ported to be higher in subsequent observational studies[4-7].

Post hoc analysis of PROWESS indicated that patients who benefit most of DAA were those at higher risk of death (defined as an APACHE II score of 25 or greater, or two or more organ failures)[8]. This discrepancy in benefit of DAA between patients at high versus low risk of death was further evaluated and proven in Administration of Drotrecogin Alpha (Activated) in Early Stage Severe Sepsis (ADDRESS) trial.[9] The differences in 28-da y mortality rates in the two groups in this study were not statistically significant; 17% of 1,297 patients receiving placebo and 18.5% of 1,316 treated patients who were at low risk of death (P = 0.34) [10]. T he Extended Ev aluation of Recombinant Activated Human Protein C (ENHANCE) trial also showed that patients treated with DAA within 24 hours, had a markedly lower 28-day mortality versus patients who were treated later.[11] Of note, serious bleeding occurred in a bigger proportion of patients than those reported in PROWEESS study.[12]

Based on our data analysis, the criteria for utilization of DAA at our institution were not adequately adhered to. One of the exclusions as per our protocol is the patient not expected to survive 28 days because of uncorrectable medical condition, including poorly controlled neoplasms or other end-stage disease. In our study, of the 23 patients who died, nine (39%) were labeled as having poor prognosis due to metastatic cancer and thus were not candidates for DAA. The fact that 31% of patients who received DAA died within 48 hours, further suggests that such patients were not eligible for DAA. The other cases where the use of DAA did not meet our institutional protocol w ere 3 patients with an APACHE II score of 8, 20 and 24, e.g. less than 25. These patients did not have any episode of serious bleeding, but the patient with an APACHE II score of 24 died. Of note, DAA infusion was discontinued in this patient due to severe thrombocytopenia. The patients who had a true indication for this agent but did not receive it were not evaluated in our study. Based on our reported mean APACHE II score and n umber of dysfunctional organs, patients at our institution who received DAA had greater severity of illness than those in the PR OWESS study.[1] Based on PROWESS and ADDRESS, patients who benefit most from DAA are those at high risk of mortality, which is defined as an APACHE II score of at least 25.1,[4] Additionally, one of the inclusion criteria is the use of DAA within 24 hours of multi-organ failure due to lower

28-day mortality reported in ENHANCE trial. Based upon this fact, the high cost of the drug (96-h course of treatment with DAA for a 70kg patient is about $11,000) and the risk of bleeding, DAA use protocol was developed at our institution and limited to patients with at least two organ failures or an APACHE II score of at least 25. Patients who meet the inclusion criteria within the past 24 hours are considered eligible for DAA.

The ICU mortality rate and the 28-day mortality rate reported was higher than that reported in PROWESS study.1 This discrepancy may be attributed to the inappropriate patient selection for DAA therapy due to their poor prognosis. Additionally, patients had a higher severity of illness as noticed from the higher percentage of patients with an APACHE II score of more than 25 (93%) compared to 75% in PROWESS. The 28-day mortality rate was also higher than a mortality rate of 45% reported in a previous Canadian study5, but patients in this study had a higher APACHE II score of 31.

The rate of serious bleeding was also reported to be higher in our study than that reported in PROWESS study.1 This is acceptable in real-life scenarios away from the strict criteria in patient selection in randomized clinical trials.[12]

This MUE shows higher mortality and bleeding rates than those reported in randomized controlled trials. Due to the retrospective design of this study, the small sample size, and a potential for incomplete and inaccurate reporting, the applicability of results on a larger scale is limited. However, the study highlights the importance of MUE and institutional guidelines in improving the utilization of agents for patients who will benefit most from such expensive therapies for better patient outcome, and from the perspective of a cost-effective pharmacotherapy management.

CONCLUSION

Our retrospective analysis showed that wastage of DAA can be minimized by strictly prescribing this agent for patients who fully meet all institutional criteria for usage. This is an area of quality improvement where there is a potential for preventing such wastage by screening patients for inclusion and exclusion criteria mandated by our institutional protocol. Mortality and bleeding rates were higher in these real-life scenarios than those reported by randomized clinical trials, but due to the study design, results are considered preliminary and need further validation.

Competing Interests: Authors disclose no competing interests.

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